



# Planning Panels Victoria

Department of Environment, Land, Water and Planning

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Melbourne Victoria 3000  
GPO Box 2392  
Melbourne, Victoria 3001  
Telephone (03) 8392 5115

29 April 2021

Kalbar Operations Pty Ltd  
C/- White & Case Lawyers  
Via email.

Dear Mr Power

## **Fingerboards Mineral Sands Mine EES Inquiry: Additional Emails from Submitter 639 - Mr Andrew Helps**

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The Inquiry and Advisory Committee (IAC) has received additional email correspondence from submitter 639 (Andrew Helps). The correspondence is in relation to Kalbar's Draft Workplan and the Toxicological Profile for Silica.

Due to the technical nature of the issues he is raising the IAC is providing these now for Kalbar to consider and provide a response on.

Could you please review the information in the e-mails and provide a response by **12 noon Wednesday 12 May 2021**. If the response is reference to existing information this should be clearly identified. The emails in question are attached and include:

- **Email Title** - Comments on KALBAR's Draft Workplan, 7/04/2021
- **Email Title** - Toxicological Profile for Silica, 12/04/2021

Following your response, the IAC will then table Mr Helps emails, this correspondence, and your response.

If you have any queries please contact Amy Selvaraj at Planning Panels Victoria on [REDACTED] or [Fingerboards.IAC@delwp.vic.gov.au](mailto:Fingerboards.IAC@delwp.vic.gov.au).

Yours sincerely

**Nick Wimbush**

Chair, Inquiry and Advisory Committee

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[REDACTED]

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**From:** Andrew Helps [REDACTED]  
**Sent:** Wednesday, 7 April 2021 12:10 PM  
**To:** Amy Selvaraj (DELWP)  
**Subject:** Comments on KALBAR's Draft Workplan  
**Attachments:** 8350.pdf

[REDACTED]

[REDACTED]

[REDACTED]

Amy,

I have had a little bit of time to look at this Work Plan (Draft) .  
What concerned me initially was the Table 2-3 (Metals in Groundwater) on page 2-17.

This document is at best scanty and would not be acceptable in many of the Asian countries because, in Australia, the consultants continue to use the significantly out of date ANZECC year 2000 standards.  
Also in most Asian countries these reports are done by the Universities and science institutes so that there is no commercial conflict in the reports.  
Unlike Australia many of the Asian Counties use USEPA/ATSDR as Baseline data providers.

The Australian system that allows the proponent to hand pick their consultants is riddled with conflict of interest  
My office in Vietnam uses US EPA and ATSDR standards and the use of these standards has had the dramatic impact of lowering environmental impacts and mammalian deaths especially in the 1- 10 year co-hort.

So I have developed a 3 page letter to you highlighting the errors in KALBAR's table 2-3.  
I felt that it was important that I write this report to assist in DELWP's assessment of the project and also as a reference for the State Coroner when the first of the community deaths occurs at Lindenow.

My experience with a similar mine in Southern Vietnam indicates that mammalian deaths could start to occur within 6 months of mine commencement.

Can you please put this up on your website along with all the other community based data.

**Andrew Helps**  
安德鲁 郝普斯  
常务董事  
**Mobile** [REDACTED]  
**UNEP Global Mercury Partnership**  
**Waste Management Partnership - designated expert**  
**Mercury added products and alternatives – designated expert**  
**Mercury Fate and Transport Group**

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**Statement of Andrew G. Helps**  
**Delegated toxic metal expert to the UNEP Minamata Convention on Mercury**

**Comments on the KALBAR Operations Draft Work Plan**

This is another fascinating document from the team of consultants working for KALBAR.

If you scroll down to page 2 and look at Table 2-3 "Metals in groundwater in Fingerboards proposed mining licence area."

In this table KALBAR provide data on 11 of the metals that the KALBAR retained consultants have found in the groundwater.

The actual lab report would in fact cover 34 metals plus Sulfur.

I have to ask the obvious question as to why KALBAR would not want the other data on metals in the groundwater reported?

The data in Table 2-3 is in Mg/L whereas the Laboratory report is in Ug/L so the people who wrote this report have in fact converted the lab data.

There must be some commercial imperative that drives the consultant to continually convert this data - I would suspect it is a client driven requirement.

It is interesting to note that through this whole process KALBAR have not provided the lab reports in the Laboratories reporting format. This is behavior that would not be tolerated in most parts of Asia these days, but obviously it is **still an acceptable practice in Victoria for the mines consultants to choose the metals that they want to report about not all the metals that are actually in the relevant sample and report.**

I would then have to question why it is that ERR have not raised this issue with KALBAR and forced full disclosure. Is this a failure by ERR due to a lack of skilled staff, or is it due to wilful blindness as an aid to getting more projects approved?

What do we know about the 11 metals in the Groundwater that KALBAR are reporting on in Table 2-3 of the Fingerboards work plan draft;

**All data from ATSDR Minimal Risk Levels and or ATSDR Substance Priority List**

- |            |                   |   |
|------------|-------------------|---|
| <b>1.</b>  | <b>Aluminium</b>  | ATSDR listed Neurological toxicant. USEPA RSL air limit 0.5200 ug/m <sup>3</sup> .<br>Theoretical Dose / Day (TDD) 10.32 mg/kg/day.       |
| <b>2.</b>  | <b>Arsenic</b>    | ATSDR Rank #1 as a Carcinogen. USEPA Resident air limit 0.00065 ug/m <sup>3</sup> .<br>Chronic Oral ingestion 0.0003 mg/kg/day            |
| <b>3.</b>  | <b>Barium</b>     | ATSDR Rank #134 USEPA Resident air limit 0.00108 ug/m <sup>3</sup> .<br>Chronic Oral 0.2 mg/kg /day. End point Renal failure              |
| <b>4.</b>  | <b>Boron</b>      | ATSDR Ranked as HEAST, Residential air limit 2.10 ug/m <sup>3</sup> .<br>Acute Inhalation risk 2.1 ug/m <sup>3</sup> , Oral 0.2 mg/kg/day |
| <b>5.</b>  | <b>Copper</b>     | ATSDR Rank #125 Chronic MRL 0.01 mg/kg/day Vic EPA limit is 33 ug/m <sup>3</sup> .  |
| <b>6.</b>  | <b>Iron</b>       | ATSDR Resident Air limit carcinogenic target risk 0.01626 ug/m <sup>3</sup> .   |
| <b>7.</b>  | <b>Manganese</b>  | ATSDR Rank #140 soluble in water ATSDR USEPA Air Limit 0.05 ug/m <sup>3</sup> .   |
| <b>8.</b>  | <b>Molybdenum</b> | ATSDR Rank #326 ATSDR MRL Air 0.00004 mg/m <sup>3</sup> tapwater 10 mg/L.   |
| <b>9.</b>  | <b>Nickel</b>     | ATSDR Rank #57 ATSDR MRL 0.00009 mg/m <sup>3</sup> tap water 20 ug/L.   |
| <b>10.</b> | <b>Strontium</b>  | ATSDR Rank #123 Same toxicity as Arsenic.   |
| <b>11.</b> | <b>Zinc</b>       | ATSDR Rank #75 ATSDR MRL 0.00260 mg/m <sup>3</sup> TDD 2.00056 mg/day.  |

So, quite conveniently, 23 metals have been omitted from this table despite the fact that the KALBAR consultants would be in possession of this data.

Why would 23 metals be deliberately omitted from this table. This is clearly a question that would be appropriately asked by the Panel Chairperson.

However to help the Panel Chairperson in this task here is the list of omitted metals:

1. **Beryllium** USEPA Regional Screening Level (CAS # 7440-41-7) Carcinogenic SL 0.00120 ug/m<sup>3</sup> Oral Chronic 0.002mg/kg/day.
2. **Bismuth** No ATSDR listed data.
3. **Cadmium** USEPA Regional Screening Level (CAS # 7440-43-97) present in the ore body but below reporting level for the ICP MS. Carcinogenic SL 0.00160 ug/m<sup>3</sup>.
4. **Cerium** USEPA Regional Screening Level (CAS # 1306-38-3) present in the water flowing from the ore body at 14 to 66 ug/L.
4. **Gallium** USEPA Regional Screening Level (CAS # 7440-55-3) present in the water in the ore body at 3 to 15 ug/L. Carcinogenic SL 0.00001 mg/m<sup>3</sup>, TDD 0.00011 mg/day. Present in the water flowing from the ore body at 3-15 ug/L.
5. **Lanthanum** USEPA Regional Screening Level (CAS # 7439-91-0) present in the water in the ore body at between 9 and 43 ug/L. Air limit is 0.00018 mg/m<sup>3</sup>. TDD is 0.00268 mg/day.
6. **Lithium** USEPA Regional Screening Level (CAS # 7439-93-2) present in the water in the ore body at 3 to 15 ug/L. Water limit is 0.3852 mg/L, TDD is 0.40442 mg/day.
7. **Manganese** USEPA Regional Screening Level (CAS # 7439-96-5) present in the water at between 93 and 120 ug/L. Water limit is 1.36531 mg/L. Air limit is 0.00102 mg/m<sup>3</sup>, TDD is 1.62443 mg/day
8. **Molybdenum** USEPA Regional Screening Level (CAS # 7439-98-7) present in the water at less than 1 ug/L. A significant risk in air, limit is 0.00005 mg/m<sup>3</sup>.
9. **Niobium** Apparently particles attached to microscopic clay particles, a very rare element and requires further investigation. No toxicology data available but full PPE recommended when handling this product even at PPB levels.
10. **Nickel** USEPA Regional Screening Level (CAS # 7439-98-7) Present in the sample at 4-12 ug/L. Air limit is 0.00462 mg/m<sup>3</sup>, TDD is 0.39114 mg/day.
11. **Lead** USEPA Regional Screening Level (CAS # 7439-92-1) Present in the sample at 6-30 ug/L. Water limit is 0.11830 mg/L, Air limit is 0.00243, TDD is 0.33094 mg/day.
12. **Strontium** The stable form of Strontium (CAS #7440-24-6) is present in the ore body and thus in the local groundwater. Our testing found it at between 28 and 69 ug/L in the groundwater and at 2-31 mg/kg in the stream sand and sludge. **There is no safe lower limit for Strontium.**
13. **Sulphur** Our testing shows Sulphur at a range of levels, 31 mg/kg out to 5,700 mg/kg in sand samples and Sulfur at between 2.0 mg/L and 3.mg/L water samples. The non-cancer hazard index for Sulfur Trioxide is 0.1000 ug/m<sup>3</sup>.
14. **Titanium** Our testing shows Titanium (CAS # 7440-32-6) in the range of 6mg/kg to 61 mg/kg. The non-cancer hazard index for Titanium is 0.00008 mg/m<sup>3</sup>. The TDD 2.27169 mg/day.
15. **Thorium** Our testing shows Thorium (CAS # 7440-29-1) in the range between 3 and 6 mg/kg. Thorium has the same rated toxicity as Arsenic.
16. **Uranium** Our testing shows Uranium (CAS# E715565) in one sample at 2 mg/kg. The non-cancer hazard index for Uranium is 0.0042 ug/m<sup>3</sup>.
17. **Vanadium** Our testing shows the toxic metal Vanadium, (CAS# 7440-62-2) is at

between 28 and 62 mg/kg in the sample.

The non Cancer hazard index for Vanadium is 0.0100 ug/m<sup>3</sup>.

**18. Yttrium** Our testing shows Yttrium (CAS# 7440-65-5) at levels between 4.8 mg/kg and 15 mg/kg with an average of 8.8 mg/kg.

Yttrium is a suspected Carcinogen with an air limit of 0.00002 mg/m<sup>3</sup> and a TDD of 0.00012 mg/day.

**19. Zinc** Our testing shows Zinc (CAS# 7440-66-6) at between 1 and 280 mg/kg. Zinc has an air limit of 0.00260 mg/m<sup>3</sup> and a TDD of 2.00056 mg/day

The relevance of all this data to the KALBAR Work Plan is obvious even to an outside observer like myself. KALBAR, like all mining and quarrying companies, have an overriding common law duty to the health and safety of their workers, the community and the environment in which KALBAR are proposing to operate this mine if it is approved.

It is difficult to see how KALBAR will be able to comply with this requirement in any form at all.

In addition, the proposed KALBAR mine is situated in the catchment of the Gippsland Lakes Internationally listed RAMSAR Wetland, Australian RAMSAR RS269.

Over the last 40 years I have assisted a number of Asian countries to obtain RAMSAR listing for various wetland sites and thus protection of these wetlands.

It is of grave concern to me that the Victorian Government is seriously entertaining a proposal to develop a toxic radioactive REE (Rare Earth Element) mine within the Gippsland Lakes Ramsar.

The fact that the table in question (Table 2-3) only outlines the presence of 11 metals indicates that the consultant that briefed the testing laboratory was either not in possession of the standard lab routine analysis sheet which would have tested for 34 metals and Sulfur or has chosen to remove a number of toxic elements from the work plan table (Table 2-3) for commercial reasons.

This action to remove 24 metals from the table is an action that destroys the consultants credibility and the credibility of the whole Draft Work Plan.

I would respectfully suggest that the Fingerboards Inquiry and Advisory Committee remove this deeply flawed so called draft work plan from the enquiry record.

Further I request that IAC write a formal letter to KALBAR rejecting this flawed document (the Draft Fingerboards Work plan) and ask that as a priority KALBAR lodge a revised version of the Draft Work Plan that includes data on the full spectrum of metals in the KALBAR ore body.

This spectrum should also include the toxicology data on the 17 magnetic and non-magnetic REO's that are known to be in the KALBAR ore body.

Again I respectfully suggest that a failure to promptly lodge this supplementary data in the correct format within 7 days of request should be regarded as a project terminating act.

I look forward to your prompt response.

Kindest Regards

Andrew Helps

[REDACTED]

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**From:** Andrew Helps [REDACTED]  
**Sent:** Monday, 12 April 2021 8:33 AM  
**To:** Amy Selvaraj (DELWP)  
**Subject:** Toxicological Profile for Silica  
**Attachments:** Toxicological profile for Silica.pdf

[REDACTED] [REDACTED]  
[REDACTED] [REDACTED]

**EXTERNAL SENDER: Links and attachments may be unsafe.**

Amy,  
I had a zoom discussion with some of my UNEP colleagues on Friday night. We were discussing airborne toxic metals in general and the development of protocols additional to the UNEP mercury partnership to cover these other metals.

My Colleague in China gave me an update with the controls and protocols additional that are being applied to the few remaining REE mines in China. China is moving to a full offshore sourcing programme for Rare Earth Elements due to the extensive pollution issue with their few remaining mines.

The key human exposure with the mines in China has actually been Silica. The main problem is the use in the mines of tracked earth moving equipment which is very good at breaking small rocks into dust.

I notice that KALBAR are proposing to use 2 Cat D10 bulldozers. These machines weigh about 78 metric tons. They have a 24" wide track shoe with a 10.3 inch pitch.

Having operated large tracked Bulldozers both in the forestry industry and later in landfills I understand the impact of the tracks on dirt roads

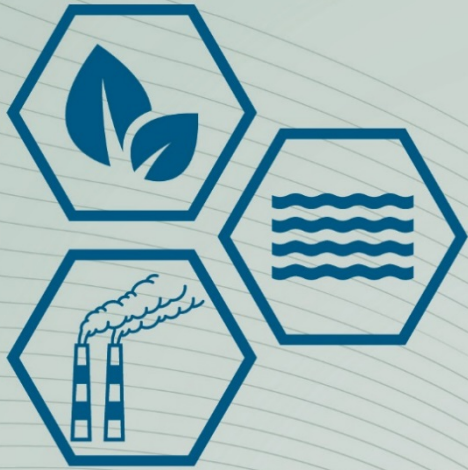
Could you please lodge the attached ATSDR Silica Toxicological profile in the KALBAR document register so that it is in the public domain.

I have already put it into my KALBAR document register and the Coronial file that I am building.

Kindest Regards

**Andrew Helps**  
安德鲁 郝普斯  
常务董事  
Mobile [REDACTED]  
**UNEP Global Mercury Partnership**  
**Waste Management Partnership - designated expert**  
**Mercury added products and alternatives – designated expert**  
**Mercury Fate and Transport Group**

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# Toxicological Profile for Silica

Draft for Public Comment

April 2017



U.S. Department of Health and Human Services  
Agency for Toxic Substances and Disease Registry

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## UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences  
Environmental Toxicology Branch  
1600 Clifton Road NE  
Mailstop F-57  
Atlanta, Georgia 30329-4027

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## FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: [www.regulations.gov](http://www.regulations.gov).  
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:  
Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences  
Environmental Toxicology Branch

Regular Mailing Address:  
1600 Clifton Road, N.E.  
Mail Stop F-57  
Atlanta, Georgia 30329-4027

Physical Mailing Address:  
4770 Buford Highway  
Building 102, 1<sup>st</sup> floor, MS F-57  
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Patrick N. Breyse, Ph.D., CIH  
Director, National Center for Environmental Health and  
Agency for Toxic Substances and Disease Registry  
Centers for Disease Control and Prevention

## QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

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### *Primary Chapters/Sections of Interest*

**Chapter 1: Public Health Statement:** The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

**Chapter 2: Relevance to Public Health:** The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

**Chapter 3: Health Effects:** Specific health effects of a given hazardous compound are reported by type of health effect (e.g., death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

**NOTE:** Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

**Pediatrics:** Four new sections have been added to each Toxicological Profile to address child health issues:

<b>Chapter 1</b>	<b>How Can (Chemical X) Affect Children?</b>
<b>Chapter 1</b>	<b>How Can Families Reduce the Risk of Exposure to (Chemical X)?</b>
<b>Section 3.7</b>	<b>Children's Susceptibility</b>
<b>Section 6.6</b>	<b>Exposures of Children</b>

### **Other Sections of Interest:**

<b>Section 3.8</b>	<b>Biomarkers of Exposure and Effect</b>
<b>Section 3.11</b>	<b>Methods for Reducing Toxic Effects</b>

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### *ATSDR Information Center*

**Phone:** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

**Internet:** <http://www.atsdr.cdc.gov>

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

*Managing Hazardous Materials Incidents* is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see <https://www.atsdr.cdc.gov/MHMI/index.asp>). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

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### ***Other Agencies and Organizations***

*The National Center for Environmental Health (NCEH)* focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: <https://www.cdc.gov/nceh/>.

*The National Institute for Occupational Safety and Health (NIOSH)* conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

*The National Institute of Environmental Health Sciences (NIEHS)* is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: <https://www.niehs.nih.gov/>.

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### ***Clinical Resources (Publicly Available Information)***

*The Association of Occupational and Environmental Clinics (AOEC)* has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: [AOEC@AOEC.ORG](mailto:AOEC@AOEC.ORG) • Web Page: <http://www.aoec.org/>.

*The American College of Occupational and Environmental Medicine (ACOEM)* is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

*The American College of Medical Toxicology (ACMT)* is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page:  
<http://www.acmt.net>.

*The Pediatric Environmental Health Specialty Units (PEHSUs)* is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

*The American Association of Poison Control Centers (AAPCC)* provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page:  
<http://www.aapcc.org/>.

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## CONTRIBUTORS

### CHEMICAL MANAGER(S)/AUTHOR(S):

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ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

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Mary Kawa, M.A.  
SRC, Inc., North Syracuse, NY

### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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## PEER REVIEW

A peer review panel was assembled for silica. The panel consisted of the following members:

1. Dr. Michael Greenberg, Emergency Medicine, Drexel University, Philadelphia, Pennsylvania;
2. Dr. Kyle Steenland, Department of Environmental and Occupational Health, Emory University, Atlanta, Georgia; and
3. Dr. Kenneth D. Rosenman, Department of Medicine, Michigan State University, East Lansing, Michigan.

These experts collectively have knowledge of silica's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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# 1. PUBLIC HEALTH STATEMENT FOR SILICA

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on silica, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

Silica is a naturally occurring compound and is widespread in the environment. It is of particular concern in areas adjacent to crystalline silica mining, processing, and transporting facilities.

If you are exposed to silica, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

## WHAT IS SILICA?

Silica is another name for the chemical compound composed of silicon and oxygen with the chemical formula  $\text{SiO}_2$ , or silicon dioxide. There are many forms of silica. All silica forms are identical in chemical composition, but have different atom arrangements. Silica compounds can be divided into two groups, crystalline (or c-silica) and amorphous silica (a-silica or non-crystalline silica). c-Silica compounds have structures with repeating patterns of silicon and oxygen. a-Silica chemical structures are more randomly linked when compared to c-silica. All forms of silica are odorless solids composed of silicon and oxygen atoms. Silica particles become suspended in air and form non-explosive dusts. Silica may combine with other metallic elements and oxides to form silicates.

Silica is abundant in the environment and has many uses. Over 95% of the earth's crust is made of silica-containing minerals and c-silica. Quartz is one form of c-silica commonly found in the environment. Approximately 12% of the earth's crust by volume is quartz. Other less common forms of c-silica, including tridymite and cristobalite, are found in rocks and soils. Silica sand and gravel are used for building and construction, hydraulic fracturing, ceramics, and abrasives. Silica sand melts to glass and has been used throughout history to make glass. Crystal quartz forms of silica are used in jewelry, electronics, and the optical component industry. Some gemstones, such as amethyst, tiger's eye, agate, carnelian, chalcedony, and onyx are forms of silica.

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Kieselguhr or diatomaceous earth, silica gel, and precipitated silica are forms of a-silica. a-Silica compounds have uses as fillers, insulators, absorption agents, scourers, catalyst supports, packing material, and filtration. Diatomaceous earth and silica gel are also used as carriers for pesticides to control insects, mites, and ticks.

### **WHAT HAPPENS TO SILICA WHEN IT ENTERS THE ENVIRONMENT?**

Silica is a naturally occurring compound that is abundant in the environment. Quartz is an important component of soils and rocks and may be found on every part of every continent. It is the major component (90–95%) of all sand and silt fractions in soil. Silica is also naturally occurring in other less common forms, including cristobalite, tridymite, diatomite, agate, amethyst, chalcedony, and flint. Silica does not break down in the environment, although it may change forms (e.g., lightning strikes or burning of agricultural wastes containing silica) or undergo transport by natural processes (e.g., weathering) and human activities (e.g., brick and ceramics manufacturing). As part of the natural movement of silica between earth and organisms, silica particles are carried by wind and water currents, and settle out of water into sediment. Dissolved silica is extracted by certain species of microscopic marine organisms, such as diatoms and radiolarians, to form their structures and shells, and some forms of silica accumulate in plants or crops (e.g., rice and wheat).

### **HOW MIGHT I BE EXPOSED TO SILICA?**

You may be exposed to silica compounds from the air, indoor dust, food, water, soil, and various consumer products. Silica compounds can be released into the environment by natural, industrial, and farming activities.

Silica is a common air contaminant. The primary nonwork-related silica exposure route is thought to be inhalation of c-silica during the use of commercial products containing quartz. Silica is found in many commercial products.

c-Silica is emitted as a component of particulate emissions into the environment. Residents near quarries or sand and gravel operations or drilling involving fracking may be exposed to elevated levels of respirable c-silica. Local meteorological conditions, such as wind and rain, especially in deserts and areas near recent volcanic eruptions and mine dumps, are expected to influence the location and spread of silica-containing dust.

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People may be exposed to silica through their diet. a-Silica compounds are used as pesticides that are applied to crops and are used near food handling and preparation areas. Silica is used in food packaging; therefore, food is expected to be an important source of exposure to silica for most people.

Human exposure to c-silica that have the potential to impact human health occurs mainly in industrial and occupational settings. c-Silica is used throughout industry and is recognized as an important occupational hazard. People who work where silica is mined or used are exposed to higher levels of these substances than the general population. Workplace exposure also occurs for people with jobs that require frequent handling or use of silica substances, such as ceramic manufacturing, construction, and foundries. Industrial hygiene practices, such as engineering controls, tailored work practices, respirators, and worker training, are used to minimize potential silica health hazards.

### **HOW CAN SILICA ENTER AND LEAVE MY BODY?**

The most important route of exposure to c-silica and a-silica is through air containing these compounds. Only very small particles of silica, less than 5 microns, are more likely to be deposited in the lungs. Small amounts of silica compounds deposited in the lungs may be coughed up and swallowed. Once in your body, silica compounds remain for long periods of time in the lungs and tissues surrounding the lungs. Some silica is distributed to the kidneys and the lymphatic system, an important part of the immune system. Silica compounds are not broken down by the body. Small amounts of silica compounds leave the body in the urine.

### **HOW CAN SILICA AFFECT MY HEALTH?**

Health effects of c-silica and a-silica in people are found in workers exposed for long periods of time (typically  $\geq 10$  years) or with extremely heavy exposure over a short period of time (acute silicosis). There is no evidence that breathing small amounts of silica compounds found in the environment causes any health effects in humans. No health effects are shown to occur in humans from eating food or drinking water contaminated with c-silica or a-silica or from exposure of the skin to these compounds.

***Crystalline Silica.*** Many studies have examined the health effects of c-silica in workers. Results of these studies show that potential effects of long-term occupational exposure to c-silica might include silicosis (a lung disease), chronic obstructive pulmonary disease (COPD), lung cancer, increased risk of tuberculosis, effects on the kidney, and autoimmune diseases. Of these, silicosis and lung cancer pose the greatest risks to human health.

## 1. PUBLIC HEALTH STATEMENT

Silicosis is a progressive, irreversible lung disease. No other chemical, including a-silica, can cause silicosis. Silicosis is classified as several different types (simple silicosis, progressive massive fibrosis [PMF], acute silicosis, and accelerated silicosis). All types of silicosis can cause death due to failure of the respiratory system. The time from first exposure to c-silica to the development of silicosis may be as short as a few weeks for acute silicosis or as long as 20 or more years for simple silicosis and PMF. The severity of silicosis may continue to slowly increase over decades even after exposure has been stopped. The current number of silicosis cases in the United States is not known; however, it has been estimated that during the period of 1987–1997, approximately 3,600–7,300 new silicosis cases were diagnosed yearly in workers in the United States.

Several government agencies have classified c-silica as a lung carcinogen in humans. Results of studies indicate that c-silica can cause lung cancer in workers, with increased risks in smokers. However, conflicting results regarding the association between inhalation of respirable c-silica and lung cancer, as well as adverse effects to the kidney and autoimmune diseases, have been reported. Despite inconsistent results, available evidence supports an association between occupational exposure to c-silica and increased risks for these effects. Available data in humans and laboratory animals are not sufficient to demonstrate a causal relationship between oral exposure to c-silica and any adverse effect outcome. Adverse effects of dermal exposure to c-silica have not been reported.

Some studies have shown harmful effects to the kidneys and associations with autoimmune diseases. These could have been caused by exposure to c-silica or could occur spontaneously or could have developed from exposure to other chemicals or mixtures of chemicals. Some studies examining the relationship between c-silica exposure and kidney effects and autoimmune diseases show an association between c-silica exposure and kidney and autoimmune diseases, while others do not show an association. Therefore, it is difficult to interpret the results of these studies. Compared to silicosis, kidney and autoimmune diseases are observed in a small number of workers.

***Amorphous Silica.*** Compared to the large number of studies on c-silica, few studies have studied the effects of breathing a-silica, with most data obtained from animal studies. In workers, lung fibrosis (thickened, stiffened tissue of the lungs due to damage and scarring) has been reported in a-silica workers, although it is possible that these workers were also exposed to c-silica at the same time. Animal studies show reversible damage to the lung. Other than lung effects, no other effects associated with inhaled a-silica have been established.



## 1. PUBLIC HEALTH STATEMENT

For more information on health effects of c-silica and a-silica, see Chapters 2 and 3.

**HOW CAN SILICA AFFECT CHILDREN?**

This section discusses potential health effects of c-silica and a-silica exposure in humans from when they're first conceived to 18 years of age.

Health effects of c-silica and a-silica have been shown only to occur in people working in silica industries, most typically following prolonged exposure. Exposures to children during sensitive developmental windows of time/time periods may put them at increased or decreased risk of health effects from exposure to hazardous substances. Based on available scientific evidence, it is not known with certainty, if children, when similarly exposed to silica, will have the same health effects as adults.

**HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO SILICA?**

If your doctor finds that you have been exposed to significant amounts of c-silica or a-silica, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

To date, exposure to c-silica and a-silica at levels that produce health effects has on been reported in workers who have been exposed for a prolonged period of time in silica industries. There are no known human health effects that occur from exposure to any silica compound at levels typically found in general non-workplace environments. Several regulations and recommendations are in place to protect workers from adverse effects from exposure to silica.

**ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SILICA?**

There are no known medical tests to determine if you have been exposed to c-silica or a-silica. For workers exposed to silica compounds, periodic x-rays and tests for lung function are recommended to look for abnormalities. Workers should also be evaluated for tuberculosis, kidney function, and autoimmune diseases.

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**WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?**

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The Department of Energy (DOE), NIOSH, and OSHA have set limits for exposure to c-silica levels air in occupational settings. For a-silica, DOE, NIOSH, and OSHA have set limits of levels in air in occupational settings. EPA has not recommended guidelines for c-silica or a-silica in water.

**WHERE CAN I GET MORE INFORMATION?**

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

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- Write to:  
Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences  
1600 Clifton Road NE  
Mailstop F-57  
Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site:

<http://www.atsdr.cdc.gov>.

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## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SILICA IN THE UNITED STATES

Silica occurs naturally in crystalline and amorphous (or non-crystalline) forms, referred to as c-silica and a-silica, respectively. In general, silica is considered poorly water soluble and chemically unreactive in the environment. Both c- and a- forms of silica have surfaces composed of siloxane (covalently bonded silicon and oxygen; Si-O-Si) and silanol groups (Si-OH). Exposure to water will break silicon-oxygen bonds on the surface of silica to form silanols. In general, c-silica surfaces tend to have more order, although some c-silica is found with an outer layer of a-silica. a-Silica may contain a c-silica component from exposure to high temperatures and pressures (e.g., flux calcination). Thus, for a single polymorph of c- or a-silica, surface chemistry of the compound may vary, depending upon production method and degree of hydration. The water solubility of silica has some variability due to differences in trace metal impurities, hydration, temperature, and particle size. Solubility is lower for c-silica polymorphs than for a-silica, and anhydrous a-silica dissolves less rapidly than hydrated a-silica. Silica particles may be transported by wind or water currents as part of the biogeochemical silica cycle. As part of the biogeochemical silica cycle, silica deposits settle out of water into sediment.

Silica is ubiquitous; over 95% of the earth's crust is made of minerals containing silica and c-silica. At least a trace amount of c-silica, in the form of quartz, is present in all soils. Silica is naturally released into the environment through the weathering of rocks, volcanic activity, and biogenic sources (e.g., diatoms). Human activities such as mining and farming also result in the release of silica into the environment. Silica levels in environmental media vary depending upon the location and sampling site. Local meteorological conditions, such as wind and rain, especially in deserts and areas near recent volcanic eruptions and mine dumps, are expected to influence the location and spread of silica-containing dust. Remote continental air has a background gravimetric airborne dust concentration of 0.04 mg/m<sup>3</sup> with ≥10% c-silica content. In urban areas across the United States, the measured mean 24-hour average ambient c-silica concentration ranged from 0.0009 to 0.008 mg/m<sup>3</sup> for particles in the size range of 2.5–15 μm (aerodynamic diameter). Dissolved silica concentrations of natural waters are 13 ppm for lakes, 3–15 ppm for major rivers, 1–10 ppm for sea water, 2–60 ppm for wells, and 50–300 ppm for wells in volcanic fields or oil fields.

Human exposure to c-silica is known to occur in industrial and occupational settings. c-Silica is recognized as an important occupational inhalation hazard. The general population is exposed to silica

## 2. RELEVANCE TO PUBLIC HEALTH

through air, indoor dust, food, water, soil, and various consumer products. Both *c*-silica and *a*-silica are found in many commercial products (e.g., bricks, mortar, plaster, caulk, granite and engineered stone kitchen counter tops, roofing granules, wallboard, concrete cleansers, skin care products and soaps, art clays and glazes, talcum powder). Inhalation of *c*-silica during the use of commercial products containing quartz is expected to be the predominant, non-occupational silica exposure route. Silica is also a common air contaminant. Industrial emissions, forest fires, crop burning, and wind erosion of soil may spread both *a*-silica and *c*-silica particles. Exposure to silica is also expected to occur for the general public through the diet. *a*-Silica compounds are used as pesticides for crops and are used near food handling and preparation areas. *a*-Silica is used in food packaging, and in food, cosmetics, and pharmaceuticals as anticaking agents or carriers. *a*-Silica accumulates in some plants and crops including rice, millet, sugarcane, and wheat. Although quantitative data are not available, water containing diatomite fragments and quartz particles is a potential source of exposure for the general population.

All forms of silica are considered to be poorly soluble particles. There are limited analytical methods reported for the analysis of silica in biological materials. Very limited information is available regarding absorption of silica following dermal or oral contact; however, these pathways of exposure are not expected to be significant. Inhaled silica particles, not cleared by mucociliary escalators or coughing, are embedded and remain in the lung.

### 2.2 SUMMARY OF HEALTH EFFECTS

Throughout this toxicological profile, the term *c-silica* refers to crystalline silica; non-crystalline amorphous silica is referred to as *a-silica*. Note that due to significant differences in toxicokinetics of ultrafine and nanoparticles compared to larger respirable particles, silica nanoparticles are not considered in this profile.

*c*-Silica and *a*-silica are not single entities. Each exists in several forms (polymorphs) with different surface chemistry characteristics. For a single polymorph (e.g., quartz, cristobalite), surface characteristics may vary due to processing and particle aging, even for polymorphs within the same silica industry. Biological activity (potency) of both *c*-silica and *a*-silica is affected by particle surface chemistry. These differences in surface chemistry may, in part, play a role in differences observed for exposure-response relationships and inconsistent results for some health effects.

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The exposure route of concern for c-silica and a-silica compounds is inhalation. Adverse health effects of inhalation exposure to c-silica and a-silica have been observed in studies of occupational exposure to particles that are of respirable size (<10 µm). Respirable particles of c-silica, which are deposited throughout the alveolar region of the lung and distributed to associated lymph tissue, produce a cascade of effects that result in the development of silicosis, a progressive, irreversible, fibrotic lung disease. It has been hypothesized that the severity of silicosis is related to the c-silica particle burden in the lung. No known adverse effects occur from exposure to particles that exceed the respirable size range or from incidental exposure to low levels of c-silica in the environment (e.g., at beaches). Regarding oral exposure to c-silica, available data in humans and laboratory animals are not sufficient to demonstrate an association for any adverse effect outcome. No information on the effects of oral a-silica in humans was identified, and very few studies evaluating adverse effects of oral a-silica in animals have been conducted. Available animal studies either do not identify adverse effects at the doses tested or do not provide sufficient data to determine the toxicological significance of observed effects (e.g., changes in organ weights in the absence of histopathological changes). No association between dermal exposure and adverse effects has been reported.

***Health Effects of Crystalline Silica***

*Silicosis Morbidity and Mortality:* Health effects associated with occupational exposure to c-silica are silicosis (a progressive, fibrotic lung disease), COPD, lung cancer, renal toxicity, increased risk of tuberculosis, and autoimmune diseases. Of these, silicosis and lung cancer pose the greatest concern to human health.

Silicosis is a progressive, irreversible, fibrotic lung disease resulting from inhalation and pulmonary deposition of respirable dust containing c-silica. The causal relationship between inhalation of c-silica and development of this severe, debilitating lung disease is well-established and has been recognized since ancient times. Silicosis does not result from inhalation of any other substance, including a-silica. Silicosis is not a single disease entity, but is classified as different types (simple silicosis, progressive massive fibrosis [PMF], acute silicosis, and accelerated silicosis). All types of silicosis can result in death due to respiratory failure. Cumulative c-silica exposure, expressed as mg/m<sup>3</sup>-year, is the most important factor in the development of silicosis. Cumulative exposures typically are reported as stratified ranges or as the median of stratified ranges. Time from first exposure to onset of disease varies inversely with cumulative exposure and may be as short as a few weeks for acute silicosis or as long as 20 or more years for simple silicosis and PMF. Due to the long latency period, silicosis may not be diagnosed until after

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exposure has ended. Disease severity continues to slowly increase over decades even after exposure has been discontinued, possibly due to c-silica dust that is retained in the lungs.

The current number of silicosis cases in the United States is not known; however, it has been estimated that during the period of 1987–1997, approximately 3,600–7,300 new silicosis cases were diagnosed yearly in the United States. Reported risk estimates for silicosis in occupational exposure studies vary, with many factors potentially influencing study outcome, including study design (inclusion of decedents, length of follow-up period, frequency of health assessments, adjustment for smoking), and c-silica surface characteristics. These likely factors contribute to the wide range of reported incidences of silicosis (<10% to as high as approximately 80%). In the United States, 13,744 deaths were attributed to silicosis from 1968 to 1990 and 4,313 deaths were attributed to silicosis from 1979 to 1990. Silicosis mortality trends have shown a marked decline over the past 50 years due to improved industrial hygiene standards and more stringent regulatory standards and guidelines. However, silicosis deaths in younger adults (ages 15–44 years) have not declined since 1995, which may reflect more recent, intense exposures, such as those associated with construction and abrasive blasting industries.

Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis. However, a no-observed-adverse-effect level (NOAEL) for silicosis has not been defined, with silicosis and death due to silicosis observed for the lowest cumulative exposure ranges reported. For the lowest cumulative exposure range reported in the available literature (0–0.2 mg/m<sup>3</sup>-year), silicosis was observed in 5 of 3,330 gold miners. At the cumulative exposure range of 0.1–1.23 mg/m<sup>3</sup>-year, death due to silicosis was observed in 2,857 of 74,040 mining and pottery workers in China. Cumulative exposure levels reported in other occupational studies have been higher.

*Lung Cancer:* The International Agency for Research on Cancer, the National Institute of Occupational Safety and Health, and the National Toxicology Program 13<sup>th</sup> Report on Carcinogens have classified c-silica (respirable size) as a Group 1 (definite) human lung carcinogen. IARC acknowledged that some occupational exposure studies did not show an association between c-silica exposure and lung cancer, possibly due to the characteristics of c-silica in different occupational settings or other factors affecting its biological activity; in addition, other confounding factors and biases may have influenced study results (e.g., errors in estimating c-silica exposure levels, absence [or presence and severity] of silicosis, adequate control of confounding from smoking, and unaccounted occupational co-exposures that may have contributed to lung cancer risk).



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Compared to other occupational lung carcinogens, such as asbestos, the occupational risk of c-silica-induced lung cancer is low, requiring large study populations to achieve adequate power to detect and quantify c-silica-related cancer risk. Results of pooled and meta-analyses, which provide the strongest support for the carcinogenicity of c-silica in the lung, show increased risks of lung cancer in c-silica workers, with risks exhibiting dependence upon cumulative exposure. Results of a cohort study of over 30,000 workers in China indicate that c-silica can induce lung cancer in the absence of silicosis. Smoking, as in all studies of potential lung carcinogens, could be a confounding factor in studies examining the relationship between c-silica exposure and lung cancer. However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking.

*Other Adverse Health Effects of Inhaled Crystalline Silica:* Occupational exposure to respirable c-silica is also associated with adverse effects to the kidney and autoimmune diseases. However, these effects have been studied much less than silicosis, and study results have not been consistent regarding associations between c-silica exposure and increased risks. Unlike silicosis, no renal or autoimmune diseases are uniquely associated with exposure to c-silica.

A wide-spectrum of renal pathologies (called silicon nephropathy) have been associated with occupational exposure to c-silica, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, glomerulonephritis, and renal damage associated with autoimmune disorders (e.g., anti-neutrophil cytoplasm antibody [ANCA]-associated vasculitis). Relative to silicosis, the incidence of renal disease is very low in silica-exposed cohorts (<1 versus <10–80%). Results of a pooled analysis show that the risk of renal disease and mortality due to renal disease increased with cumulative exposure. Comparison of exposure-response data for renal effects and silicosis shows that renal toxicity typically occurs at higher cumulative exposure levels than silicosis.

Exposure to respirable c-silica has been associated with increased risks of a wide spectrum of autoimmune disorders, including systemic sclerosis (scleroderma), rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis. Similar to renal effects, the incidence of autoimmune disorders is low compared to silicosis. Data for each specific disease are inadequate to determine exposure-response relationships.

***Health Effects of Amorphous Silica.*** Relative to the abundance of data on c-silica, few studies have evaluated the effects of inhaled a-silica. Data are insufficient to determine whether or not a-silica causes

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lung disease in humans; however, silicosis has not been observed in epidemiological studies in workers with long-term exposure to a-silica with no known exposure to c-silica. Numerous occupational studies in the 1930s–1980s report an increased incidence of pneumoconiosis in diatomaceous earth workers exposed to a-silica; however, interpretation of results is complicated due to co-exposures to c-silica.

Results of animal studies indicate that inhalation exposure to a-silica causes pulmonary toxicity, including inflammation, cellular infiltrates, reversible fibrosis, and reduced lung function, following acute-, intermediate-, and chronic-duration exposure. However, in contrast to c-silica, progressive fibrosis was not observed and most effects were reversible. Results of a study examining the effects of a 5-day inhalation exposure of rats to a-silica polymorphs yield NOAEL and lowest-observed-adverse-effect level (LOAEL) values for bronchial hypertrophy and cellular infiltrates of 1 and 5 mg/m<sup>3</sup>, respectively. Similar pulmonary effects have been reported in animals following intermediate- and chronic-duration inhalation exposure; however, NOAEL values were not identified.

Other than pulmonary effects, no other effects associated with inhaled a-silica have been established.

### 2.3 MINIMAL RISK LEVELS (MRLs)

**Crystalline Silica.** Effects on the respiratory system are the most sensitive effects of inhaled c-silica. However, identification of a no-effect or threshold level for silicosis is highly uncertain due to several factors. For example, in one study for the lowest reported cumulative exposure range of 0–0.2 mg/m<sup>3</sup>-year, silicosis was observed (Steenland and Brown 1995a). Cumulative exposure ranges identifying a no-effect level for silicosis have not been identified. In addition, the long latency period between exposure and time to onset of symptoms or diagnosis of silicosis could affect identification of a no-effect level for silicosis if follow-up periods are not sufficiently long. Exclusion of decedents and poor or inadequate health records also contribute uncertainty of risks for silicosis. Furthermore, due to the variable surface chemistry characteristics, the biological potency of c-silica can vary between and among c-silica polymorphs. Therefore, even if a no-effect level could be identified for a particular occupational cohort, that level may cause silicosis in a different occupational cohort due to differences in surface chemistry of c-silica.

LOAEL values for silicosis have been identified in several studies; however, silicosis is a serious adverse effect that has the potential to cause death due to respiratory failure or lung cancer. Given the serious

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nature of silicosis and the uncertainties associated with identification of a no-effect level, no MRLs were derived for inhaled c-silica for any exposure duration.

Available data for oral exposure to c-silica are insufficient to derive oral MRLs for any exposure duration.

***Amorphous Silica.*** Relative to the abundance of data on c-silica, few studies have evaluated the effects of inhaled a-silica. Data are insufficient to determine whether or not a-silica causes lung disease in humans; however, silicosis has not been observed in epidemiological studies in workers with long-term exposure to a-silica with no known exposure to c-silica (Choudat et al. 1990; Plunkett and Dewitt 1962; Volk 1960; Wilson et al. 1979). Numerous occupational studies in the 1930s–1980s report an increased incidence of pneumoconiosis in diatomaceous earth workers exposed to a-silica; however, interpretation of results is complicated due to co-exposures to c-silica (Beskow 1978; Caldwell 1958; Cooper and Jacobson 1977; Cooper and Sargent 1984; Dutra 1965; Legge and Rosencrantz 1932; Smart and Anderson 1952; Vigliani and Mottura 1948).

As reviewed below, available data from animal studies indicate that inhalation exposure to a-silica causes pulmonary toxicity, including pulmonary inflammation, increases in cellular infiltrates, reversible fibrosis, reduced lung function, and respiratory distress (Arts et al. 2007; Groth et al. 1981; Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Warheit et al. 1991, 1995). Pulmonary effects observed following exposure to a-silica are reversible and progressive fibrosis is not observed, in contrast to the pulmonary effects of c-silica. Results of animal studies also indicate that different polymorphs of a-silica have different toxicological potencies (Arts et al. 2007; Warheit et al. 1991, 1995). Other than pulmonary effects, no other effects associated with inhaled a-silica have been established.

*Acute-Duration Exposure:* Arts et al. (2007) examined the effects of a 5-day inhalation exposure of rats to three types of a-silica polymorphs: silica gel (Syloid 74), precipitated silica (Zeosil 45), and pyrogenic silica (Cab-O-Sil M5). After the final day of exposure, microscopic examination of lung tissue showed differences between the three polymorphs. For silica gel, NOAEL and LOAEL values of 5 and 25 mg/m<sup>3</sup>, respectively, were identified for accumulation of alveolar macrophages in male rats (females not examined). For precipitated silica, NOAEL and LOAEL values for alveolar granulocyte infiltrates were 1 and 5 mg/m<sup>3</sup>, respectively, in males and 5 and 25 mg/m<sup>3</sup>, respectively, in females. For pyrogenic silica, NOAEL and LOAEL values for accumulation of alveolar macrophages were 1 and 5 mg/m<sup>3</sup>, respectively, in male rats (females not examined). The incidence of bronchial/bronchiolar hypertrophy was increased in rats exposed to precipitated and pyrogenic silica at 25 mg/m<sup>3</sup>, although the incidence of

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hypertrophy was not increased for silica gel. Warheit et al. (1991, 1995) observed increased neutrophils in bronchoalveolar lavage fluid of rats exposed to colloidal silica (Ludox) and precipitated silica (Zeofree 80) for 2 weeks. The NOAEL and LOAEL values for colloidal silica were 10.1 and 50.5 mg/m<sup>3</sup>, respectively. The LOAEL value for precipitated silica was 10 mg/m<sup>3</sup>; a NOAEL was not identified. However, NOAEL and LOAEL values for the Arts et al. (2007) and Warheit et al. (1991, 1995) studies are not directly comparable, as microscopic examination of lung tissue was not conducted in the Warheit et al. (1991, 1995) studies. Respiratory distress, a serious adverse effect, was observed in rats exposed for 2 weeks to three  $\alpha$ -silica polymorphs: fumed hydrophilic silica (Aerosil 200), fumed hydrophobic silica (Aerosil R 974), and precipitated hydrophobic silica (Sipernat 22S) (Reuzel et al. 1991). For all three polymorphs, respiratory distress was observed at the lowest concentration tested, with LOAEL values of 17, 31, and 46 mg/m<sup>3</sup> for fumed hydrophilic silica, fumed hydrophobic silica, and precipitated hydrophobic silica, respectively. However, relative potency of the different polymorphs cannot be determined from this study, as respiratory effects were observed at the lowest tested concentration for each polymorph. Although all  $\alpha$ -silica polymorphs have not been evaluated for acute respiratory toxicity, results of acute inhalation studies in rats indicate that the biological activity of  $\alpha$ -silica varies between polymorphs.

*Intermediate-Duration Exposure:* Results of intermediate-duration inhalation studies show a wide range of toxicological potencies for  $\alpha$ -silica polymorphs (Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Warheit et al. 1991, 1995). Respiratory effects, including fibrosis, increased cellularity, inflammation, accumulation/aggregation of alveolar macrophages (granulomas), and increased collagen content were observed in rats exposed to  $\geq 1$  mg/m<sup>3</sup> of fumed hydrophilic silica (Aerosil 200) for 13 weeks (Reuzel et al. 1991); a NOAEL was not identified. Similar effects, except fibrosis, were also observed following exposure to fumed hydrophobic silica (Aerosil R974) and precipitated silica (Sipernat 22S) at 30 mg/m<sup>3</sup>; no other exposure levels were tested (Reuzel et al. 1991). In contrast, NOAEL and LOAEL values of 10 and 50 mg/m<sup>3</sup>, respectively, were identified for less serious respiratory effects (inflammation, hyperplasia, increased neutrophils in bronchoalveolar lavage fluid) following a 4-week exposure to colloidal silica (Ludox) (Johnston et al. 2000; Lee and Kelly 1992). Additional information on intermediate-duration inhalation exposure is provided in Section 3.2.1.2.

*Chronic-Duration Exposure:* Studies in monkeys, rats, guinea pigs, and rabbits also show adverse respiratory effects, including fibrosis, reduced lung function, and macrophage accumulation, following chronic-duration inhalation exposure to several  $\alpha$ -silica polymorphs (Groth et al. 1981; Schepers 1981) (see Section 3.2.1.2 for additional information). However, comparison of potency between polymorphs

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cannot be conducted as studies only evaluated single exposure levels. Furthermore, as only single exposure levels were evaluated, data are not suitable to serve as the basis for a chronic-duration inhalation MRL for  $\alpha$ -silica.

*Conclusions:* The biological activity of silica compounds varies based upon surface chemistry of the compound (Donaldson and Borm 1998; Greenberg et al. 2007; Guthrie 1995; Mossman and Churg 1998; Mossman and Glenn 2013). Even for a single polymorph, surface chemistry may vary depending upon production method, degree of hydration, and aging (Fubini et al. 1995; Rimola et al. 2013; Zhuravlev 2000). Numerous polymorphs of  $\alpha$ -silica exist, each with different surface chemistry properties and, therefore, the potential for different biological potencies. Although analytical techniques exist to distinguish between  $\alpha$ -silica polymorphs, most are too sophisticated for routine measurements (IARC 1997). Therefore, exposures typically are reported as  $\alpha$ -silica, rather than as specific  $\alpha$ -silica polymorphs.

As reviewed above, results of the animal studies provide evidence that toxicological potency for respiratory effects can differ between different  $\alpha$ -silica polymorphs. Given the important role of surface chemistry in the toxicological potency of silica compounds, there is considerable uncertainty regarding identification of NOAEL or LOAEL values that could serve as the basis of development of inhalation MRLs, as values based on a single  $\alpha$ -silica polymorph may not apply to all forms of  $\alpha$ -silica. Therefore, inhalation MRLs for  $\alpha$ -silica have not been developed for any exposure duration.

As discussed in Section 2.2, no information on the effects of oral  $\alpha$ -silica in humans was identified, and available animal studies either do not identify adverse effects at the doses tested or do not provide sufficient data to determine the toxicological significance of observed effects. Therefore, available data for  $\alpha$ -silica are insufficient to derive oral MRLs for  $\alpha$ -silica for any exposure duration.

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## 3. HEALTH EFFECTS

### 3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of silica. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

***Selection of Literature.*** Studies in humans identify effects to the respiratory, renal, and immune systems as the targets of inhaled respirable c-silica. These effects are the focus of the health effect sections on inhaled c-silica. The literature on the health effects of occupational exposure of humans to inhaled respirable c-silica is extensive, including numerous recently published reviews. This profile describes results of a subset of these studies that provide information on exposure-response relationships. There is also extensive literature on the effects of inhaled c-silica in laboratory animals; however, due to the abundance of information on the effects of c-silica in humans, animal studies on c-silica are not included in this profile. In contrast to the large amount of information available on the effects of inhaled c-silica, information about the effects of oral exposure to c-silica and inhalation and oral exposure to a-silica is sparse; therefore, studies in laboratory animals are reviewed and included in these sections to supplement human data. Studies on adverse effects of dermal exposure to c-silica and a-silica in humans or laboratory animals were not identified. Studies included in Chapter 3 were identified primarily from recent reviews, literature searches, and tree-searching of important literature. General descriptions of health effects of c-silica and a-silica were taken from numerous, recent reviews, as indicated throughout Chapter 3.

***Surface Structure and Biological Activity.*** As discussed in Section 4.2 (Chemical and Physical Properties), c-silica and a-silica exist in several forms (polymorphs), each with different surface chemistry characteristics, including incorporation of trace metals or other compounds. The biological activity and, thereby, the potency to induce adverse effects is likely related to surface characteristics (see Section 3.5.2, Mechanism of Toxicity). Furthermore, for the same polymorph, biological potency may vary due to modifications of surface characteristics from processing or aging. Due to differences in biological activity, in addition to other factors (e.g., study design, length of follow-up period, inclusion of decedents, adjustments for smoking status, etc.), exposure-response relationships across silica industries and even

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within the same silica industry can differ, making it difficult to define exposure-response relationships that apply to general c-silica or a-silica categories.

Note that due to significant differences in toxicokinetics of ultrafine and nanoparticles compared to larger respirable particles, silica nanoparticles are not considered in this profile.

**Overview: *Health Effects Crystalline Silica.*** Health effects associated with inhalation of respirable c-silica are silicosis, lung cancer, renal toxicity, autoimmune disorders, COPD, and increased risk of tuberculosis. Silicosis, a progressive fibrotic, potentially fatal lung disease caused by occupational exposure to respirable c-silica, is a well-established effect that has been recognized since ancient times. Silicosis does not result from inhalation of any other substance, including a-silica, and is not associated with incidental exposure to low levels of c-silica in the environment (e.g., at beaches). Numerous occupational exposure studies provide evidence that inhaled c-silica causes lung cancer, and IARC (2012), NIOSH (2002), and NTP (2014) classify c-silica as a carcinogen. Although the studies on renal toxicity and autoimmune diseases are not as extensive as those for silicosis and lung cancer, available evidence supports an association between occupational exposure to c-silica and increased risks for these effects. Results of a recent study of over 42,000 workers in China showed a significant positive trend for cumulative c-silica exposure and mortality from heart disease (Liu et al. 2014). Available data in humans and laboratory animals are not sufficient to demonstrate a causal relationship between oral exposure to c-silica and any adverse effect outcome. Adverse effects of dermal exposure to c-silica have not been reported.

**Overview: *Health Effects of Amorphous Silica.*** Relative to the abundance of data on the effects of c-silica, few studies have evaluated the health effects from exposure to a-silica, with most data obtained from animal studies. Pulmonary fibrosis has been reported in a-silica workers, although co-exposure to c-silica could not be ruled out. Animal studies show that inhalation of a-silica produces pulmonary inflammation, and reversible fibrosis, but silicosis is not observed. Other than pulmonary effects, no other effects associated with inhaled a-silica have been established. Available data in humans and laboratory animals are not sufficient to demonstrate a causal relationship between oral exposure to a-silica and any adverse effect outcome. Adverse effects of dermal exposure to a-silica have not been reported.



### 3. HEALTH EFFECTS

#### 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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**3.2.1 Inhalation Exposure**

The highest NOAEL values and all LOAEL values for a-silica from each reliable study for each end point in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. As noted previously, animal studies for c-silica were not considered due to the extensive literature on c-silica toxicity in humans. Summaries of epidemiology studies and exposure-response data are presented in Tables 3-2 through 3-16.

**3.2.1.1 Death**

**Crystalline Silica.** Prolonged occupational exposure can result in death due to silicosis or lung cancer. Details are provided in Sections 3.2.1.2 (Systemic Effects, Respiratory Effects) and 3.2.1.7 (Cancer).

**Amorphous Silica.** No studies evaluating death in humans following inhalation exposure to a-silica were identified.

In an acute study, no mortalities were observed in rats exposed to a-silica at 477 mg/m<sup>3</sup> for 4 hours (Lewinson et al. 1994). In a 2-week study in rats, 4/10 males and 2/10 females died following exposure to 209 mg/m<sup>3</sup> 6 hours/day for 5 days/week; no mortalities were observed at ≤87 mg/m<sup>3</sup> (Reuzel et al. 1991). In other studies, no treatment-related changes in survival were reported in laboratory animals (rats, rabbits, guinea pigs, and monkeys) exposed to a-silica for 6 hours/day, 5 days/week at concentrations up to 25 mg/m<sup>3</sup> for 1 week (Arts et al. 2007), 150 mg/m<sup>3</sup> for 4 weeks (Lee and Kelly 1992), 30 mg/m<sup>3</sup> for 13 weeks (Reuzel et al. 1991), up to 9.9 mg/m<sup>3</sup> for up to 18 months (Groth et al. 1981), or 126 mg/m<sup>3</sup> for 8 hours/day, 7 days/week for 12–24 months (Schepers 1981).

**3.2.1.2 Systemic Effects****Respiratory Effects.****Crystalline Silica.**

Silicosis: Pathologic Features and Clinical Presentation. Unless otherwise noted, information in the following section was taken from these reviews: Bang et al. (2015); Banks et al. (1986); Beckett et al. (1997); Castranova and Vallyathan (2000); Ding et al. (2002); EPA (1996); Fujimura 2000); Greaves (2000); Greenberg et al. (2007); IARC (1997); Leung et al. (2012); Mossman and Churg (1998);

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Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Rat (Wistar)	6 hr/d 5 d/wk 2 wk (WB)					209 (4/10 M died, 2/10 F died)	Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)
<b>Systemic</b>								
2	Rat (Wistar)	6 hr/d 5 d (N)	Resp	5 M	25 M (accumulation of alveolar macrophages, mild bronchial/bronchiolar hypertrophy)			Arts et al. 2007 Silica gel (Syloid 74)
			Bd Wt	25 M				
3	Rat (Wistar)	6 hr/d 5 d (N)	Resp	1	5 (intra-alveolar granulocytic infiltrates, mild bronchial/bronchiolar hypertrophy)			Arts et al. 2007 Precipitated silica (Zeosil 45)
			Bd Wt	25				
4	Rat (Wistar)	6 hr/d 5 d (N)	Resp	1 M	5 M (accumulation of alveolar macrophages, intra-alveolar granulocytic infiltrates, mild bronchial/bronchiolar hypertrophy)			Arts et al. 2007 Pyrogenic silica (Cab-O-Sil M5)
			Bd Wt	25 M				

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Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
5	Rat (Wistar)	6 hr/d 5 d/wk 2 wk (WB)	Resp			17	(respiratory distress, inflammation, pneumonia, granulomas)	Reuzel et al. 1991 Fumed hydrophilic silica (Aerosil 200)
6	Rat (Wistar)	6 hr/d 5 d/wk 2 wk (WB)	Resp			31	(increased lung weight, respiratory distress, increased cellularity, edema, granulomas)	Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)
7	Rat (Wistar)	6 hr/d 5 d/wk 2 wk (WB)	Resp			46	(respiratory distress, increased lung weight, increased cellularity, pneumonia)	Reuzel et al. 1991 Precipitated hydrophobic (Sipernat 22S)
8	Rat (CrI:CD BR)	6 hr/d 5 d/wk 2 wk (N)	Resp	10.1 M	50.5 M (25-fold increase of neutrophils in BAL)			Warheit et al. 1991, 1995 Colloidal silica (Ludox)
9	Rat (CrI:CD BR)	6 hr/d 3 d (N)	Resp		10 M (40% increased neutrophils and 200% increased LDH activity in BAL)			Warheit et al. 1995 Precipitated silica (Zeofree 80)

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Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )			
<b>INTERMEDIATE EXPOSURE</b>									
<b>Systemic</b>									
10	Rat (Fischer- 344)	6 hr/d 5 d/wk 13 wk (WB)	Resp				50.4 M (lung inflammation, proliferative responses, fibrosis)	Johnston et al. 2000 Fumed hydrophilic silica (Aerosil 200)	
11	Rat (CrI:DC BR)	6 hr/d 5 d/wk 4 wk (WB)	Resp	10 M	50 M (inflammation, hyperplasia)			Lee and Kelly 1992 Colloidal silica (Ludox)	No treatment-related changes in hepatic or renal clinical chemistry.
			Hepatic	150 M					
			Renal	150 M					
			Bd Wt	150 M					

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Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
12	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)	Resp				1 (increased cellularity, inflammation, increased collagen content, fibrosis)	Reuzel et al. 1991 Fumed hydrophilic silica (Aerosil 200)
			Cardio	30				
			Gastro	30				
			Hemato	6	30	(2- to 3-fold increase in neutrophils)		
			Musc/skel	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Dermal	30				
			Ocular	30				
			Bd Wt	30				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
13	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)	Resp			30	(increased lung weight, increased cellularity, inflammation, granuloma, increased collagen content)	Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)
			Cardio	30				
			Gastro	30				
			Musc/skel	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Dermal	30				
			Ocular	30				
			Bd Wt	30				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
14	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)	Resp			30	(increased lung weight, increased cellularity, inflammation, increased collagen content)	Reuzel et al. 1991 Precipitated hydrophobic (Sipernat 22S)
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Musc/skel	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Dermal	30				
			Ocular	30				
Bd Wt	30							
15	Rat (CrI:CD BR)	6 hr/d 5 d/wk 4 wk (N)	Resp	10.1 M	50.5 M (200-fold increase of neutrophils in BAL)		Warheit et al. 1991, 1995 Colloidal silica (Ludox)	
16	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophilic silica (Aerosil 200)	No treatment-related changes in immune organ weight or histology.



## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency/ Route	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
17	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)	No treatment-related changes in immune organ weight or histology.
<b>Neurological</b>								
18	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophilic silica (Aerosil 200)	No treatment-related changes in brain weight or nervous tissue histology.
19	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)	No treatment-related changes in brain weight or nervous tissue histology.
<b>Reproductive</b>								
20	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophilic silica (Aerosil 200)	No treatment-related changes in reproductive organ weight or histology.
21	Rat (Wistar)	6 hr/d 5 d/wk 13 wk (WB)		30			Reuzel et al. 1991 Fumed hydrophobic silica (Aerosil R 974)	No treatment-related changes in reproductive organ weight or histology.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
<b>CHRONIC EXPOSURE</b>								
<b>Systemic</b>								
22	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)	Resp		9.9 M (macrophage/mononuclear cell aggregates, impaired pulmonary function)		Groth et al. 1981 Fumed silica (NS)	
			Cardio	9.9 M				
			Gastro	9.9 M				
			Hemato	9.9 M				
			Hepatic	9.9 M				
			Renal	9.9 M				
			Endocr	9.9 M				
			Dermal	9.9 M				
			Bd Wt	9.9 M				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
23	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)	Resp		9.4 M (macrophage/mononuclear cell aggregates, impaired pulmonary function)		Groth et al. 1981 Silica gel (NS)	
			Cardio	9.4 M				
			Gastro	9.4 M				
			Hemato	9.4 M				
			Hepatic	9.4 M				
			Renal	9.4 M				
			Endocr	9.4 M				
			Dermal	9.4 M				
			Bd Wt	9.4 M				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
24	Monkey (Cynomolgus)	6 hr/d 5 d/wk 18 mo (WB)	Resp		6.9 M (macrophage/mononuclear cell aggregates, impaired pulmonary function)		Groth et al. 1981 Precipitated silica (NS)	
			Cardio	6.9 M				
			Gastro	6.9 M				
			Hemato	6.9 M				
			Hepatic	6.9 M				
			Renal	6.9 M				
			Endocr	6.9 M				
			Dermal	6.9 M				
Bd Wt	6.9 M							
25	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	9.9 M			Groth et al. 1981 Fumed silica (NS)	
			Cardio	9.9 M				
			Gastro	9.9 M				
			Hemato	9.9 M				
			Hepatic	9.9 M				
			Renal	9.9 M				
			Endocr	9.9 M				
			Dermal	9.9 M				
Bd Wt	9.9 M							

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
26	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	9.4 M			Groth et al. 1981 Silica gel (NS)	
			Cardio	9.4 M				
			Hemato	9.4 M				
			Hepatic	9.4 M				
			Renal	9.4 M				
			Endocr	9.4 M				
			Dermal	9.4 M				
			Bd Wt	9.4 M				
27	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	6.9 M			Groth et al. 1981 Precipitated silica (NS)	
			Cardio	6.9 M				
			Gastro	6.9 M				
			Hemato	6.9 M				
			Hepatic	6.9 M				
			Renal	6.9 M				
			Endocr	6.9 M				
			Dermal	6.9 M				
Bd Wt	6.9 M							

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
28	Rat (NS)	8 hr/d 7 d/wk 15 mo (WB)	Resp		126	(increased lung weight, macrophage accumulation)	Schepers 1981 Precipitated silica (HI-SIL 233)	
29	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	9.9 M			Groth et al. 1981 Fumed silica (NS)	
			Cardio	9.9 M				
			Gastro	9.9 M				
			Hemato	9.9 M				
			Hepatic	9.9 M				
			Renal	9.9 M				
			Endocr	9.9 M				
			Dermal	9.9 M				
			Bd Wt	9.9 M				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
30	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	9.4 M			Groth et al. 1981 Silica gel (NS)	
			Cardio	9.4 M				
			Gastro	9.4 M				
			Hemato	9.4 M				
			Hepatic	9.4 M				
			Renal	9.4 M				
			Endocr	9.4 M				
			Dermal	9.4 M				
			Bd Wt	9.4 M				
31	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)	Resp	6.9 M			Groth et al. 1981 Precipitated silica (NS)	
			Cardio	6.9 M				
			Gastro	6.9 M				
			Hemato	6.9 M				
			Hepatic	6.9 M				
			Renal	6.9 M				
			Endocr	6.9 M				
			Dermal	6.9 M				
			Bd Wt	6.9 M				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency/ (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
32	Gn Pig (NS)	8 hr/d 7 d/wk 24 mo (WB)	Resp		126	(increased lung weight, macrophage accumulation)	Schepers 1981 Precipitated silica (HI-SIL 233)	
33	Rabbit (NS)	8 hr/d 7 d/wk 12 mo (WB)	Resp		126	(macrophage accumulation)	Schepers 1981 Precipitated silica (HI-SIL 233)	
			Cardio		126	(increased cardiac ventricular pressure)		
<b>Immuno/ Lymphoret</b>								
34	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in immune organs.
35	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in immune organs.
36	Monkey (Cynomolgus)	6 hr/d 5 d/wk 18 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in immune organs.



## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency/ Route	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
37	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in immune organs.
38	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in immune organs.
39	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in immune organs.
40	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in immune organs.
41	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in immune organs.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
42	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in immune organs.
<b>Reproductive</b>								
43	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in reproductive organs.
44	Monkey (Cynomolgus)	6 hr/d 5 d/wk 13 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in reproductive organs.
45	Monkey (Cynomolgus)	6 hr/d 5 d/wk 18 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in reproductive organs.
46	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in reproductive organs.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation

(continued)

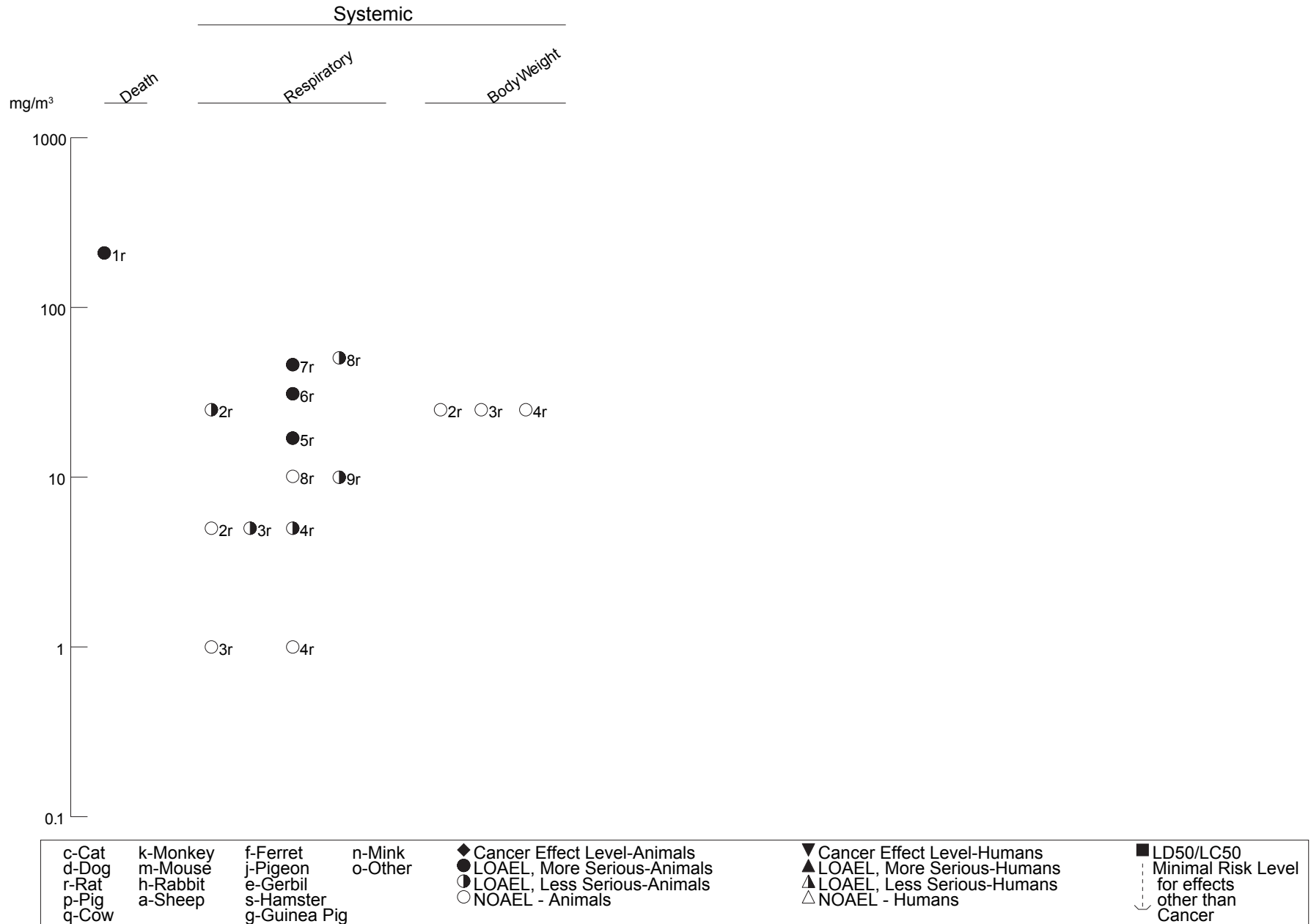
Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency/ Route	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
47	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in reproductive organs.
48	Rat (Sprague- Dawley)	6 hr/d 5 d/wk 12 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in reproductive organs.
49	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		9.9 M			Groth et al. 1981 Fumed silica (NS)	No treatment-related histopathological lesions in reproductive organs.
50	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		9.4 M			Groth et al. 1981 Silica gel (NS)	No treatment-related histopathological lesions in reproductive organs.
51	Gn Pig (Hartley)	6 hr/d 5 d/wk 12 mo (WB)		6.9 M			Groth et al. 1981 Precipitated silica (NS)	No treatment-related histopathological lesions in reproductive organs.

<sup>a</sup> The number corresponds to entries in Figure 3-1.

BAL = bronchoalveolar lavage fluid; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; (N) = nose-only; NOAEL = no-observed-adverse-effect level; NS = not specified (trade name not reported); Resp = respiratory; x = time(s); (WB) = whole body; wk = week(s)

3. HEALTH EFFECTS

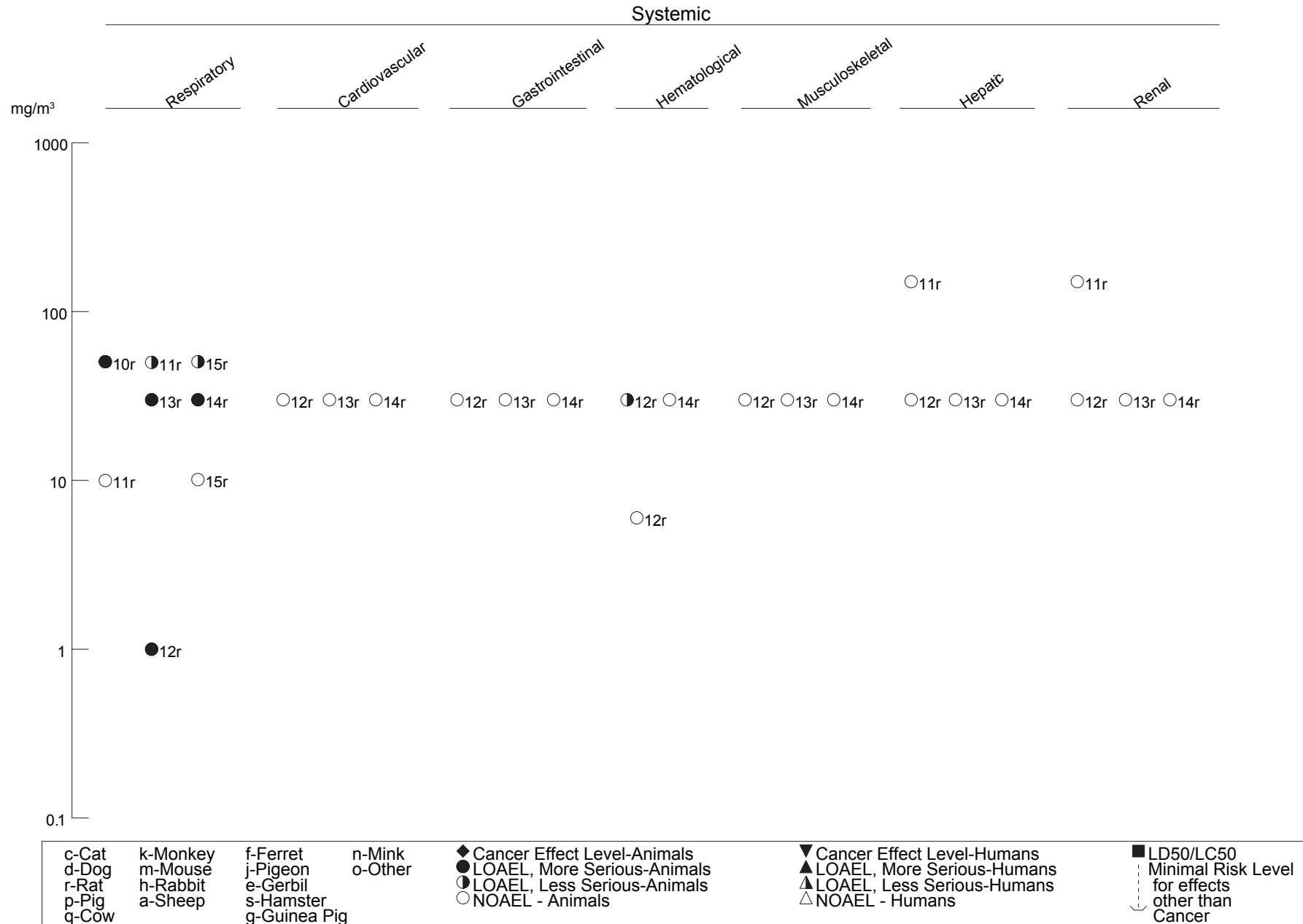
Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation  
Acute (≤14 days)



3. HEALTH EFFECTS

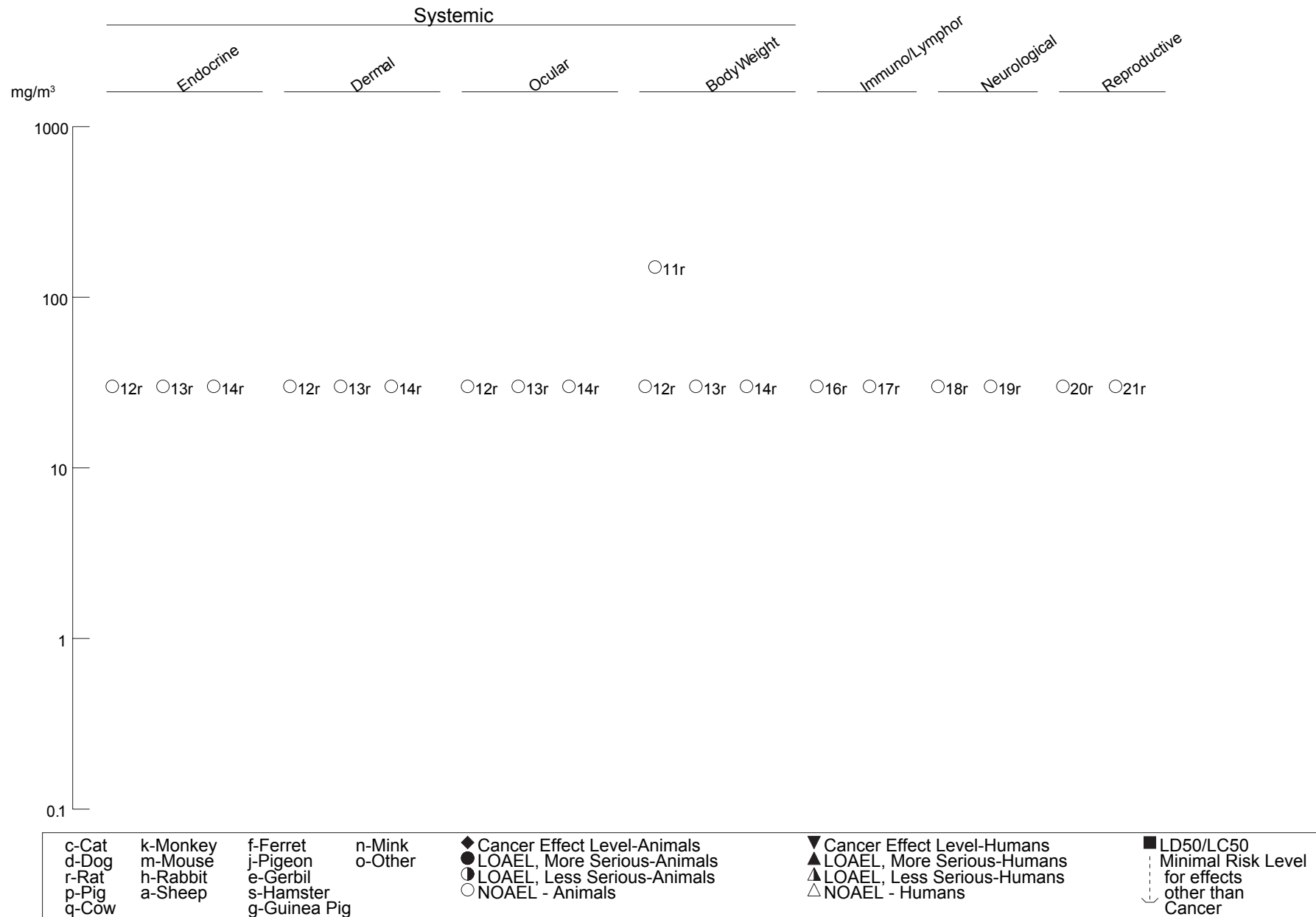
Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)

Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)  
Intermediate (15-364 days)

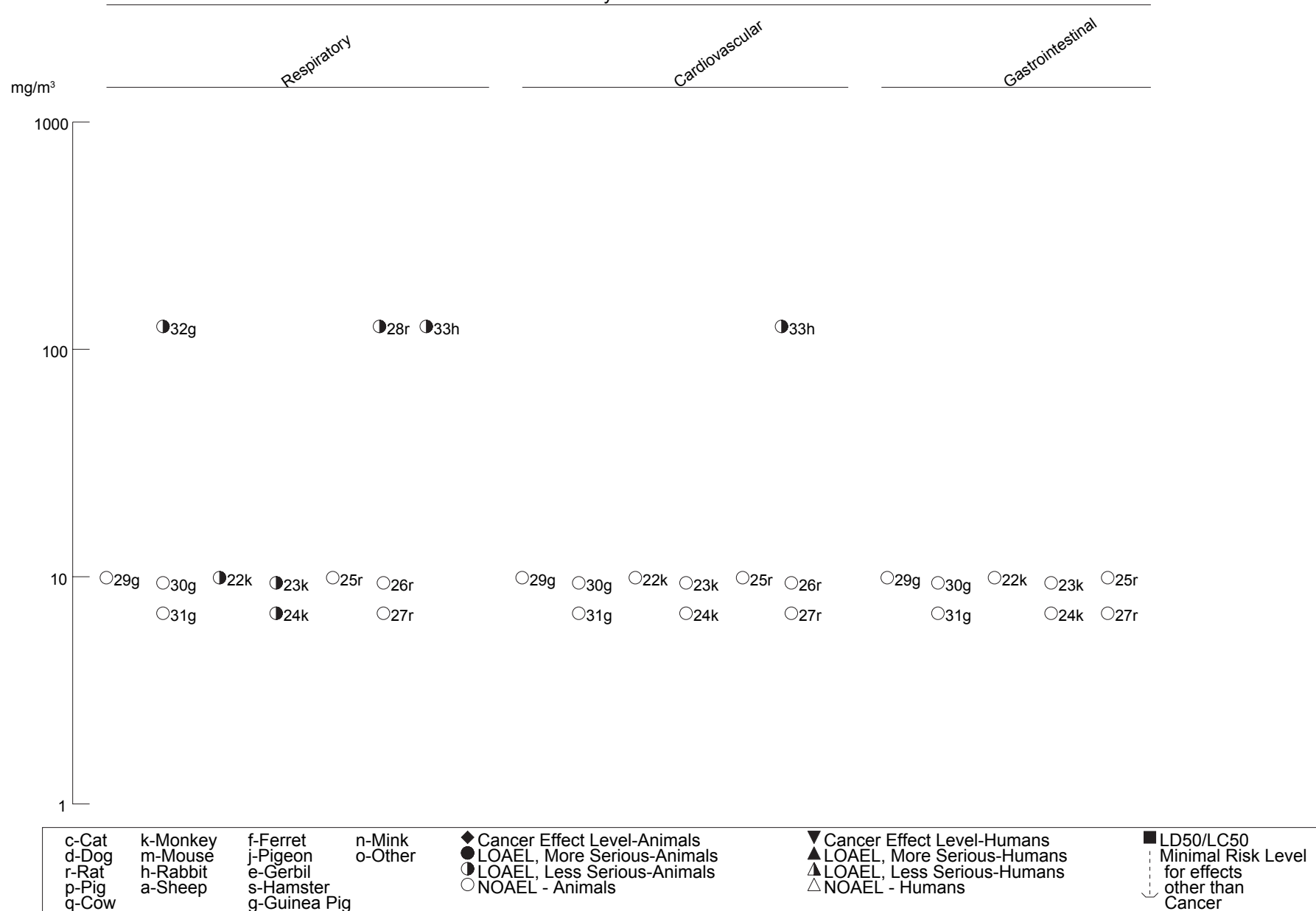


3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)

Chronic (≥365 days)

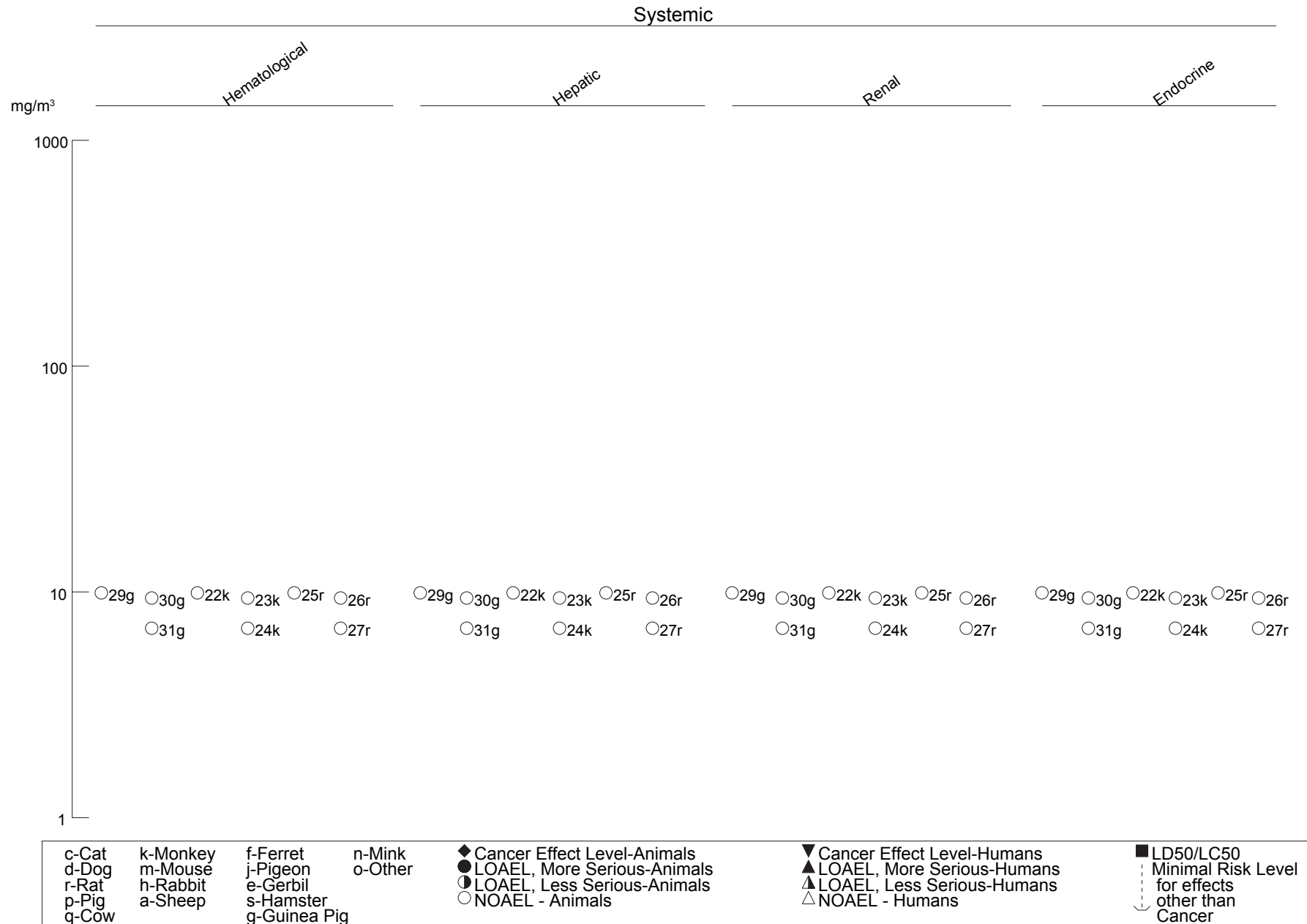
Systemic



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)

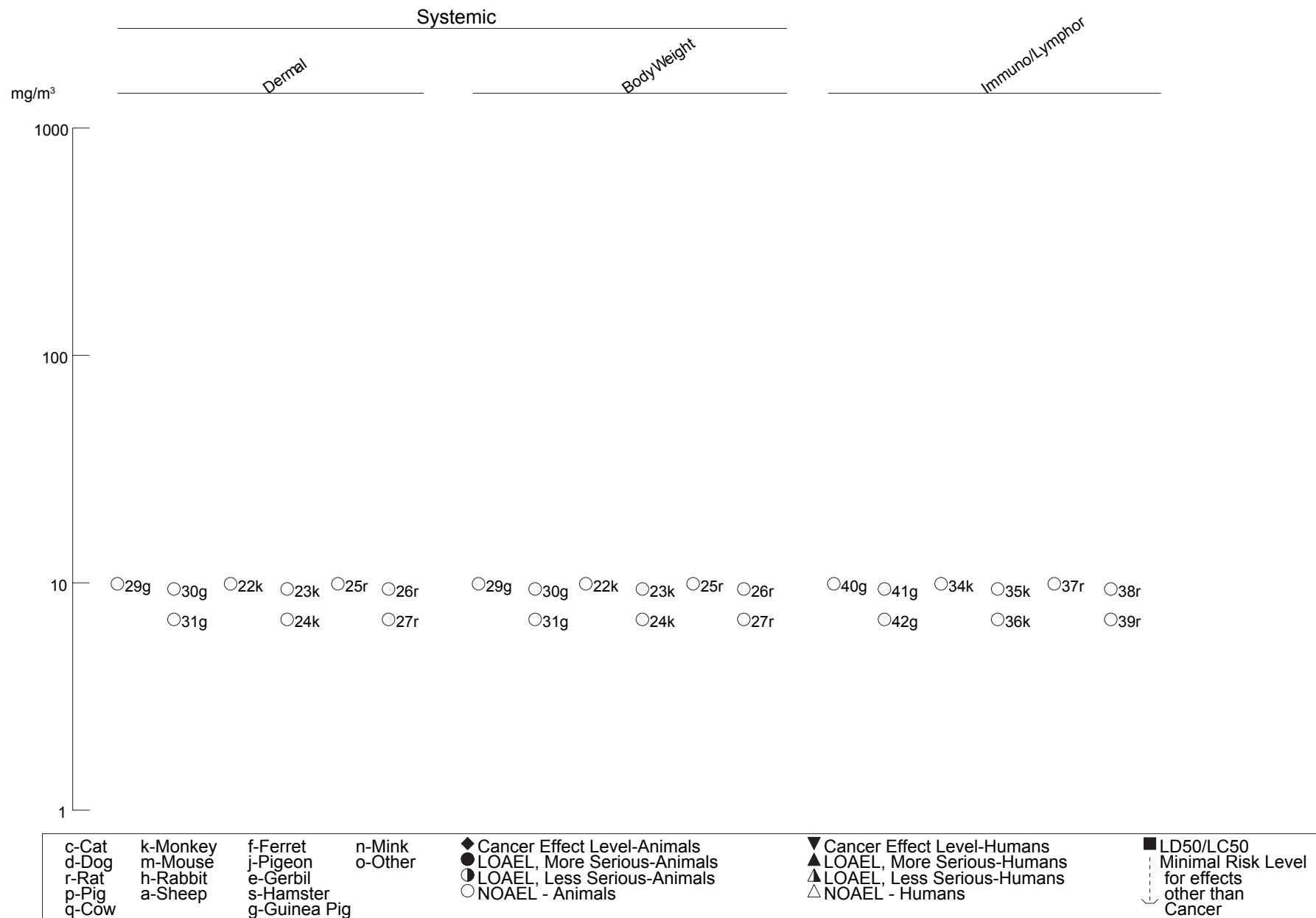
Chronic (≥365 days)





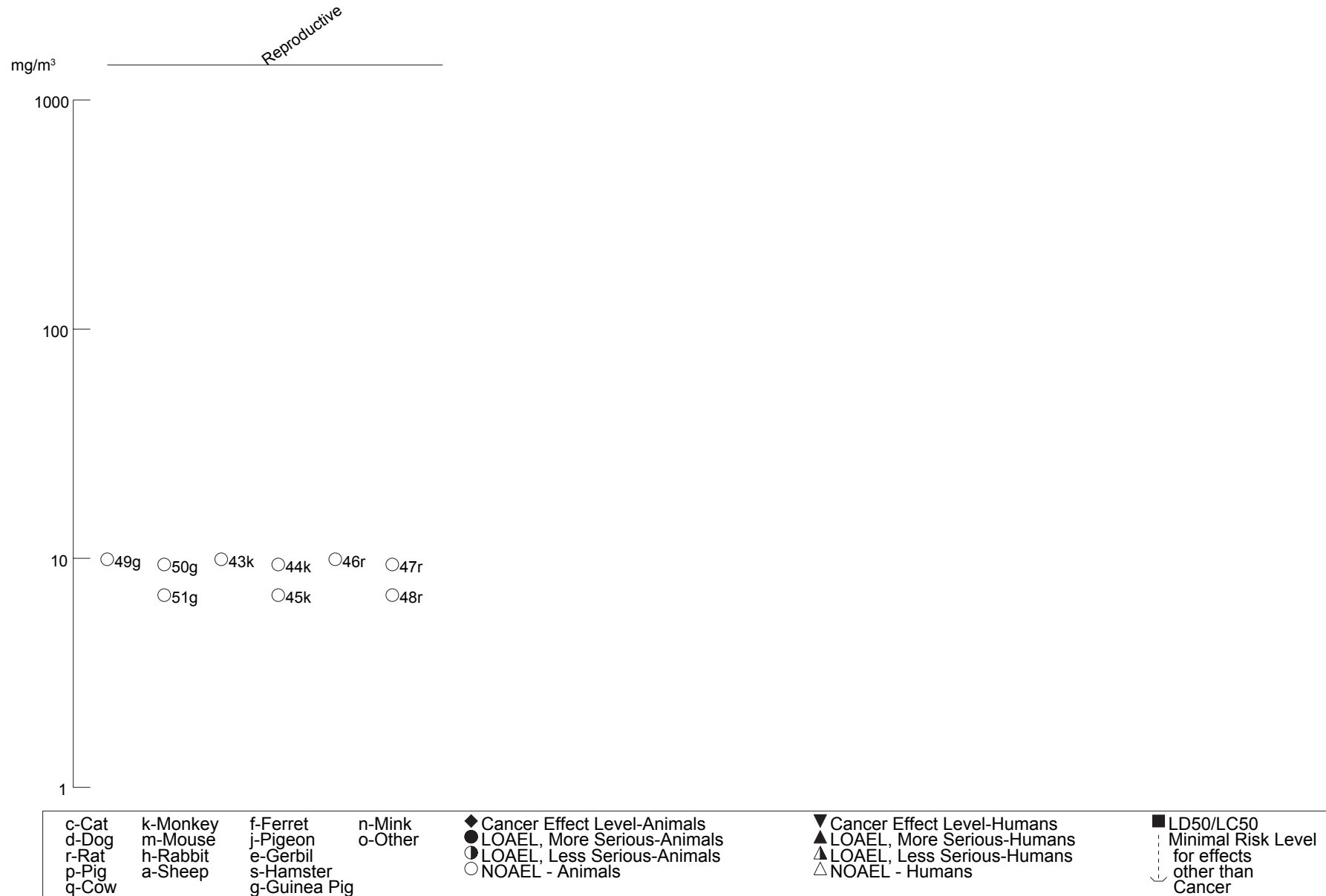
3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)  
Chronic (≥365 days)



3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to Amorphous Silica - Inhalation (Continued)  
Chronic (≥365 days)



## 3. HEALTH EFFECTS

Mossman and Glenn (2013); NIOSH (2002); Peters (1986); Rimal et al. (2005); Steenland (2005); Steenland and Ward (2014); and Stratta et al. (2001a).

Silicosis is one of the oldest known occupational diseases, reported by ancient Greeks and Romans. It has only been observed following occupational exposure to respirable c-silica and not through exposure to c-silica in ambient air (Beckett et al. 1997; Steenland and Ward 2014). As stated by Steenland and Ward (2014), “while there is also some low-level c-silica exposure on beaches and in ambient air in general, there is no evidence such low-level exposure causes health effects.” Silicosis is a progressive, irreversible, fibrotic lung disease resulting from inhalation and pulmonary deposition of respirable dust containing c-silica. The causal relationship between inhalation of c-silica and development of this severe, debilitating lung disease is well-established and not under dispute. No other substances are known to produce the unique pathological changes observed in silicosis. In the United States, despite improved industrial hygiene methods and more stringent recommended exposure limits, new cases of silicosis continue to be diagnosed. There is no known curative treatment for silicosis.

Silicosis is not a single disease entity, but is classified as different types: acute silicosis (also called silicoproteinosis or alveolar proteinosis), simple silicosis (also called chronic or nodular silicosis), progressive massive fibrosis (PMF) (also called conglomerate silicosis or complicated silicosis; a progression of simple silicosis), and accelerated silicosis (a rapidly progressive form of simple (chronic) silicosis). Type and severity of silicosis can be influenced by the intensity (frequently referred to as concentration), frequency, and duration of exposure. Cumulative c-silica dose, expressed as  $\text{mg}/\text{m}^3\text{-year}$ , is the most important factor in the development of silicosis. All types of silicosis can be fatal, with death resulting from respiratory failure. Time from first exposure to onset of disease (i.e., the latency period) varies inversely with intensity of exposure and may be as short as a few weeks for acute silicosis to as long as 20 or more years for simple silicosis and PMF. Due to the long latency period, patients may not be diagnosed until several years after exposure has ended. Disease severity may continue to slowly increase over decades even after exposure has been discontinued, possibly due to c-silica dust that is retained in the lung. Thus, cessation of exposure does not necessarily prevent development or progression of silicosis. Silicosis is diagnosed based on a known history of exposure to dust containing c-silica and radiographic findings, including the presence of nodules on chest radiograph or computed tomography (CT) scan, along with ruling out other diseases that may mimic silicosis (e.g., fungal infections, sarcoidosis). Pulmonary function tests are useful for determining severity, but not as useful diagnostic tool for silicosis as no pattern of lung function abnormality is specific for c-silica exposure or silicosis.

## 3. HEALTH EFFECTS

*Simple silicosis.* Simple silicosis, also called chronic or nodular silicosis, is the most common type of silicosis. It occurs following long periods (10–≥20 years) of continuous exposure to relatively low levels of c-silica dust, although “relatively low levels” has not been defined in quantitative terms. Simple silicosis can be either a restrictive, obstructive, or mixed lung disease characterized by diffuse, multiple nodular lesions in lung parenchyma and associated lymphoid tissue and lymph nodes, and fibrotic lesions of the pleura. Nodules, are typically small ( $\leq 1$  mm in diameter) and more prominent in upper lobes of the lung; those in close proximity to small and medium airways cause narrowing and distortion of the airway lumen. Fibrotic nodules appear as concentric arrangements of whorled collagen fibers with central hyalinized zones; calcification and necrosis occur to varying degrees. Nodules also may contain c-silica inclusions. Macrophages, fibroblasts, and lymphocytes are observed at the periphery of the nodules, and the pleura may appear thickened. Early in disease development, radiography typically shows small, round opacities of the upper lung. With disease progression, nodules become larger and denser and may be observed in the lower lung in more severe cases. Scarring and hypertrophy of bronchial-associated lymphoid tissue and intrapulmonary lymph nodes lead to compression of larger airways.

Early symptoms of simple silicosis are dyspnea on heavy exertion and dry cough; however, some patients may be asymptomatic. Pulmonary function and general health typically may not be compromised during the early stages. As the disease progresses, frequency and intensity of cough increases and sputum production may occur; dyspnea also occurs more frequently with less exertion. Decrements in lung function are often observed (e.g., nonreversible airflow obstruction, volume restriction, impaired gas exchange, pulmonary hypertension, right heart strain, and cor pulmonale), which may lead to right heart enlargement. In the later stages, hypoxemia may develop.

*Progressive Massive Fibrosis (PMF).* PMF, also called conglomerate silicosis or complicated silicosis, is a progression of simple silicosis. The factors that determine progression of simple silicosis to complicated silicosis have not been defined, but cumulative exposure and tuberculosis are risk factors. Complicated silicosis can develop after exposure to c-silica ceases.

Nodular lung lesions become larger (diameter  $>1$ – $2$  cm) and coalesce to form masses of hyalinized connective tissue, leading to destruction of the surrounding pulmonary architecture, including bronchioles and blood vessels. Necrosis and cavitation of lesions occur and PMF develops. Restricted lung volume, reduced pulmonary compliance, and poor gas exchange are observed. Compromised pulmonary function

### 3. HEALTH EFFECTS

can lead to right ventricular failure, congestive heart failure, and increased risk of pneumothorax. General health significantly declines, and severe pulmonary damage can result in death.

*Acute silicosis.* Acute silicosis, also called silicoproteinosis or alveolar proteinosis, is a rapidly progressive alveolar filling disease associated with heavy, intense exposure (not quantitatively defined) to fine c-silica dusts, such as those generated during sandblasting, rock drilling, or milling and tunneling. The time to onset for acute silicosis varies from a few weeks to <10 years after the start of exposure, but most cases typically occur within 1–5 years. Acute silicosis frequently results in death due to respiratory failure. Like simple and complicated silicosis, acute silicosis progresses in the absence of further exposure.

Pathologically, acute silicosis is characterized by alveolar filling with an eosinophilic-granular, lipid-rich fluid containing debris from damaged cells, and interstitial inflammation with infiltration by neutrophils and alveolar macrophages containing lamellar bodies. Diffuse interstitial fibrosis often develops and extensive damage to the alveolar epithelium occurs. On radiography, diffuse alveolar opacification is observed in the middle and lower lobes.

Symptoms of acute silicosis include dyspnea, labored breathing, dry cough, decreased pulmonary function, compromised gas exchange, fever, fatigue, and weight loss. As the disease progresses, cyanosis and respiratory failure develop. Death from respiratory failure often occurs within a few months of the onset of symptoms.

*Accelerated silicosis.* Accelerated silicosis, associated with intense exposure to fine c-silica dusts, is a rapidly progressive form of simple (chronic) silicosis. It develops 5–10 years after the start of exposure and is typically associated with more moderate exposure (compared to simple silicosis). Symptoms are similar to those of simple silicosis. Accelerated silicosis is associated with significant morbidity and mortality.

*Silicotuberculosis—a complication of silicosis.* A complication of silicosis is superimposed pulmonary infection with mycobacteria or fungi. The most common form of infection in c-silica-exposed workers is tuberculosis (silicotuberculosis). The risk of tuberculosis infection increases with the severity of silicosis, although some occupational exposure studies have reported an increased risk of tuberculosis in c-silica workers in the absence of silicosis (Cowie 1994; teWaterNaude et al. 2006). Based on worker compensation claims in California during the period 1946–1979, Goldsmith et al. (1995) estimated the

## 3. HEALTH EFFECTS

rate of death in males with silicotuberculosis as approximately 50 times greater than that of the general population. The prevalence of silicotuberculosis in the United States decreased with advances in tuberculosis drug therapy. However, due to the recent increase in drug-resistant tuberculosis, the potential for superimposed tuberculous infection in c-silica workers is a growing concern. The prevalence of silicotuberculosis is exacerbated by human immunodeficiency virus (HIV) epidemics, particularly in low-income countries (Rees and Murray 2007).

Silicosis Morbidity: Incidence and Exposure-Response Data. The current number of silicosis cases in the United States is not known (NIOSH 2002). Rosenman et al. (2003) estimated that during the period of 1987–1997, approximately 3,600–7,300 new silicosis cases were diagnosed yearly in the United States. However, it is likely that this incidence is underestimated due to the lack of a national surveillance system for silicosis (Steenland and Ward 2014). Recent surveillance data for silicosis showed no decrease in hospitalization due to silicosis in the United States over the time period 1993–2011 (Filius et al. 2015). The incidence of silicosis is higher in less-developed countries; for example, approximately 6,000 new cases of silicosis per year are diagnosed in China (Leung et al. 2012; Steenland and Ward 2014).

Several studies provide exposure-response data for silicosis incidence based on cumulative exposure (expressed as  $\text{mg}/\text{m}^3\text{-year}$ ) for various industries, including underground hardrock mining (Chen et al. 2001; Churchyard et al. 2004; Hnizdo and Sluis-Cremer 1993; Kreiss and Zhen 1996; Muir et al. 1989a, 1989b; Steenland and Brown 1995a), granite quarry mining and production (Ng and Chan 1994), diatomaceous earth mining and milling (Hughes et al. 1998; Park et al. 2002), and porcelain production (Mundt et al. 2011). Study details are provided in Table 3-2. Results of these studies show that the risk of silicosis increases with cumulative exposure. However, risk estimates are not directly comparable across study designs that used different outcome metrics, follow-up periods, or statistical approaches to estimate risk. Another complication is that various industrial processes generate different types of c-silica particles (e.g., particle size, surface reactivity, fibrogenic potential) (see Section 3.5.2, Mechanism of Toxicity; Section 4.2, Chemical and Physical Properties).

Chen et al. (2001) compared cumulative risks of silicosis for four hardrock mining cohorts (Chen et al. 2001; Hnizdo and Sluis-Cremer 1993; Kreiss and Zhen 1996; Steenland and Brown 1995a) (Figure 3-2). Relationships between cumulative exposure and cumulative risks (estimated through the end of the follow-up periods) were similar across the cohorts, with each showing an exponential increase in cumulative risk with increasing cumulative exposure. For a cumulative exposure of  $4.5 \text{ mg}/\text{m}^3\text{-year}$  (a 45-year exposure to  $0.1 \text{ mg}/\text{m}^3$ ), cumulative risks ranged from approximately 55 to 90%. Cumulative

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Chen et al. 2001	<u>Study design:</u> retrospective cohort <u>Industry:</u> tin mining (four mines) <u>Location:</u> China	<u>Cohort:</u> 3,010 male (92.9%) and female tin miners employed for at least 1 year during 1960–1965, with follow- up through 1994 <u>Adjustments:</u> historical exposure information and task description of the job title <u>Statistical analysis:</u> Weibull model	Categories (C) for cumulative exposure to c-silica dust, calculated using reported cumulative total dust exposure and the mean c-silica dust concentration of 3.6% (midpoint): - C1: <0.36 (0.18) - C2: 0.36–0.72 (0.54) - C3: >0.72–1.4 (1.08) - C4: >1.4–2.2 (1.80) - C5: >2.2–2.9 (2.52) - C6: >2.9–3.6 (3.24) - C7: >3.6–5.4 (4.50) - C8: >5.4 (>5.4)	Silicosis cases: 1,015 (33.7% of cohort) Silicosis diagnosed post-exposure: 684 (67.4% of silicosis cases)  Time after first exposure to onset of silicosis (mean±SD): 21.3±8.6 years  Number of silicosis cases/workers in exposure group: - C1: 2/3,010 - C2: 24/2,677 - C3: 126/2,343 - C4: 127/1,717 - C5: 196/1,288 - C6: 141/902 - C7: 244/638 - C8: 155/221  Cumulative risk of silicosis (%): - C1: 0.10 - C2: 1.0 - C3: 7.0 - C4: 14.5 - C5: 28.5 - C6: 40.5 - C7: 66.3 - C8: 91.7  Lifetime risk exposure to 0.1 mg/m <sup>3</sup> for 45 years (4.5 mg/m <sup>3</sup> -year): 55%

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Churchyard et al. 2004 (with some data reported in Collins et al. 2005)	<u>Study design</u> : cross-sectional <u>Industry</u> : gold mining <u>Location</u> : South Africa	<u>Cohort</u> : 520 current black gold miners, 37–60 years of age, recruited during November 2000 through March 2001; no follow-up period or assessment of previously employed miners <u>Adjustments</u> : none <u>Statistical analysis</u> : logistic regression	Cumulative exposure to respirable quartz: <u>Mean±SD</u> : 8.2±2.88 <u>Median</u> : 7.95 <u>Range</u> : 0–22.68 <u>Categories (C) for cumulative exposure (mid-point)</u> : - C1: 0–0.80 (0.4) - C2: 0.80–0.99 (0.9) - C3: 0.99–1.24 (1.12) - C4: 1.24–1.48 (1.36) - C5: 1.48–3.08 (2.28) <u>Duration of exposure (mean)</u> : 2.18 years	Silicosis cases: 93 (19%)  Miners with silicosis per exposure group (%) (as reported in Collins et al. 2005): - C1: 11 (10.7) - C2: 8 (8.2) - C3: 18 (17.5) - C4: 23 (22.1) - C5: 33 (32.0)  The prevalence of silicosis (%) significantly increased with cumulative exposure (p<0.001). Estimated prevalence of silicosis by cumulative exposure (number with silicosis/number workers in exposure category): - C1: 10.7 (11/103) - C2: 8.2 (8/97) - C3: 17.5 (18/103) - C4: 22.1 (23/104) - C5: 32.0 (33/103)  For each unit increase for cumulative exposure (mg/m <sup>3</sup> -year), the odds of silicosis increased by 3.2.



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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Hnzido and Sluis-Cremer 1993	<p><u>Study design:</u> longitudinal retrospective</p> <p><u>Industry:</u> gold mining</p> <p><u>Location:</u> South Africa</p>	<p><u>Cohort:</u> 2,235 white gold miners employed as underground gold miners from 1938 for at least 10 years, with follow-up to 1991</p> <p><u>Adjustments:</u> cumulative risk was adjusted for loss of workers who did not develop silicosis but whose exposure reached only a certain level (not specified); no adjustment was made for exposure to radon daughters in the mines</p> <p><u>Statistical analysis:</u> cumulative risk calculated by Kaplan-Meier method</p>	<p>Cumulative respirable c-silica exposure (composed mainly of quartz and silicates, based on a 30% c-silica content in dust):</p> <p>Mean (SD): 6.6 (2.7)</p> <p>Range: 1.2–18.7</p> <p>Cumulative exposure category (C) midpoints:</p> <ul style="list-style-type: none"> <li>- C1: 0.3</li> <li>- C2: 0.9</li> <li>- C3: 1.5</li> <li>- C4: 2.1</li> <li>- C5: 2.7</li> <li>- C6: 3.3</li> <li>- C7: 3.9</li> <li>- C8: 4.5</li> </ul>	<p>Silicosis cases: 313 (14% of cohort)</p> <p>Number of silicosis cases/workers in exposure group:</p> <ul style="list-style-type: none"> <li>- C1: 0/2,218</li> <li>- C2: 9/2,014</li> <li>- C3: 48/1,540</li> <li>- C4: 85/984</li> <li>- C5: 93/515</li> <li>- C6: 53/197</li> <li>- C7: 20/55</li> <li>- C8: 5/11</li> </ul> <p>Silicosis risk increased exponentially with cumulative dust exposure. The increase in risk accelerated at the cumulative exposure category C4. Risk per unit of cumulative c-silica dust exposure [mean (SE)]:</p> <ul style="list-style-type: none"> <li>- C1: –</li> <li>- C2: 0.002 (0.001)</li> <li>- C3: 0.016 (0.002)</li> <li>- C4: 0.045 (0.005)</li> <li>- C5: 0.099 (0.010)</li> <li>- C6: 0.156 (0.021)</li> <li>- C7: 0.222 (0.048)</li> <li>- C8: 0.227 (0.060)</li> </ul>

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Hughes et al. 1998	<u>Study design:</u> retrospective cohort <u>Industry:</u> diatomaceous earth industry <u>Location:</u> California	<u>Cohort:</u> 1,809 white workers in the diatomaceous earth industry with a minimum of 12 months of employment during 1942–1987; no follow-up period <u>Adjustments:</u> age <u>Statistical analysis:</u> Poisson regression	Categories for cumulative exposure to c-silica dust: <ul style="list-style-type: none"> <li>- C1: ≤1</li> <li>- C2: &gt;1–≤3</li> <li>- C3: &gt;3–≤6</li> <li>- C4: &gt;6</li> </ul>	Total silicosis cases: 81 (4.5%)  Risk of silicotic opacities on radiography significantly increased with cumulative exposure (p for trend: <0.001). Relative risk (95% CI): <ul style="list-style-type: none"> <li>- C1: 1</li> <li>- C2: 4.35 (1.7, 11.06)</li> <li>- C3: 20.13 (8.2, 49.7)</li> <li>- C4: 40.37 (16.1, 101.3)</li> </ul> Risks of radiographic opacities for cumulative exposure of 2.0 mg/m <sup>3</sup> -year for dust concentrations: <ul style="list-style-type: none"> <li>- &lt;0.50 mg/m<sup>3</sup>: 1.1%</li> <li>- &gt;0.50 mg/m<sup>3</sup>: 3.7%</li> </ul> Risks of radiographic opacities for cumulative exposure of 4.0 mg/m <sup>3</sup> -year for dust concentrations: <ul style="list-style-type: none"> <li>- &lt;0.50 mg/m<sup>3</sup>: 3.3%</li> <li>- &gt;0.50 mg/m<sup>3</sup>: 12.4%</li> </ul>
Kreiss and Zhen 1996	<u>Study design:</u> community-based random sample survey <u>Industry:</u> hard rock mining <u>Location:</u> Colorado	<u>Cohort:</u> 100 miners and 34 controls ≥40 years of age; range of follow-up period for individual miners: 0–56 years <u>Adjustments:</u> age, years since last exposure, packyears of smoking <u>Statistical analysis:</u> Logistic regression	Categories for cumulative c-silica exposure: <ul style="list-style-type: none"> <li>- C1: 0</li> <li>- C2: &gt;0–1</li> <li>- C3: &gt;1–2</li> <li>- C4: &gt;2–3</li> <li>- C5: &gt;3</li> </ul>	Prevalence of silicosis increased with cumulative exposure.  Prevalence (%): <ul style="list-style-type: none"> <li>- C1: 0</li> <li>- C2: 12.5</li> <li>- C3: 26.3</li> <li>- C4: 55.6</li> <li>- C5: 83.3</li> </ul>

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Muir et al. 1989a,1989b	<u>Study design:</u> longitudinal retrospective cohort <u>Industry:</u> gold and uranium mining <u>Location:</u> Ontario	<u>Cohort:</u> 2,109 gold and uranium miners employed during the period 1940–1959, with follow-up to 1982 or end of exposure, whichever occurred first; no follow-up period. <u>Adjustments:</u> none reported <u>Statistical analysis:</u> Weibull model	Categories of cumulative exposure and numbers of miners in each category: - C1: 0–0.499 (1,313) - C2: 0.5–0.999 (582) - C3: 1.0–1.499 (103) - C4: 1.5–1.999 (48) - C5: >2.0 (63)	Silicosis cases: 32  Estimates of cumulative exposures [in mg/m <sup>3</sup> -year (95% CI)] associated with risks of developing silicosis: - 1% risk: 6.1 (4.1, 8.9) - 2% risk: 8.5 (5.6, 12.8) - 5% risk: 13.2 (7.8, 22.5) - 10% risk: 18.7 (9.7, 36.1)
Mundt et al. 2011	<u>Study design:</u> epidemiological cohort <u>Industry:</u> porcelain manufacturing (100 plants) <u>Location:</u> Germany	<u>Cohort:</u> 17,644 workers (46.8% male) employed more than 6 months and participating in a screening program for silicosis in 1985–1987, with follow-up through 2005 <u>Adjustments:</u> age, sex, smoking <u>Statistical analysis:</u> Cox proportional hazards	Cumulative exposure to respirable c-silica: - ≤0.5 (referent) - >0.5–1.0 - >1.0–1.5 - >1.5–3.0 - >3 - ≤3 (referent) - >3–4 - >4–5 - >5–6 - >6	Cumulative exposure to >3 mg/m <sup>3</sup> -year was associated with an increased risk of silicosis.  Number of silicosis cases per cumulative exposure, not lagged: - ≤0.5 (referent): 4 - >0.5–1.0: 1 - >1.0–1.5: 2 - >1.5–3.0: 2 - >3: 31 - ≤3 (referent): 9 - >3–4: 1 - >4–5: 4 - >5–6: 6 - >6: 20  Silicosis hazard ratios (95% CI), not lagged: - ≤0.5: reference - >0.5–1.0: 0.3 (<0.1–2.6) - >1.0–1.5: 0.7 (0.1–3.8) - >1.5–3.0: 0.4 (0.1–2.2)

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
				<ul style="list-style-type: none"> <li>- &gt;3: 3.1 (1.1–9.3)</li> <li>- ≤3: reference</li> <li>- &gt;3–4: 0.9 (0.1–7.5)</li> <li>- &gt;4–5: 5.3 (1.6–17.3)</li> <li>- &gt;5–6: 7.3 (2.6–20.8)</li> <li>- &gt;6: 6.8 (3.0–15.3)</li> </ul>
				<p>Number of silicosis cases per cumulative exposure, lagged by 10 years:</p> <ul style="list-style-type: none"> <li>- ≤0.5 (referent): 5</li> <li>- &gt;0.5–1.0: 2</li> <li>- &gt;1.0–1.5: 1</li> <li>- &gt;1.5–3.0: 2</li> <li>- &gt;3: 30</li> <li>- ≤3 (referent): 10</li> <li>- &gt;3–4: 3</li> <li>- &gt;4–5: 4</li> <li>- &gt;5–6: 4</li> <li>- &gt;6: 19</li> </ul>
				<p>Silicosis hazard ratios (95% CI), lagged by 10 years:</p> <ul style="list-style-type: none"> <li>- ≤0.5: reference</li> <li>- &gt;0.5–1.0: 0.7 (0.1–3.7)</li> <li>- &gt;1.0–1.5: 0.4 (0.1–3.7)</li> <li>- &gt;1.5–3.0: 0.5 (0.1–2.4)</li> <li>- &gt;3: 3.7 (1.4–9.9)</li> <li>- ≤3: reference</li> <li>- &gt;3–4: 2.9 (0.8–10.6)</li> <li>- &gt;4–5: 4.9 (1.5–15.7)</li> <li>- &gt;5–6: 5.2 (1.6–16.9)</li> <li>- &gt;6: 6.7 (3.0–14.9)</li> </ul>

## 3. HEALTH EFFECTS

**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Ng and Chan 1994	<u>Study design</u> : cross-sectional <u>Industry</u> : granite industry <u>Location</u> : Hong Kong	<u>Cohort</u> : 206 current and 132 previous granite workers employed for at least 1 year in 1967–1985; decedents were not included; specific follow-up period was not specified <u>Adjustments</u> : age and smoking <u>Statistical analysis</u> : linear regression	Cumulative exposure to respirable quartz: <0.25→10	Prevalence (%) of rounded opacities on x-ray for cumulative exposures: - <0.25: 0 - 0.25–<1.00: 0 - 1.00–<5.00: 12.77 - 5.00–<10.00: 25.00 - >10.00: 21.67  Prevalence (%) of irregular opacities on x-ray for cumulative exposures: - <0.25: 0 - 0.25–<1.00: 0 - 1.00–<5.00: 19.15 - 5.00–<10.00: 21.67 - >10.00: 46.31  Analysis by linear regression predicted risks of 6 and 8% for rounded and irregular opacities, respectively, for a 50-year-old worker with a cumulative exposure of 2.0 mg/m <sup>3</sup> -year.
Park et al. 2002	<u>Study design</u> : historical cohort study <u>Industry</u> : diatomaceous earth mining and processing <u>Location</u> : California	<u>Cohort</u> : 2,342 white, male workers employed for at least 12 months during 1942–1994, with follow-up through 1994 <u>Adjustments</u> : calendar time, age, smoking, Hispanic ethnicity, time since first observation <u>Statistical analysis</u> : Poisson regression	Cumulative exposure to c-silica dust: - Mean: 2.16 - Maximum: 62.52	Workers diagnosed with silicosis: 70  Excess lifetime risk estimates (per 1,000 workers) for radiographic silicosis increased with increasing dust concentration (mg/m <sup>3</sup> ). Risk estimates were based on the assumption of exposure to a constant respirable c-silica concentration for 45 years.

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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
				<p>Excess lifetime risk (per 1,000 workers) for all cumulative exposures for respirable c-silica concentrations of:</p> <ul style="list-style-type: none"> <li>- 0.001: 6.2</li> <li>- 0.005: 17.0</li> <li>- 0.010: 26.0</li> <li>- 0.020: 39.0</li> <li>- 0.030: 50.0</li> <li>- 0.040: 59.0</li> <li>- 0.050: 68.0</li> <li>- 0.060: 76.0</li> <li>- 0.070: 83.0</li> <li>- 0.080: 90.0</li> <li>- 0.090: 96.0</li> <li>- 0.100: 100.0</li> <li>- 0.200: 150.0</li> </ul> <p>Excess lifetime risk for cumulative exposures &lt;10 mg/m<sup>3</sup>-year for respirable c-silica concentrations of:</p> <ul style="list-style-type: none"> <li>- 0.001: 1.6</li> <li>- 0.005: 7.8</li> <li>- 0.010: 16.0</li> <li>- 0.020: 31.0</li> <li>- 0.030: 46.0</li> <li>- 0.040: 60.0</li> <li>- 0.050: 75.0</li> <li>- 0.060: 89.0</li> <li>- 0.070: 100.0</li> <li>- 0.080: 120.0</li> <li>- 0.090: 130.0</li> <li>- 0.100: 140.0</li> <li>- 0.200: 260.0</li> </ul>

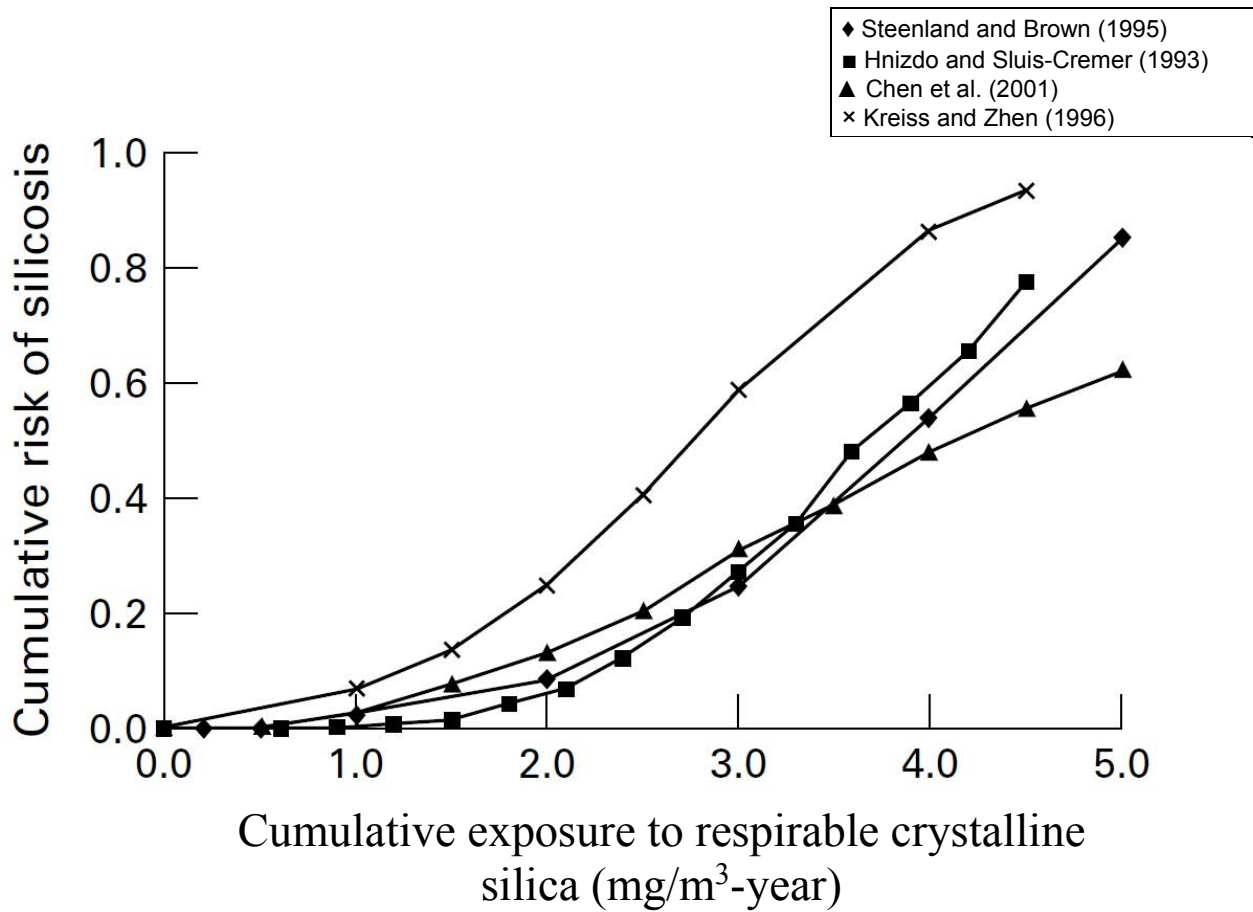
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**Table 3-2. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Steenland and Brown 1995a	<u>Study design:</u> longitudinal retrospective cohort <u>Industry:</u> gold mining <u>Location:</u> South Dakota	<u>Cohort:</u> 3,330 white male underground gold miners employed for at least 1 year during 1940–1965, with follow-up through 1990; average exposure duration: 9 years <u>Adjustments:</u> age, calendar time <u>Statistical analysis:</u> Poisson regression	Cumulative exposure categories (midpoint): - C1: 0–0.2 (0.1) - C2: 0.2–0.5 (0.35) - C3: 0.5–1.0 (0.75) - C4: 1.0–2.0 (1.5) - C5: 2.0–3.0 (2.5) - C6: 3.0–4.0 (3.5) - C7: >4.0	Silicosis cases: 170  Number of silicosis cases/workers in exposure group: - C1: 5/3,330 - C2: 5/1,800 - C3: 15/1,060 - C4: 33/684 - C5: 44/331 - C6: 42/125 - C7: 26/52  Lifetime risk for each exposure category based on a 45-year exposure (first and second numbers of risk range are adjusted and unadjusted risks, respectively): - C1: 0.002 - C2: 0.005 - C3: 0.017–0.022 - C4: 0.060–0.084 - C5: 0.167–0.245 - C6: 0.403–0.534 - C7: 0.678–0.844  Estimated lifetime risk for exposure to 0.09–0.1 mg/m <sup>3</sup> for 45 years: 35–47%

CI = confidence interval; SD = standard deviation; SE = standard error

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**Figure 3-2. Cumulative Risk of Silicosis versus Cumulative Exposure to Respirable Crystalline Silica**

Source: Reproduced from Chen et al. (2001) with permission from BMJ Publishing Group Ltd.



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risks will vary depending on length of follow-up period. Substantially lower risk estimates in a mining cohort were reported by Muir et al. (1989a, 1989b). For example, risks of 1 and 10% were associated with cumulative exposures of 6.1 and 18.7 mg/m<sup>3</sup>-year, respectively. However, it is possible that risks were underestimated due to the lack of a post-employment follow-up period (EPA 1996; NIOSH 2002). A study of a mining cohort published after Chen et al. (2001) showed that the incidence of silicosis significantly increased with cumulative exposure (p for trend <0.001) (Churchyard et al. 2004). For the highest cumulative exposure category of 1.48–3.08 mg/m<sup>3</sup>-year, the incidence of silicosis was 32%.

Similar risks were predicted for a cohort of granite workers, with predicted risks of 6 and 8% for rounded and irregular radiographic opacities, respectively, for a cumulative exposure of 2.0 mg/m<sup>3</sup>-year (Ng and Chan 1994). However, risks in this cohort may have been underestimated because decedents were not included.

In a study of white male diatomaceous earth workers, excess lifetime risk (extrapolated to age 85 years) of silicosis for a 45-year exposure to 0.1 mg/m<sup>3</sup> respirable silica was estimated to be 10% (Park et al. 2002). In a previous study of these workers, Hughes et al. (1998) estimated the risks of silicosis for a cumulative exposure of 2 mg/m<sup>3</sup>-year of 1.1 and 3.7% for exposures to c-silica dust concentrations of <0.5 and >0.5 mg/m<sup>3</sup> respectively. For porcelain workers, risks for silicosis were significantly increased for cumulative exposures of ≥3 mg/m<sup>3</sup>-year (Mundt et al. 2011). For a cumulative exposure range of 4–5 mg/m<sup>3</sup>-year, lagged by 10 years (to account for latency period), the hazard ratio was 4.9 (95% CI 1.5, 15.7) when combining all exposure categories <3.0 mg/m<sup>3</sup> as referent.

The exposure-response data on silicosis reported in the studies above are briefly summarized in Table 3-3. For the lowest cumulative exposure range reported in the available literature (0–0.2 mg/m<sup>3</sup>-year), silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). Churchyard et al. (2004) reported that at a cumulative exposure range of 0–0.8 mg/m<sup>3</sup>-year, 11/520 gold miners were diagnosed with silicosis. In summary, data from morbidity studies consistently demonstrate an exposure-response relationship between cumulative exposure to respirable c-silica and silicosis over a wide range of exposure scenarios in several industries.

Silicosis Mortality: Exposure-Response Data. Progression of silicosis can result in death due to respiratory failure. There is considerable uncertainty regarding the number of annual deaths that occur worldwide due to silicosis. Driscoll et al. (2005) estimated that approximately 8,800 deaths per year occur worldwide due to silicosis. The Global Burden of Disease Study (GBD 2015) estimated that

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**Table 3-3. Summary of Exposure-Response Data for Silicosis Morbidity**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0–0.2	Silicosis cases/exposed workers: 5/3,330
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0–0.80	Silicosis cases/exposed workers: 11/103
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>0-1	Prevalence of silicosis (%): 12.5
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0.2–0.5	Silicosis cases/exposed workers: 5/1,800
Ng and Chan 1994	Granite	Cross-sectional	<0.25	Prevalence of silicosis (%): 0
Ng and Chan 1994	Granite	Cross-sectional	0.25–<1.00	Prevalence of silicosis (%): 0
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	0.3	Silicosis cases/exposed workers: 0/2,218
Chen et al. 2001	Tin mining	Retrospective cohort	<0.36	Silicosis cases/exposed workers: 2/3,010
Chen et al. 2001	Tin mining	Retrospective cohort	0.36–0.72	Silicosis cases/exposed workers: 24/3,010
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>0.5–1.0 (no lag)	HR (95% CI): 0.3 (<0.1–2.6)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>0.5–1.0 (10-year lag)	HR (95% CI): 0.7 (0.1–3.7)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0.5–1.0	Silicosis cases/exposed workers: 15/1,060
Chen et al. 2001	Tin mining	Retrospective cohort	>0.72–1.4	Silicosis cases/exposed workers: 126/3,010
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0.80–0.99	Silicosis cases/exposed workers: 8/97
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	0.9	Silicosis cases/exposed workers: 9/2,014
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0.99–1.24	Silicosis cases/exposed workers: 18/103

## 3. HEALTH EFFECTS

**Table 3-3. Summary of Exposure-Response Data for Silicosis Morbidity**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.0–1.5 (no lag)	HR (95% CI): 0.7 (0.1, 3.8)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.0–1.5 (10-year lag)	HR (95% CI): 0.4 (0.1, 3.7)
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>1–2	Prevalence of silicosis (%): 26.3
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	1.0–2.0	Silicosis cases/exposed workers: 33/684
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>1–≤3	RR (95% CI): 4.35 (1.7, 11.06)
Ng and Chan 1994	Granite	Cross-sectional	1.00–<5.00	Prevalence of silicosis (%): 12.77
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	1.24–1.48	Silicosis cases/exposed workers: 23/104
Chen et al. 2001	Tin mining	Retrospective cohort	>1.4–2.2	Silicosis cases/exposed workers: 127/3,010
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	1.48–3.08	Silicosis cases/exposed workers: 33/103
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	1.5	Silicosis cases/exposed workers: 48/1,540
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.5–3.0 (no lag)	HR (95% CI): 0.4 (0.1, 2.2)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.5–3.0 (10-year lag)	HR (95% CI): 0.5 (0.1, 2.4)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	2.0–3.0	Silicosis cases/exposed workers: 44/331
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>2–3	Prevalence of silicosis (%): 55.6
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	2.1	Silicosis cases/exposed workers: 85/984

## 3. HEALTH EFFECTS

**Table 3-3. Summary of Exposure-Response Data for Silicosis Morbidity**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Park et al. 2002	Diatomaceous earth	Historical cohort	2.16	Silicosis cases/exposed workers: 70/2,342
Chen et al. 2001	Tin mining	Retrospective cohort	>2.2–2.9	Silicosis cases/exposed workers: 196/3,010
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	2.7	Silicosis cases/exposed workers: 93/515
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>3	Prevalence of silicosis (%): 83.3
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>3 (no lag)	HR (95% CI): 3.1 (1.1, 9.3)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>3.0 (10-year lag)	HR (95% CI): 3.7 (1.4, 9.9)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	3.0–4.0	Silicosis cases/exposed workers: 42/125
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>3–≤6	RR (95% CI): 20.13 (8.2, 49.7)
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	3.3	Silicosis cases/exposed workers: 53/197
Chen et al. 2001	Tin mining	Retrospective cohort	>3.6–5.4	Silicosis cases/exposed workers: 141/3,010
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	3.9	Silicosis cases/exposed workers: 20/55
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	>4.0	Silicosis cases/exposed workers: 26/52
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	4.5	Silicosis cases/exposed workers: 5/11
Ng and Chan 1994	Granite	Cross-sectional	5.00–<10.00	Prevalence of silicosis (%): 25.00
Chen et al. 2001	Tin mining	Retrospective cohort	>5.4	Silicosis cases/exposed workers: 155/3,010
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>6	RR (95% CI): 40.37 (16.1, 101.3)
Ng and Chan 1994	Granite	Cross-sectional	>10.00	Prevalence of silicosis (%): 21.67

Ci = confidence interval; HR = hazard ratio; RR = rate-ratio

## 3. HEALTH EFFECTS

55,000 and 46,000 deaths occurred worldwide in 1990 and 2013, respectively. In the United States, 13,744 deaths were attributed to silicosis from 1968 to 1990 and 4,313 deaths were attributed to silicosis from 1979 to 1990 (Beckett et al. 1997; Castranova and Vallyathan 2000). Due to improved industrial hygiene standards and more stringent regulatory standards and guidelines, silicosis mortality trends show a marked decline over the past 50 years (Bang et al. 2008, 2015). In 1965, 1,065 deaths were attributed to silicosis compared to 165 deaths in 2004 (Bang et al. 2015). During the period 2001–2010, silicosis was identified as the underlying or contributing cause of 1,437 deaths, with 164 deaths (death rate: 0.74 per 1 million; 95% CI: 0.62, 0.85) in 2001 and 101 deaths (death rate: 0.39 per 1 million; 95% CI: 0.31, 0.47) in 2010 ( $p$  for trend = 0.002) (Bang et al. 2015). However, silicosis deaths in younger adults (ages 15–44) have not declined since 1995, which may reflect more recent, intense exposures, such as those associated with construction, abrasive blasting, and fracking industries (CDC 1998a, 1998b; Esswein et al. 2013; Mazurek and Attfield 2008).

Cohorts show that silicosis mortality increases with cumulative exposure (Checkoway et al. 1997; Chen et al. 2012; Hedlund et al. 2008; Hughes et al. 2001; McDonald et al. 2005; Park et al. 2002; Vacek et al. 2011). Study details are provided in Table 3-4. Results of these studies show statistically significant exposure-related trends for mortality rate and odds ratios (ORs) for workers exposed to c-silica in the diatomaceous earth, metal and ore mining, granite, pottery, and sand industries. A study of iron ore workers found that silicosis mortality increased with cumulative exposure; at the highest exposure category examined,  $>7$  mg/m<sup>3</sup>-year, the adjusted mortality rate, was 140 deaths per 100,000 person years of exposure (Hedlund et al. 2008). Based on data from a cohort of white male U.S. diatomaceous earth workers, Park et al. (2002) estimated an excess lifetime risk of death from silicosis of 54 per 1,000 (95% CI: 17, 150) for exposure to a c-silica dust concentration of 0.05 mg/m<sup>3</sup> over a working lifetime. As a reference, OSHA (1997) seeks to keep excess lifetime risks of serious disease below 1 per 1,000.

Results and details of pooled analyses on the relationship between c-silica exposure and silicosis mortality are summarized in Table 3-5 (Mannetje et al. 2000a, 2000b).

Mannetje et al. (2002b) conducted a pooled analysis of 65,980 workers from 10 cohorts from the diatomaceous earth, granite, sand, mining, and pottery industries. The risk of death was increased for all exposure levels (range: 4.45–42.33 mg/m<sup>3</sup>-years), with standardized risk ratios ranging from 3.1 (95% CI: 2.5, 4.0) to 4.8 (95% CI: 3.7, 6.2) (Mannetje et al. 2002b). Similar results were observed in a pooled analysis of 18,364 workers from six cohorts from the diatomaceous earth, granite, sand, and mining industries (Mannetje et al. 2002a). Mannetje et al. (2002a) pooled data from six of the cohorts evaluated

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**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Checkoway et al. 1997	<u>Study design:</u> historical cohort study <u>Industry:</u> diatomaceous earth mining and processing <u>Location:</u> California	<u>Cohort:</u> 2,342 white, male workers employed for at least 12 months during 1942–1987, with follow-up through 1994 <u>Adjustments:</u> age, calendar year, duration of follow-up, Hispanic ethnicity <u>Statistical analysis:</u> Poisson regression model	Cumulative exposure for respirable c-silica: - <0.5 (referent) - 0.5–<1.1 - 1.1–<2.1 - 2.1–<5.0 - ≥5.0	SMR for all deaths due to nonmalignant respiratory disease (except infections) was significantly increased. - Number of deaths: 67 - SMR (95% CI): 2.01 (1.56, 2.55).  Deaths due to nonmalignant respiratory disease increased with cumulative exposure. Rate ratios (95% CI) lagged by 0 and 15 years to accommodate disease latency: 0-year lag: - <0.5 (reference): 7 [1] - 0.5–<1.1: 8 [1.52 (0.55, 4.20)] - 1.1–<2.1: 10 [1.98 (0.75, 5.22)] - 2.1–<5.0: 12 [2.34 (0.91, 6.00)] - ≥5.0: 30 [4.79 (2.01, 11.9)] - Trend slope: 1.08 (1.03, 1.13) 15-year lag: - <0.5 (reference): 10 [1] - 0.5–<1.1: 9 [2.04 (0.77, 5.45)] - 1.1–<2.1: 8 [1.96 (0.71, 5.43)] - 2.1–<5.0: 13 [3.17 (1.25, 8.05)] - ≥5.0: 27 [5.35 (2.23, 12.8)] - Trend slope: 1.08 (1.03, 1.14)

## 3. HEALTH EFFECTS

**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Chen et al. 2012	<u>Study design:</u> retrospective cohort study <u>Industry:</u> metal mines (tungsten, iron, copper, tin) and pottery factories <u>Location:</u> China	<u>Cohort:</u> 74,040 workers (85.8% males) employed for at least 12 months during 1960–1974, with follow-up through 2003; control: 24,731; low exposure: 15,438; medium exposure: 16,878; high exposure: 16,993 <u>Adjustments:</u> gender, year of hire, age at hire, type of mine/factory <u>Statistical analysis:</u> Cox proportional hazards regressions	Cumulative c-silica dust exposure: <ul style="list-style-type: none"> <li>- Control: &lt;0.01</li> <li>- Low: 0.01–1.23</li> <li>- Medium: 1.24–4.46</li> <li>- High: &gt;4.46</li> </ul>	HR (95% CI) for death due to nonmalignant respiratory disease (p-value for positive trend: <0.001): <ul style="list-style-type: none"> <li>- Control: 1</li> <li>- Low: 1.89 (1.60, 2.24)</li> <li>- Medium: 4.28 (3.74, 4.91)</li> <li>- High: 6.68 (5.85, 7.61)</li> </ul> HR increase for death due to nonmalignant respiratory disease per 1 mg/m <sup>3</sup> -year increase in cumulative c-silica dust exposure: 1.069 (1.064, 1.074)  SMR (95% CI) for death due to nonmalignant respiratory disease for the period 1970–2003: <ul style="list-style-type: none"> <li>- 2.32 (2.24, 2.40)</li> </ul>

## 3. HEALTH EFFECTS

**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Hedlund et al. 2008	<u>Study design:</u> follow-up mortality study <u>Industry:</u> iron ore mining <u>Location:</u> Sweden	<u>Cohort:</u> 7,729 miners employed for at least 12 months during 1923–1996, with follow-up through 2001; control <u>Adjustments:</u> year of birth and attained age <u>Statistical analysis:</u> Poisson regression	Cumulative exposure quintiles for respirable quartz: - Q1: 0–0.9 (referent) - Q2: 1–2.9 - Q3: 3–4.9 - Q4: 5–6.9 - Q5: >7	Number of deaths from silicosis: 58  Adjusted mortality rate (per 100,000 person-years): - Q1: 18.7 - Q2: 32.8 - Q3: 117 - Q4: 129 - Q4: 140  Study authors stated that “cumulative respirable quartz exposure of approximately 3 mg/m <sup>3</sup> -year and higher is associated with an increased risk of mortality due to silicosis.”



## 3. HEALTH EFFECTS

**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Hughes et al. 2001	<p><u>Study design</u>: nested case referent study</p> <p><u>Industry</u>: industrial sand plants (nine sand-producing plants)</p> <p><u>Location</u>: North America</p>	<p><u>Cohort</u>: (reported in McDonald et al. 2001) 2,670 men; employed before 1980 for at least 3 years with follow-up through 1994</p> <p><u>Adjustments</u>: smoking</p> <p><u>Statistical analysis</u>: conditional logistic regression</p>	<p>Cumulative exposure quartiles for c-silica:</p> <p>For 0-year lag time:</p> <ul style="list-style-type: none"> <li>- Q1: ≤1.5</li> <li>- Q2: 1.5–≤5.0</li> <li>- Q3: &gt;5.0–≤9.0</li> <li>- Q4: &gt;9.0</li> </ul> <p>For 15-year lag time:</p> <ul style="list-style-type: none"> <li>- Q1: ≤0.7</li> <li>- Q2: &gt;0.7–≤1.8</li> <li>- Q3: &gt;1.8–≤5.1</li> <li>- Q4: &gt;5.1</li> </ul>	<p>Deaths from silicosis: 29</p> <p>Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.03, one-tailed) was observed mortality lagged for 15 years.</p> <p>Mortality ORs (95% CI not reported) lagged by 0 and 15 years to accommodate disease latency:</p> <p>0-year lag:</p> <ul style="list-style-type: none"> <li>- Q1: 1</li> <li>- Q2: 1.27</li> <li>- Q3: 2.62</li> <li>- Q4: 2.13</li> </ul> <p>15-year lag:</p> <ul style="list-style-type: none"> <li>- Q1: 1</li> <li>- Q2: 2.54</li> <li>- Q3: 4.55</li> <li>- Q4: 5.16</li> </ul>

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**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
McDonald et al. 2005	<p><u>Study design</u>: historical cohort study with nested case-referent analysis</p> <p><u>Industry</u>: industrial sand plants (eight sand-producing plants)</p> <p><u>Location</u>: United States</p>	<p><u>Cohort</u>: 2,452 male workers employed for at least 3 years, with ≥1 month during 1940–1979, with follow-up through 2000</p> <p><u>Adjustments</u>: case-referent analysis was adjusted for matching and three categories of smoking</p> <p><u>Statistical analysis</u>: SMR: Poisson regression model Case-referent: conditional multiple logistic regression</p>	<p>Cumulative exposure quartiles for c-silica:</p> <p>For 0-year lag time:</p> <ul style="list-style-type: none"> <li>- Q1: ≤1.5</li> <li>- Q2: 1.5–≤5.0</li> <li>- Q3: &gt;5.0–≤9.0</li> <li>- Q4: &gt;9.0</li> </ul> <p>For 15-year lag time:</p> <ul style="list-style-type: none"> <li>- Q1: ≤0.7</li> <li>- Q2: &gt;0.7–≤1.8</li> <li>- Q3: &gt;1.8–≤5.1</li> <li>- Q4: &gt;5.1</li> </ul>	<p>Note: This study is an update of the cohort evaluated in Hughes et al. (2001), with an additional 5-year follow-up period and exclusion of workers from one Canadian plant.</p> <p>Deaths from nonmalignant respiratory disease: 116</p> <p>SMR (nonmalignant respiratory disease): 164 (p&lt;0.001)</p> <p>Deaths from silicosis: 26</p> <p>Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.017, one-tailed) was observed mortality lagged for 15 years.</p> <p>Mortality ORs (95% CI not reported) lagged by 0 and 15 years to accommodate disease latency:</p> <p>0-year lag:</p> <ul style="list-style-type: none"> <li>- Q1: 1</li> <li>- Q2: 0.95</li> <li>- Q3: 3.08</li> <li>- Q4: 1.90</li> </ul> <p>15-year lag:</p> <ul style="list-style-type: none"> <li>- Q1: 1</li> <li>- Q2: 2.20</li> <li>- Q3: 4.34</li> <li>- Q4: 5.45</li> </ul>

## 3. HEALTH EFFECTS

**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Park et al. 2002	<p><u>Study design</u>: historical cohort study</p> <p><u>Industry</u>: diatomaceous earth mining and processing</p> <p><u>Location</u>: California</p>	<p><u>Cohort</u>: 2,342 white, male workers employed for at least 12 months during 1942–1987, with follow-up through 1994</p> <p><u>Adjustments</u>: calendar time, age, smoking, Hispanic ethnicity, time since first observation</p> <p><u>Statistical analysis</u>: Poisson regression model; lifetime risks of death from lung disease other than cancer (LDOC), excluding pneumonia and infectious diseases</p>	<p>Cumulative exposure to c-silica estimated for each worker using historical exposure data and detailed work history files.</p> <p>Mean: 2.16 Maximum: 62.52</p>	<p>Note: This is the same cohort reported in Checkoway et al. (1997), but with an additional 5-year follow-up period.</p> <p>Number of deaths due to LDOC: 67</p> <p>Rate ratio at mean cumulative exposure: 4.2 (p&lt;0.0001)</p> <p>Rate ratio at maximum cumulative exposure: 18.4</p> <p>Rate ratio at a cumulative exposure of 1 mg/m<sup>3</sup>-year: 1.55</p> <p>Excess lifetime risk for white men exposed to 0.05 mg/m<sup>3</sup> for 45 years: 54/1,000 (95% CI: 17, 150)</p>

## 3. HEALTH EFFECTS

**Table 3-4. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Vacek et al. 2011	<u>Study design:</u> historical cohort study <u>Industry:</u> granite industry <u>Location:</u> Vermont	<u>Cohort:</u> 7,052 men employed in the Vermont granite industry from 1947 to 1998 <u>Adjustments:</u> 5-year age group, calendar year <u>Statistical analysis:</u> Poisson regression model	Cumulative exposure quintiles for respirable quartz: - Q1: ≤1.04 (referent) - Q2: 1.05–3.64 - Q3: 3.65–6.71 - Q4: 6.72–10.21 - Q5: >10.21	Number of deaths due to silicosis: 55 SMR (95% CI) for silicosis: 59.13 (44.55, 76.97); p≤0.01 Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.001) was observed. Mortality ORs (95% CI); statistical significant relative to Q1: - Q1: 1 - Q2: 2.02 (0.45, 9.09); p=0.358 - Q3: 8.62 (1.86, 39.95). p=0.006 - Q4: 12.36 (2.67, 57.2); p=0.001 - Q5: 10.55 (2.30, 48.40); p=0.002

CI = confidence interval; HR = hazard ratio; OR = odds ratio; SMR = standardized mortality ratio

## 3. HEALTH EFFECTS

**Table 3-5. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica**

Reference	Cohorts	Methods	Outcomes for pooled cohort
Mannetje et al. 2002a	<u>Six cohorts</u> Checkoway et al. 1997: <ul style="list-style-type: none"> <li>- Diatomaceous earth workers: 2,342</li> <li>- Location: United States</li> <li>- Deaths due to silicosis: 15</li> <li>- Mean exposure duration (years): 4.3</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 1.05</li> </ul> Koskela et al. 1994 <ul style="list-style-type: none"> <li>- Granite workers: 1,026</li> <li>- Location: Finland</li> <li>- Deaths due to silicosis: 14</li> <li>- Mean exposure duration (years): 9.2</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 4.63<sup>a</sup></li> </ul> Costello and Graham 1988 <ul style="list-style-type: none"> <li>- Granite workers: 5,408</li> <li>- Location: United States</li> <li>- Deaths due to silicosis: 43</li> <li>- Mean exposure duration (years): 18.0</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.71<sup>a</sup></li> </ul> Steenland et al. 2001a <ul style="list-style-type: none"> <li>- Industrial sand workers: 40,27</li> <li>- Location: United States</li> <li>- Deaths due to silicosis: 15</li> <li>- Mean exposure duration (years): 3.7</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.13<sup>a</sup></li> </ul> Steenland et al. 1995a <ul style="list-style-type: none"> <li>- Gold miners: 3,348</li> <li>- Location: United States</li> <li>- Deaths due to silicosis: 39</li> <li>- Mean exposure duration (years): 5.4</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.23<sup>a</sup></li> </ul>	<u>Study type:</u> Pooled exposure-response analysis for mortality due to silicosis or unspecified pneumoconiosis  <u>Adjustments:</u> Poisson regression: age, calendar period, original study cohort Nested case-control: age, sex, date of birth, original cohort study  <u>Literature search dates:</u> not reported  <u>Statistical analysis:</u> Poisson regression for standard life table analysis using 10 cumulative exposure categories; conditional logistic regression for nested case-control analysis  <u>Exposure for pooled cohort:</u> <ul style="list-style-type: none"> <li>- Mean exposure duration (years): 10.4</li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.62</li> </ul>	<u>Total number of workers in pooled cohort:</u> 18,364 <u>Deaths due to silicosis:</u> 150 <u>Deaths due to pneumoconiosis:</u> 20 <u>Age of death (range):</u> 32–91 years <u>Silicosis mortality:</u> 28.8 per 100,000 person years  <u>Adjusted mortality rate (per 100,000 person years):</u> <ul style="list-style-type: none"> <li>- 0–0.99: 4.7</li> <li>- 0.99–1.97: 15.9</li> <li>- 1.97–2.87: 29.2</li> <li>- 2.87–4.33: 44.2</li> <li>- 4.33–7.12: 64.3</li> <li>- 7.12–9.58: 106.4</li> <li>- 9.58–13.21: 112.6</li> <li>- 13.21–15.89: 189.2</li> <li>- 15.89–28.10: 118.0</li> <li>- &gt;28.10: 299.1</li> </ul> <u>Adjusted risk ratio (95% CI):</u> <ul style="list-style-type: none"> <li>- 0–0.99: 1.00 (referent)</li> <li>- 0.99–1.97: 3.39 (1.42, 8.08)</li> <li>- 1.97–2.87: 6.22 (2.56, 15.12)</li> <li>- 2.87–4.33: 9.40 (3.71, 23.80)</li> <li>- 4.33–7.12: 13.69 (5.04, 37.18)</li> <li>- 7.12–9.58: 22.64 (7.88, 65.10)</li> <li>- 9.58–13.21: 23.97 (8.05, 71.32)</li> <li>- 13.21–15.89: 40.25 (13.25, 122.3)</li> <li>- 15.89–28.10: 25.11 (8.09, 77.91)</li> <li>- &gt;28.10: 63.63 (19.87, 203.8)</li> </ul>

## 3. HEALTH EFFECTS

**Table 3-5. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica**

Reference	Cohorts	Methods	Outcomes for pooled cohort
	de Klerk and Musk 1998 - Gold miners: 2,213 - Location: Australia - Deaths due to silicosis: 44 - Mean exposure duration (years): 26.8 - Mean cumulative exposure (mg/m <sup>3</sup> -year): 11.37 <sup>a</sup>		<u>Risk ratio (95% CI%) for nested case control analysis based on:</u> - Cumulative exposure (mg/m <sup>3</sup> -year): 1.04 (1.03, 1.06) - Log transformed cumulative exposure (log mg/m <sup>3</sup> -year): 2.08 (1.71, 2.53) - Average exposure over working period (mg/m <sup>3</sup> ): 2.77 (1.80, 4.26) - Exposure duration (years): 1.04 (1.02, 1.06)  <u>Cumulative risk of death for exposure from ages 20 to 65 years for concentrations of:</u> - 0.1 mg/m <sup>3</sup> (equivalent to 4.5 mg/m <sup>3</sup> -year): 13 per 1,000 - 0.05 mg/m <sup>3</sup> (equivalent to 2.25 mg/m <sup>3</sup> -year): 6 per 1,000

## 3. HEALTH EFFECTS

**Table 3-5. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica**

Reference	Cohorts	Methods	Outcomes for pooled cohort
Mannetje et al. 2002b	<p><u>Studies (n=29) by location and industry:</u></p> <ul style="list-style-type: none"> <li>- United States, diatomaceous earth workers (Checkoway et al. 1993, 1996, 1997; Seixas et al. 1997)</li> <li>- Finland, granite workers (Koskela 1995; Koskela et al. 1987a, 1987b, 1994)</li> <li>- United States, granite workers (Costello and Graham 1988; Davis et al. 1983; Eisen et al. 1984; Theriault et al. 1974)</li> <li>- United States, industrial sand workers (Steenland et al. 2001a)</li> <li>- China, pottery workers (Chen et al. 1992; Dosemeci et al. 1993; McLaughlin et al. 1992)</li> <li>- South Africa, gold miners (Hnizdo and Murray 1998; Hnizdo and Sluis-Cremer 1991, 1993; Hnizdo et al. 1997; Page-Shipp and Harris 1972; Reid and Sluis-Cremer 1996)</li> <li>- United States, gold miners (Brown et al. 1986; Steenland and Brown 1995a, 1995b; Zumwalde et al. 1981)</li> <li>- Australia, gold miners (de Klerk and Musk 1998; de Klerk et al. 1995; Hewson 1993)</li> </ul> <p><u>10 occupational cohorts (C) identified from the studies above (number of workers):</u></p> <p>C1: United States, diatomaceous earth workers (2,342)  C2: Finland, granite workers (1,026)  C3: United States, granite workers (5,408)  C4: United States, industrial sand workers (4,027)  C5: China, pottery workers (9,017)  C6: China, tin miners (7,858)  C7: China, tungsten miners (28, 481)  C8: South Africa, gold miners (2,260)  C9: United States, gold miners (3,348)</p>	<p><u>Study type:</u> Pooled exposure-response analysis for mortality due to silicosis, by location and industry</p> <p><u>Literature search dates:</u> not reported</p> <p><u>Adjustments:</u> not reported for overall cohorts</p> <p><u>Statistical analysis:</u> conditional logistic regression</p> <p><u>Exposure:</u> cumulative exposure (mg/m<sup>3</sup>-year; median) quintiles for pooled cohort:  Q1: not reported  Q2: 4.45  Q3: 9.08  Q4: 16.26  Q5: 42.33</p> <p><u>Respirable c-silica (mg/m<sup>3</sup>; median; maximum) by cohort :</u>  C1: 0.18; 2.43  C2: 0.59; 3.60  C3: 0.05; 1.01  C4: 0.04; 0.40  C5: 0.22; 2.10  C6: 0.19; 1.95  C7: 0.32; 4.98  C8: 0.19; 0.31</p>	<p><u>Pooled cohort</u>  Total number of workers: 65,980  OR (95% CI) for quintiles:  - Q1: 1.0  - Q2: 3.1 (2.5, 4.0)  - Q3: 4.6 (3.6, 5.9)  - Q4: 4.5 (3.5, 5.8)  - Q5: 4.8 (3.7, 6.2)</p> <p><u>SRRs and p-value for trend for silicosis mortality for exposure quartiles by cohort:</u>  C1<sup>b</sup>: p&lt;0.001  C2<sup>b</sup>: p&lt;01001  C3:  - Q1: 1.00  - Q2: 2.02  - Q3: 1.23  - Q4: 4.14  - p=0.10  C4:  - Q1: 0  - Q2: 1.22  - Q3: 2.91  - Q4: 7.39  - p&lt;0.00001  C5:  - Q1:34.8  - Q2: 4.13  - Q3: 44.3  - Q4: 77.3  - p&lt;0.0001  C6:  - Q1: 1.62  - Q2: 7.81</p>

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**Table 3-5. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica**

Reference	Cohorts	Methods	Outcomes for pooled cohort
	C10: Australia, gold miners (2,213)	C9: 0.05; 0.24 C10:0.43; 1.55	- Q3: 11.2 - Q4: 6.21 - p=0.05
		<u>Cumulative exposure (mg/m<sup>3</sup>- year; median, maximum) by cohort:</u> C1: 1.05, 62.71 C2: 4.63, 100.98 C3: 0.71, 50.00 C3: 0.13, 8.265 C5: 6.07, 63.16 C6: 5.27, 83.09 C7: 8.56, 232.26 C8: 4.23, 9.28 C9: 0.23, 6.20 C10: 11.37, 50.22	C7: - Q1: 31.6 - Q2: 53.2 - Q3: 73.0 - Q4:69.1 - p=0.02 C8: SRRs could not be calculated because no deaths were coded to silicosis as the underlying cause C9 <sup>b</sup> : p=0.10 C10: - Q1: 1.00 - Q2: 1.97 - Q3: 4.06 - Q4: 4.23 - p<0.001

<sup>a</sup>Exposures were estimated by Mannerje et al. (2002b) (not reported in original publication), based on data provided by the original investigators.

<sup>b</sup>SRRs cannot be calculated as there were no deaths in the lowest exposure quartile; trend test can be conducted.

CI = confidence interval; OR = odds ratio; SRR = standardized rate ratio



## 3. HEALTH EFFECTS

in the Mannetje et al. (2002b) study; however, four cohorts were excluded because of a different classification of disease for silicosis, which included silicosis, pneumoconiosis, and silicotuberculosis. The adjusted silicosis mortality rate increased from 4.7 per 100,000 person years for the lowest (non-referent) exposure category (0–0.99 mg/m<sup>3</sup>-year) to 299.1 per 100,000 person years for the highest exposure category (>28 mg/m<sup>3</sup>-year). The adjusted rate ratio increased with increasing exposure and was significantly increased for all exposure categories, ranging from 3.39 to 63.63 in the 0.99–1.97 and >28 mg/m<sup>3</sup>-year categories, respectively. The study authors estimated risks of death through age 65 for a 45-year exposure to 0.1 and 0.05 mg/m<sup>3</sup> to be 13 per 1,000 and 6 per 1,000, respectively.

Exposure-response data on silicosis mortality reported in the studies discussed above are summarized in Table 3-6. Note that effect estimates in Table 3-6 generally are not comparable to each other, as reference groups differ. At the lowest reported cumulative exposure range of 0.01–1.23 mg/m<sup>3</sup>-year, risk of death due to silicosis in 74,040 metal miners and potters was increased by approximately 90% (hazard ratio [HR]: 1.89; 95% CI: 1.60, 2.24) (Chen et al. 2012). At the next highest cumulative exposure range of 0.5–<1.1 mg/m<sup>3</sup>-year, eight silicosis-related deaths were reported in 2,342 diatomaceous earth workers, although the rate ratio (RR: 1.52 [95% CI: 0.55, 4.20]) did not indicate an increase in risk (Checkoway et al. 1997). Data summarized in Table 3-6 are from several different silica industries and, therefore, it is likely that that differences in study methods, exposure settings, or other external factors may explain risk differences between and within industries. However, overall, these data demonstrate that the risk of death due to silicosis increases with cumulative exposure to respirable c-silica.

In addition to the studies discussed above, numerous studies published since 1987 report significantly increased standardized mortality ratios (SMRs), mortality odds ratios, or hazard ratios for death due to silicosis and associated nonmalignant respiratory diseases, but do not report quantitative cumulative exposure estimates or exposure-response data specifically expressed in terms of mg/m<sup>3</sup>-year (Bang et al. 2008; Brown et al. 1997; Calvert et al. 2003; Checkoway et al. 1993; Chen et al. 1992; Cherry et al. 2013; Chiyotani et al. 1990; Costello et al. 1995; Costello and Graham 1988; deKlerk and Musk 1998; deKlerk et al. 1995; Goldsmith et al. 1995; Koskela et al. 1987b, 1994; Marinaccio et al. 2006; Mehnert et al. 1995; Ng et al. 1990; Steenland and Brown 1995b; Thomas and Stewart 1987; Tse et al. 2007; Ulm et al. 2004; Zambon et al. 1987).

Decreased Lung Function in the Absence of Silicosis. Several studies have shown that occupational exposure to c-silica causes decreases in lung function in workers with no radiographic evidence of silicosis (Ehrlich et al. 2011; Hertzberg et al. 2002; Malmberg et al. 1993; Meijer et al. 2001; Mohner et

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**Table 3-6. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Chen et al. 2012	Metal mining; pottery	Retrospective cohort	0.01–1.23	HR: 1.89 (1.60, 2.24)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	0.5–<1.1 (0 lag time)	Number of deaths: 8/2,342 RR (95% CI): 1.52 (0.55, 4.20)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	0.5–<1.1 (15-year lag)	Number of deaths: 9/2,342 RR (95% CI): 2.04 (0.77, 5.45)
Hughes et al. 2001	Sand plants	Nested case referent	>0.7–≤1.8 (15-year lag)	OR <sup>a</sup> : 2.54
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	0.99–1.97	RR (95% CI): 3.39 (1.42, 8.08)
Vacek et al. 2011	granite	historical cohort study	1.05–3.64	OR: 2.02 (0.45, 9.09); p=0.358
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	1.1–<2.1 (0 lag time)	Number of deaths: 10/2,342 RR (95% CI): 1.98 (0.75, 5.22)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	1.1–<2.1 (15-year lag)	Number of deaths: 8/2,342 RR (95% CI): 1.96 (0.71, 5.43)
Chen et al. 2012	Metal mining	Retrospective cohort	1.24–4.46	HR: 4.28 (3.74, 4.91)
Hughes et al. 2001	Sand plants	Nested case referent	1.5–≤5.0 (0 lag time)	OR <sup>a</sup> : 1.27
Hughes et al. 2001	Sand plants	Nested case referent	>1.8–≤5.1 (15-year lag)	OR <sup>a</sup> : 4.55
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	1.97–2.87	RR (95% CI): 6.22 (2.56, 15.12)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	2.1–<5.0 (0 lag time)	Number of deaths: 12/2,342 RR (95% CI): 2.34 (0.91, 6.00)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	2.1–<5.0 (15-year lag)	Number of deaths: 13/2,342 RR (95% CI): 3.17 (1.25, 8.05)
Park et al. 2002	Diatomaceous earth	Historical cohort	2.16	RR: 4.2 (p<0.0001)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	2.87–4.33	RR (95% CI): 9.40 (3.71, 23.80)
Vacek et al. 2011	granite	historical cohort study	3.65–6.71	OR: 8.62 (1.86, 39.95); p=0.006
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	4.33–7–12	RR (95% CI): 13.69 (5.04, 37.18)

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**Table 3-6. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	4.45	OR (95% CI): 3.1 (2.5, 4.0)
Chen et al. 2012	Metal mining	Retrospective cohort	>4.46	HR: 6.68 (5.85, 7.61)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	≥5.0 (0 lag time)	Number of deaths: 30/2,342 RR (95% CI): 4.79 (2.01, 11.9)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	≥5.0 (15-year lag)	Number of deaths: 27/2,342 RR (95% CI): 5.35 (2.23, 12.8)
Hughes et al. 2001	Sand plants	Nested case referent	>5.0–≤9.0 (0 lag time)	OR <sup>a</sup> : 2.62
Hughes et al. 2001	Sand plants	Nested case referent	>5.1 (15-year lag)	OR <sup>a</sup> : 5.16
Vacek et al. 2011	Granite	historical cohort study	6.72–10.21	OR: 12.36 (2.67, 57.2); p=0.001
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	7.12–9.58	RR (95% CI): 22.64 (7.88, 65.10)
Hughes et al. 2001	Sand plants	Nested case referent	>9.0 (0 lag time)	OR <sup>a</sup> : 2.13
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	9.58–13.21	RR (95% CI): 23.97 (8.05, 71.32)
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	9.08	OR (95% CI): 4.6 (3.6, 5.9)
Vacek et al. 2011	Granite	historical cohort study	>10.21	OR: 10.55 (2.30, 48.40); p=0.002
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	13.21–15.89	RR (95% CI): 40.25 (13.25, 122.3)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	15.89–28.10	RR (95% CI): 25.11 (8.09, 77.91)
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	16.26	OR (95% CI): 4.5 (3.5, 5.8)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	>28.10	RR (95% CI): 63.63 (19.87, 203.8)

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**Table 3-6. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios**

Reference	Industry	Study type	Cumulative exposure (mg/m <sup>3</sup> -year)	Outcome
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	42.33	OR (95% CI): 4.8 (3.7, 6.2)

<sup>a</sup>95% CI not reported.

CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio

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**Table 3-7. Effects of Occupational Exposure to c-Silica on Pulmonary Function in Workers with No Radiographic Evidence of Silicosis**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Ehrlich et al. 2011	<u>Study design:</u> cross-sectional <u>Industry:</u> gold mining <u>Location:</u> South Africa	<u>Cohort:</u> 520 male, black gold miners; 37–60 years of age; mean years of service 21.8 (range: 6.3–34.5); number of workers with no evidence of radiographic silicosis reported <u>Adjustments:</u> smoking, tuberculosis, silicosis <u>Statistical analysis:</u> multivariate analysis	Cumulative respirable quartz (mg/m <sup>3</sup> -year) - Mean (SD): 1.15 (0.44) - Median: 1.13 - Range: 0–3.08  Cumulative respirable dust (mg/m <sup>3</sup> -year): - Mean (SD): 8.2 (2.90) - Median: 7.95 - Range: 0–22.68	For workers without silicosis in this cohort (based on cumulative dust data), for a 30-year exposure to a mean respirable dust concentration of 0.37 mg/m <sup>3</sup> (0.01 mg/m <sup>3</sup> -year), the loss in FVC would be 208 mL (95% CI: 3, 412).
Hertzberg et al. 2002	<u>Study design:</u> cross-sectional <u>Industry:</u> automotive foundry <u>Location:</u> Midwestern United States	<u>Cohort:</u> 1,028 former (mean employment duration: 19.9 years) and current (18.3 years) workers, employed before 1986, with no radiographic evidence of silicosis <u>Adjustments:</u> weight, height, age, ethnicity, smoking status, other c-silica exposure <u>Statistical analysis:</u> logistic regression	Cumulative c-silica exposure quartiles (mg/ m <sup>3</sup> -year; calculated from mg/d/m <sup>3</sup> ): - Q1: <0.66 - Q2: 0.66–2.0 - Q3: >2.0–5.9 - Q4: >5.9	In smokers, but not nonsmokers, percent predicted values for FVC, FEV <sub>1</sub> , and FEV <sub>1</sub> /FVC decreased with increasing exposure. <u>Smokers</u> FVC % predicted (SD): - Q1: 93.47 (11.85) - Q2: 90.54 (15.53) - Q3: 88.83 (13.43) - Q4: 84.36 (18.55) - p-value for trend: 0.0013 FEV <sub>1</sub> % predicted (SD): - Q1: 94.97 (14.85) - Q2: 92.58 (18.75) - Q3: 93.72 (15.88) - Q4: 85.24 (22.67) - p-value for trend: 0.011

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**Table 3-7. Effects of Occupational Exposure to c-Silica on Pulmonary Function in Workers with No Radiographic Evidence of Silicosis**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
				FEV <sub>1</sub> /FVC % predicted (SD): <ul style="list-style-type: none"> <li>- Q1: 77.1 (7.2)</li> <li>- Q2: 77.7 (8.3)</li> <li>- Q3: 77.3 (6.4)</li> <li>- Q4: 70.4 (11)</li> <li>- p-value for trend: 0.0013</li> </ul>
				<u>Nonsmokers</u> FVC % predicted (SD): <ul style="list-style-type: none"> <li>- Q1: 96.31 (10.56)</li> <li>- Q2: 94.1 (10.92)</li> <li>- Q3: 85.41 (23.06)</li> <li>- Q4: 89.89 (10.9)</li> <li>- p-value for trend: 0.1468</li> </ul>
				FEV <sub>1</sub> % predicted (SD): <ul style="list-style-type: none"> <li>- Q1: 108.1 (15.15)</li> <li>- Q2: 100.31 (14.44)</li> <li>- Q3: 91.44 (22.87)</li> <li>- Q4: 97.29 (15.47)</li> <li>- p-value for trend; 0.1037</li> </ul>
				FEV <sub>1</sub> /FVC % predicted (SD): <ul style="list-style-type: none"> <li>- Q1: 79.6 (4.4)</li> <li>- Q2: 81.2 (3.9)</li> <li>- Q3: 76.2 (7.5)</li> <li>- Q4: 79.2 (4.7)</li> <li>- p-value for trend: 0.5696</li> </ul>

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**Table 3-7. Effects of Occupational Exposure to c-Silica on Pulmonary Function in Workers with No Radiographic Evidence of Silicosis**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Malmberg et al. 1993	<u>Study design:</u> longitudinal study with 12-year follow-up <u>Industry:</u> granite industry <u>Location:</u> Sweden	<u>Cohort:</u> 45 granite crushers without pleural plaques and 45 age- and smoking-matched referents; pulmonary function evaluated in 1976 and 1988; mean exposure employment duration in 1988: 22 years <u>Adjustments:</u> none reported <u>Statistical analysis:</u> Wilcoxon's signed rank test, Mann-Whitney U test, multiple regression	Average respirable concentration (mg/m <sup>3</sup> ) 1976–1988: - Dust: 0.83 - c-Silica: 0.18 - Percent c-silica in dust: 23	Statistically significant differences in lung function values (percent predicted mean±SD) were observed for workers compared to referents for the FEV <sub>1</sub> /VC, FEF <sub>50</sub> , and Phase III (slope of alveolar flow). However, differences were very small and not are not likely to represent a clinically significant decrease.  FEV <sub>1</sub> /VC (%): - Referent: 76.2 (6.55) - Worker: 73.0 (9.45) - p-value: <0.01 FEF <sub>50</sub> : - Referent: 5.1 (1.52) - Worker: 4.52 (1.82) - p-value: <0.05 Phase III: - Referent: 1.1 (0.63) - Worker: 1.45 (1.66) - p-value: <0.005

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**Table 3-7. Effects of Occupational Exposure to c-Silica on Pulmonary Function in Workers with No Radiographic Evidence of Silicosis**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Meijer et al. 2001	<u>Study design:</u> cross-sectional <u>Industry:</u> concrete <u>Location:</u> Netherlands	<u>Cohort:</u> 144 concrete workers with no radiographic evidence of silicosis (mean employment duration: 11.3 years) and 110 controls <u>Adjustments:</u> smoking, allergies <u>Statistical analysis:</u> multiple linear regression	Mean (SD) (mg/ m <sup>3</sup> -year) cumulative exposure: 0.566 (0.548)	<p>No statistically significant increases in the prevalence of chronic respiratory symptoms (asthma, cough, phlegm, wheeze, and dyspnea) in workers compared to controls.</p> <p>A statistically significant increase was observed for work-related upper respiratory symptoms (WRURS) and work-related lower respiratory symptoms (WRLRS) for workers compared to controls.</p> <p>Percent with WRURS (SD):</p> <ul style="list-style-type: none"> <li>- Control: 7 (6.4)</li> <li>- Workers: 30 (20.8)</li> <li>- p=0.01</li> </ul> <p>Percent with WRLRS (SD):</p> <ul style="list-style-type: none"> <li>- Control: 4 (3.6)</li> <li>- Workers: 17 (11.8)</li> <li>- p=0.02</li> </ul> <p>A statistically significant (p=0.02) decrease was observed for FEV<sub>1</sub>/FVC (%), although the difference was very small (2.2%) and not likely to be clinically significant. No differences were observed for FVC, FEV<sub>1</sub>, or MMEF.</p> <p>OR (95% CI) for self-reported symptoms of COPD: 11.1 (2.8, 43.5)</p>



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**Table 3-7. Effects of Occupational Exposure to c-Silica on Pulmonary Function in Workers with No Radiographic Evidence of Silicosis**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Mohner et al. 2013a, 2013b	<u>Study design</u> : nest case-control <u>Industry</u> : uranium mine <u>Location</u> : Germany	<u>Cohort</u> : 1,421 uranium miners born between 1954 and 1956 with no radiographic evidence of silicosis (mean employment duration: 12.8 years) <u>Adjustments</u> : smoking <u>Statistical analysis</u> : linear mixed regression	Cumulative exposure groups (EG) for respirable quartz (mg/m <sup>3</sup> -year): - EG1: <0.1412 (referent) - EG2: 0.1412–0.2950 - EG3: 0.2950–0.5660 - EG4: 0.5560–0.9386 - EG5: 0.9386–1.2847 - EG6: >1.2847	ORs (95% CI) for incidence of stage I COPD (based on spirometry): - EG1: 1 - EG2: 1.83 (1.05, 3.19) - EG3: 2.65 (1.54, 4.58) - EG4: 2.47 (1.39, 4.38) - EG5: 1.78 (0.86, 3.69) - EG6: 3.83 (1.93, 7.57)  Cumulative exposure to 1 mg/m <sup>3</sup> -year (respirable quartz) was calculated associated with a 2.75% decrease in FEV <sub>1</sub> /FVC (p<0.001) and an increased OR for COPD (stage I) of 1.81 (95% CI: 1.27, 2.56).

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEF<sub>50</sub> = forced mid-expiratory flow; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; MMEF = maximal mid-expiratory flow; OR = odds ratio; SD = standard deviation; VC = vital capacity

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al. 2013a, 2013b); see Table 3-7 for study details. In general, decrements in lung function are small and, while statistically significant, are of questionable clinical significance. Statistically significant trends ( $p \leq 0.01$ ) were observed for decreased forced vital capacity (FVC), forced expiratory volume in 1 second ( $FEV_1$ ), and  $FEV_1/FVC$  in smokers in an automotive foundry; however, decreases from the lowest ( $< 0.66 \text{ mg/m}^3\text{-year}$ ) to the highest ( $> 5.9 \text{ mg/m}^3\text{-year}$ ) exposure groups were small (approximately 9%). No effects on lung function were observed for nonsmokers in this cohort. In a cohort of granite industry workers, a statistically significant decrease in  $FEV_1/VC$  (vital capacity) was observed in workers compared to referents, although the decrease in workers was only 4% (Malmberg et al. 1993). Similarly, in concrete workers, a 2.2% decrease in  $FEV_1/FVC$  was statistically significant ( $p = 0.02$ ) (Meijer et al. 2001). Based on results of spirometry testing in a cohort of uranium miners, cumulative exposure to  $1 \text{ mg/m}^3\text{-year}$  was associated with a 2.75% decreased in  $FEV_1/FVC$  ( $p < 0.001$ ) and an increased risk of stage I COPD (OR: 1.81; 95% CI: 1.27, 2.56) (Mohner et al. 2013a, 2013b). Other studies showed similar small changes in lung function, although exposure data were not reported (Chia et al. 1992; Eisen et al. 1995).

Chronic Obstructive Pulmonary Disease (COPD). The American Thoracic Society defines COPD as a progressive lung disease involving the airways and/or pulmonary parenchyma, resulting in airflow obstruction that is not fully reversible (Qaseem et al. 2011). It manifests with a wide range of symptoms, including dyspnea, poor exercise tolerance, chronic cough with or without sputum production, and wheezing to respiratory failure or cor pulmonale (Qaseem et al. 2011). A diagnosis of COPD includes respiratory symptoms and airflow obstruction defined as postbronchodilator  $FEV_1:FVC$  ratio of  $< 0.70$  (Qaseem et al. 2011). Chronic obstructive pulmonary disease is associated with an abnormal inflammatory response to inhaled noxious gases, vapors, fumes, cigarette smoke, and respirable particulates, including c-silica (Brüske et al. 2014; Hnizdo and Vallyathan 2003; Qaseem et al. 2011).

Results of several occupational exposure studies show that COPD occurs in the presence and absence of radiological evidence of silicosis (Begin et al. 1995; Brüske et al. 2014; Cowie et al. 1993; Ehrlich et al. 2011; Hertzberg et al. 2002; Hnizdo 1990; Hnizdo and Vallyathan 2003). A recent meta-analysis of six studies (Bakke et al. 2004; Hertzberg et al. 2002; Jorna et al. 1994; Malmberg et al. 1993; Meijer et al. 2001; Ulvestad et al. 2001) evaluated the association between occupational exposure to c-silica and COPD (Brüske et al. 2014). Statistically significant decreases in the mean difference of  $FEV_1$  % predicted (-4.62; 95% CI: -7.17, -2.06) and the standard mean difference in  $FEV_1$  (-0.27; 95% CI: -0.40, -0.14) were observed in workers exposed to c-silica dust compared to workers with “no/low” exposure. The standard mean difference of the  $FEV_1:FVC$  ratio also was significantly decreased in exposed workers

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compared to “no/low” exposure workers (-0.41; 95% CI: -0.54, -0.28). Results of this meta-analysis are consistent with COPD. However, it remains unclear if inhalation of c-silica causes pathological changes in the lungs that lead to the development of COPD or if COPD represents changes that lead to the development of silicosis (Hnizdo and Vallyathan 2003).

Lung Cancer. The association between occupational exposure to respirable c-silica and lung cancer is reviewed in Section 3.2.1.7.

***Amorphous Silica.*** Human data are insufficient to determine whether or not a-silica causes lung disease in humans. Silicosis has not been observed in epidemiological studies in workers with long-term exposure to a-silica with no known exposure to c-silica (Choudat et al. 1990; Plunkett and Dewitt 1962; Volk 1960; Wilson et al. 1979). However, a German case-series study reported silicosis in 4/28 workers exposed to a-silica that was not contaminated by quartz, although contamination by small amounts of cristobalite could not be ruled out (reviewed by Merget et al. 2002). Similarly, Vitums et al. (1977) reported pulmonary fibrosis in 11/40 workers exposed to a-silica dust, characterized by reticular and/or nodular abnormalities in chest radiographs. Numerous occupational studies in the 1930s–1980s reported an increased incidence of pneumoconiosis in diatomaceous earth workers exposed to a-silica; however, the majority of reports indicated that it was exposure to calcined diatomite (which also contains c-silica), rather than raw diatomite, that was associated with pneumoconiosis (Beskow 1978; Caldwell 1958; Cooper and Jacobson 1977; Cooper and Sargent 1984; Dutra 1965; Legge and Rosencrantz 1932; Smart and Anderson 1952; Vigliani and Mottura 1948). No evidence of pneumoconiosis was observed in potato workers exposed to inorganic dusts with high levels of diatomaceous earth and crystalline quartz (~10%) (Jorna et al. 1994).

Reduced pulmonary function has been reported in cross-sectional studies of workers exposed to a-silica; however, exposures to c-silica as well as other inorganic dusts were often present. Evidence for a potential link between a-silica and impaired lung function includes statistically significant ( $p < 0.05$ ) reduced forced expiratory flow volume in factory workers exposed to a-silica dust (Choudat et al. 1990), reduced FVC in grape workers exposed to mixed silica-dust (Gamsky et al. 1992), and reduced forced expiratory flow volume in potato workers exposed to inorganic dusts with high levels of diatomaceous earth and crystalline quartz (~10%) (Jorna et al. 1994). However, neither pulmonary function nor subjective complaints of respiratory symptoms were correlated with a calculated cumulative exposure index in a cohort of 165 workers exposed to a-silica for 1–35 years (Wilson et al. 1979, 1981). Similarly,

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lung function was not impaired in three  $\alpha$ -silica workers diagnosed with pulmonary fibrosis (Vitums et al. 1977).

As reviewed below, available data from animal studies indicate that inhalation exposure to  $\alpha$ -silica induces pulmonary toxicity, including pulmonary inflammation, granuloma formation, increased cellular infiltrates, and reduced lung function. Pulmonary effects observed following exposure to  $\alpha$ -silica are generally reversible and no progressive fibrosis is observed, in contrast to pulmonary effects of  $\gamma$ -silica. Results of acute animal studies also indicate that different polymorphs of  $\alpha$ -silica have different toxicological potencies, with precipitated and pyrogenic  $\alpha$ -silica showing greater toxicity than  $\alpha$ -silica gel and colloidal  $\alpha$ -silica following acute exposure (Arts et al. 2007; Warheit et al. 1995). However, numerous polymorphs of  $\alpha$ -silica exist, each with different surface chemistry properties and, therefore, different biological potencies (see Section 3.5.2 for additional details). In addition, as discussed in Section 4.2, even for the same polymorph, surface chemistry and, thereby, toxicological potency can vary based on production method and degree of hydration.

Acute inhalation studies indicate that exposure to various  $\alpha$ -silica polymorphs leads to inflammatory responses in the rat lung; however, the concentrations at which these effects occur can differ between polymorphs. Elevated biomarkers of cytotoxicity and inflammation in bronchoalveolar lavage fluid, increased lung and tracheobronchial lymph node weights, and mild histopathological changes (accumulation of alveolar macrophages, bronchial/bronchiolar hypertrophy, and/or intra-alveolar granulocytic infiltrates) were observed in Wistar rats following exposure to precipitated or pyrogenic silica at  $\geq 5 \text{ mg/m}^3$  for 5 days (6 hours/day), but effects were only observed following a 5-day exposure to silica gel at  $25 \text{ mg/m}^3$  (Arts et al. 2007). Additionally, minor histopathological lesions (hyperemia and/or macrophage aggregates) persisted after recovery periods of 1–3 months following exposure to precipitated or pyrogenic silica, but not silica gel (Arts et al. 2007). These data indicate that silica gel is less potent than precipitated or pyrogenic silica under the same test conditions. More serious respiratory effects were observed in Wistar rats exposed to fumed hydrophilic silica at  $17 \text{ mg/m}^3$ , fumed hydrophobic silica at  $31 \text{ mg/m}^3$ , or precipitated hydrophobic silica at  $46 \text{ mg/m}^3$  for 2 weeks (6 hours/day, 5 days/week), including respiratory distress, inflammation, pneumonia, granuloma, edema, increased cellularity, and/or increased lung weight (Reuzel et al. 1991). However, relative potency of the different polymorphs cannot be determined from this study, as respiratory effects were observed at the lowest tested concentration for each polymorph; the rationale for different concentration selection was not provided (Reuzel et al. 1991). In CrI:CD BR rats, exposure to colloidal silica for 2 weeks (6 hours/day, 5 days/week) at concentrations  $\geq 50.5 \text{ mg/m}^3$ , but not  $10.1 \text{ mg/m}^3$ , led to significantly elevated biomarkers

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of inflammation in bronchoalveolar lavage fluid; however, these changes were observed following only 3 days of exposure to precipitated silica at  $\geq 10$  mg/m<sup>3</sup> (6 hours/day), suggesting that precipitated silica is more potent than colloidal silica (Warheit et al. 1991, 1995).

Intermediate-duration inhalation studies also reported that exposure to precipitated, fumed, or colloidal  $\alpha$ -silica for 4 or 13 weeks (6 hours/day, 5 days/week) leads to inflammatory responses in the rat lung; however, available studies have limited information regarding direct comparison of potency across different polymorphs. In 4-week studies, colloidal  $\alpha$ -silica led to elevated biomarkers of inflammation in bronchoalveolar lavage fluid, inflammation, and hyperplasia in Crl:DC BR rats at  $\geq 50$  mg/m<sup>3</sup>, but not at 10 mg/m<sup>3</sup> (Lee and Kelly 1992; Warheit et al. 1991, 1995). In a 13-week study in Wistar rats, Reuzel et al. (1991) reported serious respiratory effects at the lowest tested concentrations for each polymorph tested (fumed hydrophilic silica at  $\geq 1$  mg/m<sup>3</sup>, fumed hydrophobic silica at 30 mg/m<sup>3</sup>, and precipitated hydrophobic silica at 30 mg/m<sup>3</sup>). Observed effects for all polymorphs included increased lung weight and histopathological changes including increased cellularity, inflammation, accumulation/aggregation of alveolar macrophages (granulomas), and increased collagen content; however, focal interstitial fibrosis was only observed following exposure to fumed hydrophilic silica (Reuzel et al. 1991). Focal interstitial fibrosis changes and increased collagen content persisted, but not did progress, up to 1 year following exposure to fumed hydrophilic silica at concentrations  $\geq 6$  mg/m<sup>3</sup>; for other polymorphs, increased cellularity, leukocytic infiltration, alveolar macrophage accumulation, and increased collagen content persisted for 13–39 weeks, but recovered by 1 year (Reuzel et al. 1991). Lung inflammation, proliferative responses, and alveolar septal fibrosis were also observed in F344 rats exposed to fumed hydrophilic silica for 13 weeks (6 hours/day, 5 days/week) at 50.4 mg/m<sup>3</sup> (the only concentration tested); these findings decreased during the 8-month recovery period (Johnston et al. 2000).

Chronic-duration studies also show adverse respiratory effects of  $\alpha$ -silica; however, both available studies only utilized a single exposure concentration (precluding a dose-response analysis). Early nodular pulmonary fibrosis, characterized by macrophage and mononuclear cell aggregates and reduced lung function were observed in monkeys exposed to  $\alpha$ -silica (fume, precipitated, or gel) at 15 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months; respirable concentrations were reported as 9.9 mg/m<sup>3</sup> for  $\alpha$ -silica fume, 6.9 mg/m<sup>3</sup> for precipitated  $\alpha$ -silica, and 9.4 mg/m<sup>3</sup> for  $\alpha$ -silica gel (Groth et al. 1981). Collagen fibers were observed in cell aggregates in lungs from monkeys exposed to  $\alpha$ -silica fume, but total lung collagen content was not elevated; no treatment-related changes in lung collagen were observed in monkeys exposed to precipitated  $\alpha$ -silica or  $\alpha$ -silica gel. Pathological changes in the lungs were not observed in rats or guinea pigs similarly exposed for up to 12 months, compared with controls (Groth et

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al. 1981). Another chronic study reported increased lung weights and accumulation of macrophages in alveoli, bronchioles, and lymphoid tissue in rats, guinea pigs, and rabbits exposed to precipitated  $\alpha$ -silica at 126 mg/m<sup>3</sup> for 8 hours/day, 7 days/week for 12–24 months; however, no epithelization or fibrosis were observed (Scheepers 1981). Near-complete reversal of adverse effects was observed during a recovery period of 3–9 months.

**Renal Effects.*****Crystalline Silica.***

Renal Effects Associated with Crystalline Silica Exposure. General information on renal effects associated with exposure to c-silica was taken from the following publications: Beckett et al. (1997); Ghahramani (2010); Goldsmith and Goldsmith (1993); Gomez-Puerta et al. (2013); IARC (1997); NIOSH (2002); Steenland (2005); and Steenland et al. (2002a).

“*Silicon nephropathy*” was first described in the mid-1970s in c-silica-exposed workers with overt silicosis, and was characterized by a wide-spectrum of renal pathologies, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, and glomerulonephritis. During the 1980s, renal damage associated with autoimmune disease was described in c-silica-exposed workers in the absence of silicosis (e.g., ANCA-associated vasculitis; see Section 3.2.1.3 Immunological and Lymphoreticular Effects for more details). Based on these findings, there appears to be two types of c-silica-induced renal disease: (1) caused by direct toxic effect of excessive c-silica accumulation in the kidney, and (2) caused by indirect toxic effects secondary to autoimmune disease (see Section 3.5.2 Mechanisms of Toxicity for more details).

Subsequent to initial case reports of renal disease in c-silica-exposed workers, associations between exposure to c-silica and risk of renal disease have been examined in retrospective and cross-sectional studies (Birk et al. 2009; Boujemaa et al. 1994; Calvert et al. 1997, 2003; Cocco et al. 1994; El-Safty et al. 2003; Fenwick and Main 2000; Hotz et al. 1995; Ibrahim et al. 2011; Koskela et al. 1987b; McDonald et al. 2001, 2005; Millerick-May et al. 2015; Ng et al. 1992, 1993; Rapiti et al. 1999; Rosenman et al. 2000; Steenland and Brown 1995b; Steenland et al. 1990, 1992, 2001b, 2002a, 2002b; Vupputuri et al. 2012; Wyndham et al. 1986). In general, these studies have found increased risk of kidney disease and/or subclinical signs of renal dysfunction in workers exposed to c-silica, and a limited number of studies have found increasing risk in association with increasing cumulative exposure to c-silica. Most of these studies

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have estimated risk in terms of incidence or mortality in the cohort in comparison life table analysis of data from regional or national reference populations. Most studies did not evaluate the potential contribution of other work-related factors to renal disease, including exposure to other nephrotoxicants (e.g., metals), complications from lung disease or silicosis, or differential prevalence of other risk factors (e.g., diabetes, cardiovascular disease, smoking, etc.).

Renal Disease: Incidence and Exposure-Response Data. Studies examining the exposure-relationship between c-silica and incidence of renal disease are summarized in Table 3-8 (Calvert et al. 1997; Rapiti et al. 1999; Steenland et al. 2001b). Calvert et al. (1997) evaluated the exposure-response relationship for renal disease in male gold miners exposed to mean cumulative c-silica dust levels of 0.39 mg/m<sup>3</sup>-year. The overall incidence of end-stage renal disease in this study population was 0.46% (11/2,412 workers). The standardized incidence ratio (SIR) for nonsystemic end-stage renal disease (end-stage renal disease associated with glomerulonephritis or interstitial nephritis) was 4.22 (95% CI: 1.54, 9.18), suggesting a 4-fold greater risk for gold miners compared to the U.S. population. The SIR for all end-stage renal disease was 1.37 (95% CI: 0.68, 2.46). When stratified by exposure duration, the risk of nonsystemic end-stage renal disease was markedly increased (SIR: 7.70; 95% CI: 1.59, 22.48) for workers exposed for <10 years. When stratified by cumulative exposure, the risk of nonsystemic end-stage renal disease was increased for cumulative exposures in the 0.22–<0.55 mg/m<sup>3</sup>-year tertile (SIR: 11.05; 95% CI: 3.01, 28.03), but not for higher (≥0.55 mg/m<sup>3</sup>-year) cumulative exposures. The SIR for all end-stage renal disease was 1.37 (95% CI: 0.68, 2.46). In a population of male ceramic workers, the incidence of end-stage renal disease was 0.21%, with a 3.12-fold (95% CI: 1.17, 6.98) elevated increased risk over the full cumulative exposure range of 0.2–3.8 mg/m<sup>3</sup>-year (Rapiti et al. 1999). However, exposure duration was not consistently associated with increased risk of renal disease. The SIR for end-stage renal disease was increased in a population of industrial sand workers (SIR: 1.97; 95% CI: 1.25, 2.96); however, no trend was observed with increasing exposure (Steenland et al. 2001b).

The remaining exposure-response data for renal disease come from the review of death certificates that list the presence of renal disease at death, whether or not it was the underlying cause of death (see discussion below, “Renal Disease Mortality: Exposure-Response Data”).

Results of a pooled-analysis of three cohorts provide stronger evidence for the increased risk of renal disease in workers exposed to c-silica. Steenland et al. (2002a) analyzed mortality findings from three cohorts in a pooled-cohort analysis of industrial sand workers (Steenland et al. 2001b), gold miners (Steenland and Brown 1995b), and granite workers (Costello and Graham 1988) (Table 3-9). Based on

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**Table 3-8. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure	Outcome
Calvert et al. 1997	<p><u>Study design:</u> retrospective cohort study</p> <p><u>Industry:</u> gold miners</p> <p><u>Location:</u> South Dakota, United States</p>	<p><u>Cohort:</u> 2,412 male miners employed for at least 1 year between 1940 and 1965, who were still alive on January 1, 1977</p> <p><u>Adjustments:</u> see statistical analysis</p> <p><u>Statistical analysis:</u> SIR with U.S. population as the reference. Life-table analysis, which accounts for age, race, sex, and time and calendar intervals for the U.S. population</p>	<p>Mean cumulative c-silica dust exposure (<math>\text{mg}/\text{m}^3\text{-year}</math>): 0.39</p> <p>Cumulative exposure (<math>\text{mg}/\text{m}^3\text{-year}</math>) tertiles for c-silica dust:</p> <ul style="list-style-type: none"> <li>- T1: &lt;0.22</li> <li>- T2: 0.22–&lt;0.55</li> <li>- T3: <math>\geq 0.55</math></li> </ul> <p>Exposure duration tertiles (years):</p> <ul style="list-style-type: none"> <li>- T1: &lt;5</li> <li>- T2: 5–9.9</li> <li>- T3: <math>\geq 10</math></li> </ul>	<p>The SIR for all cases of end-stage renal disease was not increased; however, the SIR for nonsystemic cases (caused by glomerulonephritis or interstitial nephritis) was increased.</p> <p>Total cases</p> <ul style="list-style-type: none"> <li>- Number of cases: 11</li> <li>- SIR (95% CI): 1.37 (0.68, 2.46)</li> </ul> <p>Nonsystemic cases</p> <ul style="list-style-type: none"> <li>- Number of cases: 6</li> <li>- SIR (95% CI): 4.22 (1.54, 9.18)</li> <li>- SIR (95% CI) [number of cases] by exposure tertile: <ul style="list-style-type: none"> <li>T1: 1.27 (0.03, 7.08) [1]</li> <li>T2: 11.05 (3.01, 28.30) [4]</li> <li>T3: 3.68 (0.09, 20.52) [1]</li> </ul> </li> <li>- SIR (95% CI) [number of cases] by duration tertile: <ul style="list-style-type: none"> <li>T1: 2.59 (0.31, 9.36) [2]</li> <li>T2: 3.86 (0.10, 21.50) [1]</li> <li>T3: 7.70 (1.59, 22.48) [3]</li> </ul> </li> </ul>



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**Table 3-8. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure	Outcome
Rapiti et al. 1999	<p><u>Study design:</u> prospective cohort study</p> <p><u>Industry:</u> ceramic workers</p> <p><u>Location:</u> Lazio, Italy</p>	<p><u>Cohort:</u> 2,820 male ceramic workers followed from 1974 to 1991 in a health surveillance program with annual medical examination</p> <p><u>Adjustments:</u> see statistical analysis</p> <p><u>Statistical analysis:</u> SIR with regional disease registry data as the reference. Life-table analysis, which accounts for age, race, sex, and time and calendar intervals for the U.S. population</p>	<p>Range of cumulative c-silica dust exposure in end-stage renal cases (mg/m<sup>3</sup>-year): 0.2–3.8</p>	<p>The SIR for incidence of end-stage renal disease was elevated.</p> <ul style="list-style-type: none"> <li>- Number of cases: 6</li> <li>- SIR (95% CI): 3.21 (1.17, 6.98)</li> <li>- SIR (95% CI) [number of cases] by latency since first exposure: <ul style="list-style-type: none"> <li>&lt;10 years: 25.0 (0.65, 139) [1]</li> <li>10–19 years: 4.65 (1.26, 11.9) [4]</li> <li>20–29 years: N/A [0]</li> <li>≥30 years: 2.85 (0.07, 15.9) [1]</li> </ul> </li> </ul>

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**Table 3-8. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Cumulative exposure	Outcome
Steenland 2005; Steenland et al. 2001b	<u>Study design:</u> historical cohort study <u>Industry:</u> industrial sand workers <u>Location:</u> United States	<u>Cohort:</u> 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure <u>Adjustments:</u> age, race, sex, calendar time <u>Statistical analysis:</u> SMR with U.S. population as the reference; standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m <sup>3</sup> -year): 0.13 <sup>a</sup> Cumulative exposure quartiles for respirable c-silica (mg/m <sup>3</sup> -year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SIR (95% CI) for end-stage renal disease was increased, but did not show an exposure-related trend over exposure quartiles. <ul style="list-style-type: none"> <li>- Number of cases: 23</li> <li>- SIR for whole cohort: 1.97 (1.25, 2.96)</li> <li>- SRR by quartile (number of cases)               <ul style="list-style-type: none"> <li>Q1: 1.00 (2) (referent)</li> <li>Q2: 3.09 (5)</li> <li>Q3: 5.22 (6)</li> <li>Q4: 7.79 (5)</li> </ul> </li> <li>- Slope [change in rate per 1 mg/m<sup>3</sup>-year increase (95% CI)]: 0.00043 (0.00027, 0.00062)</li> </ul> The SIR (95% CI) for glomerular disease was increased: <ul style="list-style-type: none"> <li>- Number of cases: 7</li> <li>- SIR: 3.85 (1.55, 7.93)</li> </ul> Comparative lifetime risks (age 75) for end-stage kidney disease incidence after 45 years of exposure: <ul style="list-style-type: none"> <li>- 0.1 mg/m<sup>3</sup> exposure: 5.1% (95% CI: 3.3, 7.3)</li> <li>- 0.01 mg/m<sup>3</sup> exposure: 0.5% (95% CI: 0.3, 0.8)</li> <li>- Background risk: 2%</li> </ul>

<sup>a</sup>Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; N/A = not applicable; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio

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**Table 3-9. Exposure-Response Analysis for Renal Disease Mortality in a Pooled Cohort of 13,382 Workers**

Cohorts	Methods	Outcomes for pooled cohort
<p><u>Pooled cohort:</u></p> <ul style="list-style-type: none"> <li>- 13,382 workers exposed to c-silica from 3 cohorts (12,783 with exposure data)</li> <li>- Total deaths with renal disease listed as underlying cause: 51 (50 deaths with exposure data)</li> <li>- Total deaths with renal disease listed as underlying or contributory cause: 204 (193 deaths with exposure data)</li> <li>- Mean exposure duration (years): 13.6<sup>a</sup></li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 1.2<sup>a</sup></li> </ul> <p><u>Three cohorts:</u></p> <p>Steenland et al. 2001b</p> <ul style="list-style-type: none"> <li>- Industrial sand workers: 4,027</li> <li>- Location: United States</li> <li>- Deaths due to renal disease (underlying cause): 13</li> <li>- Deaths due to multiple causes (renal disease listed on death certificate): 52</li> <li>- Mean exposure duration (years): 3.7<sup>b</sup></li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.13<sup>b</sup></li> </ul> <p>Steenland and Brown 1995b</p> <ul style="list-style-type: none"> <li>- Gold miners: 3,328</li> <li>- Location: United States</li> <li>- Deaths due to renal disease (underlying cause): 13</li> <li>- Deaths due to multiple causes (renal disease listed on death certificate): 42</li> <li>- Mean exposure duration (years): 5.4<sup>c</sup></li> <li>- Mean cumulative exposure (mg/m<sup>3</sup>-year): 0.23<sup>c</sup></li> </ul> <p>Costello and Graham 1988</p> <ul style="list-style-type: none"> <li>- Granite workers: 5,408</li> <li>- Location: United States</li> <li>- Deaths due to renal disease: Not reported by study authors; determined by Steenland et al. (2002a) via review of death</li> </ul>	<p><u>Cause of death:</u> renal disease (acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, renal sclerosis, and nephritis/nephropathy)</p> <p><u>Cumulative exposure quartiles for respirable c-silica (mg/m<sup>3</sup>-year):</u>  Q1: &lt;0.15 (referent)  Q2: 0.15–&lt;0.55  Q3: 0.55–&lt;1.67  Q4: ≥1.67</p> <p><u>Adjustments:</u> age, race, sex, calendar time</p> <p><u>Statistical analysis:</u> SMR with U.S. population as the reference; conventional life table analyses</p>	<p>The SMR for renal disease as the underlying cause for death was significantly increased in an exposure-related manner:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 50</li> <li>- SMR for whole cohort (95% CI): 1.41 (1.05, 1.85)</li> <li>- SMR by quartile (number of deaths)  Q1: 0.55 (4)  Q2: 0.94 (8)  Q3: 1.17 (10)  Q4: 2.23 (28)  p-value for trend = 0.0007</li> </ul> <p>Deaths due to renal disease increased with increasing cumulative exposure. OR (95% CI) by quartile of cumulative:</p> <ul style="list-style-type: none"> <li>- Q1: 1.00</li> <li>- Q2: 1.88 (0.62, 5.70)</li> <li>- Q3: 1.96 (0.66, 5.84)</li> <li>- Q4: 3.93 (1.31, 11.76)</li> </ul> <p>p-value (linear) = 0.21  p-value (log) = 0.03</p> <p>The SMR for presence of renal disease at death was significantly elevated in an exposure-related manner:</p> <ul style="list-style-type: none"> <li>- Number of cases present at death: 193</li> <li>- SMR for whole cohort (95% CI): 1.28 (1.10, 1.47).</li> <li>- SMR by quartile (number of cases)  Q1: 0.93 (32)  Q2: 0.93 (36)  Q3: 1.51 (52)</li> </ul>

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**Table 3-9. Exposure-Response Analysis for Renal Disease Mortality in a Pooled Cohort of 13,382 Workers**

Cohorts	Methods	Outcomes for pooled cohort
certificates (calculated number not reported) - Mean exposure duration (years): 18.0 <sup>d</sup> - Mean cumulative exposure (mg/m <sup>3</sup> -year): 0.71 <sup>d</sup>		Q4: 1.60 (62) p-value for trend <0.000001 The presence of renal disease at death increased with increasing cumulative exposure. OR (95% CI) by quartile of cumulative exposure: - Q1: 1.00 - Q2: 1.24 (0.77, 2.01) - Q3: 1.77 (1.10, 2.85) - Q4: 2.86 (1.73, 4.72) p-value (linear) = 0.004 p-value (log) = 0.0002  Comparative lifetime risks at age 75 (95% CI) for end-stage kidney disease incidence after 45 years of exposure: - 0.1 mg/m <sup>3</sup> exposure: 1.8% (0.8, 9.7%) - 0.01 mg/m <sup>3</sup> exposure: 0.8% (0.1, 3.4) - Background risk: 0.3%

<sup>a</sup>Mean exposure durations and cumulative exposures were estimated by Steenland et al. (2002a) (not reported in original publication), based on job-exposure matrices data provided by the original investigators for each cohort. Estimated values for each cohort were not reported by Steenland et al. (2002a).

<sup>b</sup>Exposure estimates reported here were calculated by Mannerje et al. (2002a, 2002b) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b).

<sup>c</sup>Exposure estimates reported here were calculated by Mannerje et al. (2002a, 2002b) for Steenland and Brown (1995a, 1995b).

<sup>d</sup>Exposure estimates reported here were calculated by Mannerje et al. (2002a, 2002b) for Costello and Graham (1988).

CI = confidence interval; OR = odds ratio; SMR = standardized mortality ratio

Sources: Steenland et al. (2002a); Steenland (2005)

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SMRs for the entire cohort (exposure range: 0.15– $\geq$ 1.67 mg/m<sup>3</sup>-year), excess mortality due to renal disease was observed (SMR: 1.41; 95% CI: 1.05, 1.47), with a monotonic increase over exposure quartiles (linear trend test;  $p=0.0007$ ). Based on ORs, an increased risk for renal disease as the underlying cause of death was observed in the highest quartile of  $\geq$ 1.67 mg/m<sup>3</sup>-year (OR: 3.93; 95% CI: 1.31, 11.76), but not in quartiles  $<$ 1.67 mg/m<sup>3</sup>-year. Although the log-trend value across quartiles for renal disease as the underlining cause of death was statistically significant ( $p=0.03$ ), the  $p$ -value for linear trend was not significant ( $p=0.21$ ). For the presence of renal disease at death (multiple cause), a positive linear trend was observed for SMRs across the exposure range (linear trend test;  $p<0.000001$ ). Based on ORs across quartiles, the presence of renal disease at death was increased in the 0.55– $<$ 1.67 mg/m<sup>3</sup>-year quartile (OR: 1.77; 95% CI: 1.10, 2.86) and the  $\geq$ 1.67 mg/m<sup>3</sup>-year quartile (OR: 2.86; 95% CI: 1.73, 4.72); positive trends were observed by both linear ( $p=0.004$ ) and log ( $p=0.0002$ ) trend analyses. Results of this study suggest that exposure to c-silica is associated with increased risk of death from renal disease. Based on the pooled data, comparative lifetime risks (age 75) for death from chronic end-stage renal disease after 45 years of exposure were estimated to be 0.8% (95% CI: 0.1, 3.4%) at 0.01 mg/m<sup>3</sup> and 1.8% (95% CI: 0.8, 9.7%) at 0.1 mg/m<sup>3</sup> (background risk: 0.3%) (Steenland 2005; Steenland et al. 2002a).

In addition to the studies discussed above, other studies reported statistically significant increased incidence, SIRs, or ORs for renal disease in c-silica-exposed workers, but did not report quantitative cumulative exposure estimates or exposure-response data (Fenwick and Main 2000; Steenland et al. 1990, 1992; Vupputuri et al. 2012). However, SIRs were not statistically significant for increased end-stage renal disease in a cohort of individuals diagnosed with silicosis from a silicosis registry (Steenland et al. 2002b) or for chronic pyelonephritis in a cohort of male granite workers (Koskela et al. 1987b).

Impaired Renal Function. Several cross-sectional studies provide evidence that occupational exposure to c-silica can lead to subclinical signs of renal dysfunction; however, exposure levels were not reported in these studies (Boujemaa et al. 1994; El-Safty et al. 2003; Hotz et al. 1995; Ibrahim et al. 2011; Millerick-May et al. 2015; Ng et al. 1992, 1993; Rosenman et al. 2000). Statistically significant ( $p<0.05$ ) alterations observed in exposed workers from various industries (e.g., granite quarry workers, ceramic and glass workers, and miners), compared with unexposed or low-exposed referents, include increased urinary excretion of albumin, transferrin,  $\alpha$ -1-microglobulin (AMG), and retinol-binding protein, elevated serum creatinine levels, and/or altered urinary  $\beta$ -N-acetyl-glucosaminidase (NAG) activity (Boujemaa et al. 1994; El-Safty et al. 2003; Hotz et al. 1995; Ibrahim et al. 2011; Ng et al. 1992, 1993; Rosenman et al. 2000). These effects have been observed in exposed workers with silicosis (Boujemaa et al. 1994; El-Safty et al. 2003; Ng et al. 1992; Rosenman et al. 2000) as well as in workers without silicosis (El-Safty

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et al. 2003; Hotz et al. 1995; Ibrahim et al. 2011; Ng et al. 1992;). However, two studies reported a lack of correlation between severity of silicosis and the measures of renal function listed above (Boujemaa et al. 1994; Rosenman et al. 2000). Results of these studies suggest that renal damage may occur prior to, and independently of, the development of silicosis.

Renal Disease Mortality: Exposure-Response Data. Several studies have evaluated risk of death from renal disease in c-silica-exposed workers; see study details in Table 3-10 (McDonald et al. 2005; Steenland and Brown 1995b; Steenland et al. 2001b). Steenland et al. (2001b) reported a 2.22-fold (95% CI: 1.06, 4.08) increase in the number of deaths from chronic kidney disease in industrial sand workers exposed to a mean cumulative exposure of 0.13 mg/m<sup>3</sup>-year (exposure levels estimated by Mannetje et al. 2002b). A positive trend was observed for acute renal disease (slope [change in disease rate per 1 mg/m<sup>3</sup>-year increase in exposure]: 0.00007; 95% CI: 0.00003, 0.00012), but not chronic renal disease. The risk of death from acute kidney disease was not elevated in this cohort (Steenland et al. 2001b). Similarly, a study of industrial sand workers reported a significant 2.8-fold increase (p<0.001) in deaths due to nephritis/nephrosis (McDonald et al. 2005). In gold miners exposed to a mean cumulative exposure of 11.37 mg/m<sup>3</sup>-year, there was no significant increase in the SMR for death due to either acute or chronic kidney disease; however, the SMRs for death due to chronic renal disease showed statistically significant (p≤0.05) associations with increased cumulative dust exposure (Steenland and Brown 1995b; exposure levels estimated by Mannetje et al. 2002b). Findings from these studies are not consistent and are difficult to compare due to different study designs, follow-up periods, and categorization of renal disease at death. Several other studies without quantitative exposure data have evaluated SMRs due to nonmalignant renal diseases. Increased SMRs and/or mortality odds ratios were reported in industrial sand workers, and gold, lead, and zinc miners (Cocco et al. 1994; McDonald et al. 2001; Wyndham et al. 1986). However, SMRs were not increased in pottery workers (Birk et al. 2009), granite cutters (Steenland et al. 1992), or workers from various industries categorized as having high or very-high c-silica exposure (Calvert et al. 2003).

Steenland et al. (2002a) evaluated mortality due to renal disease in a pooled analysis of 13,382 workers from three cohorts of industrial sand workers (Steenland et al. 2001b), gold miners (Steenland and Brown 1995b), and granite workers (Costello and Graham 1988); study details are summarized in Table 3-9. SMRs were estimated based on life table analysis of data from the U.S. population. For the entire cohort (exposure range: 0.15–≥1.67 mg/m<sup>3</sup>-year), increased risks were observed for renal disease as the underlying cause of death (SMR: 1.41; 95% CI: 1.05, 1.85). Examined by exposure quartiles, the risk of death due to renal disease was increased in the highest exposure quartile (≥1.67 mg/m<sup>3</sup>-year; OR: 3.93;

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**Table 3-10. Renal Disease Mortality in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
McDonald et al. 2005	<p><u>Study design:</u> historical cohort study with nested case-referent analysis</p> <p><u>Industry:</u> industrial sand workers</p> <p><u>Location:</u> United States (five states)<sup>a</sup></p>	<p><u>Cohort:</u> 2,452 male workers employed in eight plants for at least 3 years, working for <math>\geq 1</math> month during 1940–1979, with follow-up through 2000</p> <p><u>Cases:</u> 18 individuals that died from renal disease</p> <p><u>Referents:</u> two referents were identified for each case from cohort members employed at the same plant, born within 5 years (3 years if possible) of the case, first hired within 5 years (3 years if possible) of the case, and who survived the case</p> <p><u>Adjustments:</u> case-referent analysis was adjusted for matching</p> <p><u>Statistical analysis:</u> Poisson regression model (SMR); conditional multiple logistic regression (case-referent)</p>	<p>Cumulative exposure (mg/m<sup>3</sup>-year) for respirable c-silica:</p> <ul style="list-style-type: none"> <li>- <math>\leq 1</math> (referent)</li> <li>- <math>1-\leq 1.5</math></li> <li>- <math>1.5-\leq 5</math></li> <li>- <math>&gt;5</math></li> </ul>	<p>The SMR for all deaths due to nephritis/nephrosis showed a statistically significant increase:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 18</li> <li>- SMR: 2.8 (<math>p &lt; 0.001</math>)</li> </ul> <p>Deaths due to nephritis/nephrosis did not show statistically significant increases with cumulative exposure. Adjusted ORs (lagged by 0 and 15 years to accommodate disease latency):</p> <p>0-year lag</p> <ul style="list-style-type: none"> <li>- <math>\leq 1</math> (referent): 1.00</li> <li>- <math>&gt;1-\leq 1.5</math>: 0.61</li> <li>- <math>&gt;1.5-\leq 5</math>: 0.16</li> <li>- <math>&gt;5</math>: 0.16</li> </ul> <p>15-year lag</p> <ul style="list-style-type: none"> <li>- <math>\leq 0.3</math> (referent): 1.00</li> <li>- <math>&gt;0.3-\leq 1.2</math>: 0.79</li> <li>- <math>&gt;1.2-\leq 4</math>: 0.19</li> <li>- <math>&gt;4</math>: 0.19</li> </ul>

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**Table 3-10. Renal Disease Mortality in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Steenland and Brown 1995b	<p><u>Study design:</u> historical cohort study</p> <p><u>Industry:</u> gold miners</p> <p><u>Location:</u> South Dakota, United States</p>	<p><u>Cohort:</u> 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years)</p> <p><u>Adjustments:</u> see statistical analysis</p> <p><u>Statistical analysis:</u> life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with <math>\chi^2</math> tests</p>	<p>Median cumulative exposure (<math>\text{mg}/\text{m}^3\text{-year}</math>): 0.23<sup>b</sup></p>	<p>The SMRs for kidney disease were not elevated.</p> <p>Acute kidney disease:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 2</li> <li>- SMR (95% CI): 1.19 (0.14, 4.29)</li> </ul> <p>Chronic kidney disease:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 11</li> <li>- SMR (95% CI): 1.25 (0.62, 2.23)</li> </ul> <p>The SMRs for chronic renal disease showed statistically significant increases with increased cumulative dust exposure (dust-days)<sup>c</sup>:</p> <ul style="list-style-type: none"> <li>- &lt;8,000: 0.40</li> <li>- 8,000–&lt;32,000: 0.34</li> <li>- 32,000–&lt;48,000: 1.26</li> <li>- <math>\geq 48,000</math>: 2.77</li> </ul> <p><math>\chi^2=7.62</math> <math>p\leq 0.05</math></p>



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**Table 3-10. Renal Disease Mortality in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Steenland et al. 2001b	<p><u>Study design:</u> historical cohort study</p> <p><u>Industry:</u> industrial sand workers</p> <p><u>Location:</u> United States (11 states)</p>	<p><u>Cohort:</u> 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 with adequate work histories to estimate exposure</p> <p><u>Adjustments:</u> age, race, sex, calendar time</p> <p><u>Statistical analysis:</u> standard life-table analysis</p>	<p>Mean cumulative exposure to respirable c-silica (mg/m<sup>3</sup>-year): 0.13<sup>d</sup></p> <p>Cumulative exposure quartiles for respirable c-silica (mg/m<sup>3</sup>-year):</p> <p>Q1: &lt;0.10 (referent)</p> <p>Q2: 0.10–&lt;0.51</p> <p>Q3: 0.51–&lt;1.28</p> <p>Q4: ≥1.28</p>	<p>The SMRs for chronic, but not acute, kidney disease were elevated.</p> <p>Acute kidney disease:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 3</li> <li>- SMR (95% CI): 3.37 (0.70, 9.86)</li> <li>- A positive trend over exposure quartiles: Slope [change in rate per 1 mg/m<sup>3</sup>-year increase (95% CI)]: 0.00007 (0.00003, 0.00012)</li> </ul> <p>Chronic kidney disease:</p> <ul style="list-style-type: none"> <li>- Number of deaths: 10</li> <li>- SMR (95% CI): 2.22 (1.06, 4.08)</li> <li>- No trend over exposure quartiles: slope [change in rate per 1 mg/m<sup>3</sup>-year increase (95% CI)]: 0.00043 (0.00027, 0.00062)</li> </ul>

<sup>a</sup>States were identified in the companion study (McDonald et al. 2001).

<sup>b</sup>Exposures were estimated by Mannerje et al. (2002a, 2002b) (not reported in original publication), based on data provided by the original investigators.

<sup>c</sup>One dust-day is 1 day with an exposure of 1 mmpcf dust; 10 mmpcf of respirable dust = 0.1 mg c-silica/m<sup>3</sup>.

<sup>d</sup>Exposures were not reported in the original publication; however, they were estimated by Mannerje et al. (2002a, 2002b) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; mmpcf = millions of particles per cubic foot of air; OR = odds ratio; SMR = standardized mortality ratio

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95% CI: 1.31, 11.76). Over all exposure quartiles, a positive exposure trend was observed for renal disease as the underlying cause of death ( $p=0.0007$ ).

***Amorphous Silica.*** No studies evaluating renal effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in kidney clinical chemistry were observed in rats exposed to colloidal a-silica at concentrations up to 150 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 4 weeks (Lee and Kelly 1992). No treatment-related changes in kidney clinical chemistry, organ weight, or histology were observed in rats exposed to fumed or precipitated a-silica at 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). Similarly, no changes in renal clinical chemistry or histology were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

#### **Gastrointestinal Effects.**

***Amorphous Silica.*** No studies evaluating gastrointestinal effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in gastrointestinal histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991) or monkeys exposed to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

#### **Hematological Effects.**

***Amorphous Silica.*** No studies evaluating hematological effects in humans following inhalation exposure to a-silica were identified.

A significant 2–3-fold increase in neutrophil counts and slight increases in hemoglobin, packed cell volume, and erythrocyte counts were observed in rats exposed to fumed a-silica at 30 mg/m<sup>3</sup> for 13 weeks (6 hours/day, 5 days/week), compared with controls, but not at concentrations  $\leq 6$  mg/m<sup>3</sup>; after a 3-month recovery period, hematological parameters no longer differed from controls (Reuzel et al. 1991). Other

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acute- and intermediate-duration studies reported hematological changes following exposure to a-silica, including increased hemoglobin, packed cell volume, and erythrocyte count in rats exposed to fumed or precipitated a-silica at  $\geq 87$  mg/m<sup>3</sup> for 2 weeks (Reuzel et al. 1991) and increased mean neutrophil count and hemoglobin levels and decreased mean lymphocyte count in rats exposed to colloidal a-silica at 150 mg/m<sup>3</sup> for 4 weeks (Lee and Kelly 1992); however, the biological relevance of the findings could not be assessed due to the absence of quantitative data reporting.

In a chronic study, rabbits exposed to precipitated a-silica at a concentration of 126 mg/m<sup>3</sup> for 8 hours/day, 7 days/week for 12 months showed a 22% increase in erythrocyte counts, a 40% increase in hemoglobin levels, and a 12% increase in packed cell volume, compared with controls (Schepers 1981). Increased levels persisted to some degree after a 12-month recovery period. These findings are consistent with an adaptive response to observed cardiopulmonary distress in exposed rabbits, rather than evidence of an adverse hematological response to silica exposure. No treatment-related changes in hematological parameters were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

#### **Musculoskeletal Effects.**

*Amorphous Silica.* No studies evaluating musculoskeletal effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in skeletal muscle histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991)

#### **Hepatic Effects.**

*Amorphous Silica.* No studies evaluating hepatic effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in liver clinical chemistry were observed in rats exposed to colloidal a-silica at concentrations up to 150 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 4 weeks (Lee and Kelly 1992). No treatment-related changes in liver clinical chemistry, organ weight, or histology were observed in rats exposed to fumed or precipitated a-silica at 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel

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et al. 1991). Similarly, no changes in liver clinical chemistry or histology were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

**Endocrine Effects.**

*Amorphous Silica.* No studies evaluating endocrine effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in adrenal weight or endocrine organ histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No changes in adrenal, thyroid, or pancreas histology were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

**Dermal Effects.**

*Amorphous Silica.* No studies evaluating dermal effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in skin histology were observed rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991) or in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

**Ocular Effects.**

*Amorphous Silica.* No studies evaluating ocular effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in eye histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

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**Body Weight Effects.**

*Amorphous Silica.* No studies evaluating body weight effects in humans following inhalation exposure to a-silica were identified.

In concentration range-finding studies, decreased body weight gain was observed in rats exposed to a-silica 6 hours/day, 5 days/week at concentrations as low as 44 mg/m<sup>3</sup> for 2 weeks, compared with controls (Reuzel et al. 1991); however, the biological significance of these findings is unclear as the magnitude of effect was not reported. In other studies, no body weight effects were observed in rats exposed for 6 hours/day, 5 days/week at concentrations up to 25 mg/m<sup>3</sup> pyrogenic, precipitated, or gel a-silica for 1 week (Arts et al. 2007), 150 mg/m<sup>3</sup> colloidal a-silica for 4 weeks (Lee and Kelly 1992), 30 mg/m<sup>3</sup> fumed or precipitated a-silica for 13 weeks (Reuzel et al. 1991), or up to 9.9 mg/m<sup>3</sup> fumed, precipitated, or gel a-silica for up to 18 months (Groth et al. 1981).

**3.2.1.3 Immunological and Lymphoreticular Effects***Crystalline Silica.*

Autoimmune Disorders Associated with Crystalline Silica Exposure: Pathologic Features and Clinical Presentation. Unless otherwise noted, information in the following section is from the following reviews and meta-analyses: Beckett et al. (1997); Deane and El-Gabalawy (2014); Demoruelle et al. (2014); Ghahramani (2010); Gibelin et al. (2011); Gomez-Puerta et al. (2013); Hinchcliff and Varga (2008); Hogan et al. (2001); Iannello et al. (2002); IARC (1997); Lee et al. (2012, 2014); Maeda et al. (2010); Manson and Rahman (2006); McCormic et al. (2010); NIOSH (2002); Otsuki et al. (2007); Parks et al. (1999); Steenland and Goldsmith (1995); Stratta et al. (2001a); Thomeer et al. (2005); and Wu and Schiff (2004).

No immune disorders are uniquely associated with exposure to c-silica. However, a link between c-silica exposure and autoimmune disease has been proposed since the late 1950s. Since the late 1960s, numerous retrospective cohort and case-control studies have evaluated potential associations between c-silica exposure and a wide spectrum of autoimmune disorders, including systemic sclerosis (scleroderma), rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis (Bartunkova et al. 2006; Beaudreuil et al. 2005; Bovenzi et al. 1995, 2004; Brown et al. 1997; Burns et al. 1996; Calvert et al. 2003; Conrad et al. 1996; Cooper et al. 2010; Cowie 1987; Diot et al. 2002; Englert et

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al. 2000; Finckh et al. 2006; Gold et al. 2007; Gregorini et al. 1993; Hogan et al. 2001; Klockars et al. 1987; Lacey et al. 1997; Koskela et al. 1987b; Makol et al. 2011; Maitre et al. 2004; Marie et al. 2014; Nuyts et al. 1995; Rafnsson et al. 1998; Rihova et al. 2005; Rodnan et al. 1967; Rosenman and Zhu 1995; Rosenman et al. 1999; Silman and Jones 1992; Sluis-Cremer et al. 1985, 1986; Steenland and Brown 1995b; Steenland et al. 1992, 2001b; Stolt et al. 2005, 2010; Stratta et al. 2001b; Turner and Cherry 2000; Walsh 1999). In general, results of these studies indicate that c-silica-exposed workers, some with other risk factors for autoimmune diseases (e.g., genetic predisposition, other chemical exposures), may be at increased risk for developing general autoimmunity, although data for each specific disease are inadequate to determine a clear exposure-response relationship. There is some evidence that observed autoimmunity may be a complication of silicosis, but autoimmunity may occur subsequent to direct toxic effects of excessive c-silica accumulation in the lymphatic system (see Section 3.5.2 Mechanisms of Toxicity for more details). It is important to note that mortality studies underestimate the prevalence of nonlethal disorders, and occupational cohort studies are often too small to accurately estimate the risk of rare diseases, such as autoimmune disorders. Thus, quantitative risk estimates should be interpreted with caution. Brief descriptions of autoimmune diseases potentially associated with c-silica exposure are listed below.

*Systemic sclerosis (SSc).* SSc is a multisystem disease of unknown etiology, but hypothesized causes include genetic, autoimmune, and environmental factors. Certain SSc subtypes have been associated with specific autoantibodies, including antinuclear antibody, anticentromere antibody, and antitopoisomerase-1 antibody. The disease is characterized by tissue thickening and fibrosis throughout the body. The most common clinical manifestations of the disease are scleroderma (hardening of the skin) and Raynaud phenomenon (recurrent vasospasm typically in the distal extremities). Fibrosis can also cause various types of internal organ dysfunction, which can be life threatening, such as decreased pulmonary function and pulmonary arterial hypertension. Other clinical signs include musculoskeletal complaints (arthralgia, myalgia, contractures), gastrointestinal complaints (reflux, intestinal dysmotility), and abnormal cardiac conduction. The estimated prevalence of SSc in the United States is 0.0009–0.03% (Hemlick et al. 2008; Hinchcliff and Varga 2008; Makol et al. 2011; Rosenman et al. 1999). Reported incidence of SSc in retrospective cohorts of c-silica-exposed workers ranges from 0.02 to 17% (Brown et al. 1997; Calvert et al. 2003; Gold et al. 2007; Makol et al. 2011; Rosenman et al. 1999; Walsh 1999).

*Rheumatoid arthritis (RA).* RA is an autoimmune disease characterized by systemic inflammation, with the hallmark of the disease being joint inflammation (synovitis) leading to progressive arthritic symptoms. Other tissues with inflammation associated with RA include the oral mucosa, pulmonary, and

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gastrointestinal tissues. RA is associated with specific autoantibodies, including rheumatoid factor and anti-citrullinated peptide antibody (ACPA). The etiology is unknown, but multiple genetic, epigenetic, and environmental risk factors have been proposed. The estimated prevalence of RA in the general U.S. population is 0.6–1.85%; in older adults ( $\geq 60$  years of age), the estimated prevalence increases to 2.00–2.34% (Hemlick et al. 2008; Makol et al. 2011; Rasch et al. 2003; Rosenman et al. 1999). Reported incidences of RA in cohorts of workers exposed to c-silica range from 0.4 to 5.2% (Brown et al. 1997; Klockars et al. 1987; Koskela et al. 1987b; Makol et al. 2011; Rosenman and Zhu 1995; Rosenman et al. 1999; Steenland et al. 2001b; Turner and Cherry 2000).

*Systemic lupus erythematosus (SLE)*. SLE is an autoimmune disease that causes systemic inflammation. It is characterized by the presence of the antinuclear autoantibody. The etiology is unknown, but multiple genetic, epigenetic, and environmental risk factors have been proposed. Since it is a multi-system disease, clinical presentation often varies between patients. Common symptoms include a classic “malar” rash (fixed erythema over the malar eminences, tending to spare the nasolabial folds), a discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological (psychological) disorder, hematological disorder, and/or general symptoms of fatigue, weight loss, and fever. The estimated prevalence of SLE in the general U.S. population is 0.02–0.05% (Hemlick et al. 2008; Rosenman et al. 1999; Ward 2004). Estimates vary based on gender and race, with higher estimates for women (0.1% for white and Hispanic women and 0.4% for black women) compared with men (0.01 for white men and 0.05% for black men) (Hemlick et al. 2008; Makol et al. 2011; Ward 2004). Reported incidence of SLE in cohorts of c-silica-exposed workers ranges from 0.2 to 0.9% (Conrad et al. 1996; Makol et al. 2011; Rosenman et al. 1999).

*ANCA-associated vasculitis (AAV)*. Vasculitides associated with serum positivity for ANCA are autoimmune disorders that affect blood vessels systemically. The most commonly associated diseases include granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). These diseases are clinically associated with lung involvement, including diffuse alveolar hemorrhage (which can be lethal), parenchymal nodules and masses (in GPA), asthma and eosinophilic pneumonia (in CSS), or interstitial lung disease (in MPA). These diseases are often associated with renal damage (glomerulonephritis) as well, including focal glomerular necrosis and crescent formation. The estimated prevalences of GPA and vasculitis (not specified) in the United States are 0.003 and 0.03%, respectively (Gibelin et al. 2011; Makol et al. 2011). Prevalence of AAV in c-silica-exposed workers who were diagnosed with silicosis ranged from 0.8 to 2.23% (Makol et al. 2011).

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*Sarcoidosis.* Sarcoidosis is a systemic granulomatous disease of unknown etiology, but hypothesized causes include genetic, autoimmune, and environmental factors. It is proposed that genetically susceptible individuals exposed to unknown environmental triggers may develop an exaggerated inflammatory immune response. Sarcoidosis predominantly affects the lungs, although granulomas can also occur in skin, eyes, heart, liver, spleen, salivary glands, muscles, bones, kidneys, and central nervous system. It is characterized by noncaseating epithelioid granulomas that cannot be attributed to other granulomatous diseases. Patients with sarcoidosis often present with generalized symptoms (fever, fatigue, weight loss, malaise, myalgia, lymphadenopathy) as well as symptoms specific to affected organs (e.g., skin lesions, vision impairment, coughing, reduce lung function, arrhythmias, neuropathy, renal dysfunction). The estimated prevalence of sarcoidosis in the United States is 0.005–0.3% (Thomeer et al. 2005). Prevalence or incidence of sarcoidosis in c-silica-exposed workers has not been reported.

Autoimmune Disease: Incidence and Exposure-Response Data.

*Systemic sclerosis/scleroderma (SSc).* Two studies providing exposure data have evaluated the risk of SSc in c-silica-exposed workers (Steenland and Brown 1995b; Steenland et al. 2001b); however, these studies are of limited usefulness based on methods of analysis (e.g., grouping SSc with related disorders). Study details are provided in Table 3-11. In gold miners exposed to mean cumulative respirable c-silica levels of 11.37 mg/m<sup>3</sup>-year, the incidences of “other musculoskeletal diseases” and “other diseases of the skin” at death (including SSc) were increased by 2.14-fold (95% CI: 1.03, 3.94) and 2.45-fold (95% CI: 1.17, 4.51), respectively (Steenland and Brown 1995b; exposure estimates calculated by Mannetje et al. 2002b). However, the incidence of SSc, specifically, was not reported or analyzed. In industrial sand workers exposed to lower cumulative levels of respirable c-silica (0.13 mg/m<sup>3</sup>-year), the incidence of “other musculoskeletal diseases” (including SSc) was not increased (Steenland et al. 2001b; exposure estimates calculated by Mannetje et al. 2002b).

Numerous studies evaluated the potential association between SSc diagnosis and c-silica exposure; however, these studies did not report quantitative cumulative exposure estimates or exposure-response data. Several studies reported an elevated risk for SSc incidence or mortality in c-silica-exposed workers, often in individuals with silicosis (Brown et al. 1997; Cowie 1987; Diot et al. 2002; Englert et al. 2000; Marie et al. 2014; Rodnan et al. 1967; Walsh 1999), while others did not show associations with c-silica exposure (Bovenzi et al. 1995, 2004; Burns et al. 1996; Calvert et al. 2003; Gold et al. 2007; Lacey et al. 1997; Makol et al. 2011; Maitre et al. 2004; Rosenman et al. 1999; Silman and Jones 1992; Sluis-Cremer



## 3. HEALTH EFFECTS

**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
<b>Rheumatoid arthritis (RA)</b>				
Klockars et al. 1987; Koskela et al. 1987b	<u>Study design:</u> historical cohort study <u>Industry:</u> granite workers <u>Location:</u> Finland	<u>Cohort:</u> 1,026 male workers employed for at least 3 months between 1940 and 1971, with follow-up until 1981 (mean exposure duration: 12 years): <ul style="list-style-type: none"> <li>- 170 quarry and drill workers</li> <li>- 119 saw workers</li> <li>- 160 cutters/dressers/polishers</li> <li>- 452 general stone workers</li> <li>- 125 laborers</li> </ul> <u>Adjustments:</u> none <u>Statistical analysis:</u> observed versus expected incidence: Poisson distribution model <u>Incidence rates:</u> Mantel-Haenszel $\chi^2$ test	Geometric mean exposure to quartz particles <5 $\mu\text{m}$ diameter ( $\text{mg}/\text{m}^3$ ): <ul style="list-style-type: none"> <li>- Drilling: 1.47</li> <li>- Block surfacing: 0.82</li> <li>- Other tasks: 0.12–1.44</li> </ul>	Granite workers had a significantly higher incidence of free medicine grants for RA from national sickness insurance than the general population. Subjects receiving free medicines for RA: <ul style="list-style-type: none"> <li>- Observed: 19</li> <li>- Expected: 7.5</li> </ul> $p < 0.001$ Granite workers had a significantly higher incidence of disability pensions for RA than the general population. Subjects receiving disability pensions for RA: <ul style="list-style-type: none"> <li>- Observed: 10</li> <li>- Expected: 1.6</li> </ul> $p < 0.001$ Incidence rate/1,000 person years of awards of disability pensions for RA among granite workers and in general male population: <ul style="list-style-type: none"> <li>- Granite workers: 1.69</li> <li>- General population: 0.24</li> </ul> $p < 0.001$ Note: The proportions of workers with RA in the various occupational categories (e.g. drillers, cutters, general workers, etc.) were comparable to the proportion in the total cohort.

## 3. HEALTH EFFECTS

**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Steenland and Brown 1995b	<u>Study design:</u> historical cohort study <u>Industry:</u> gold miners <u>Location:</u> South Dakota, United States	<u>Cohort:</u> 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years) <u>Adjustments:</u> see statistical analysis <u>Statistical analysis:</u> life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with $\chi^2$ tests	Median cumulative exposure ( $\text{mg}/\text{m}^3\text{-year}$ ): 0.23 <sup>a</sup>	The SMR for deaths that listed the presence of arthritis (including RA) was elevated: <ul style="list-style-type: none"> <li>- Number of cases at death: 17</li> <li>- SMR (95% CI): 2.19 (1.27, 3.50)</li> </ul> Note: The number of RA cases was not specified.

## 3. HEALTH EFFECTS

**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Steenland et al. 2001b	<u>Study design:</u> historical cohort study <u>Industry:</u> industrial sand workers <u>Location:</u> United States (11 different states)	<u>Cohort:</u> 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure <u>Adjustments:</u> age, race, sex, calendar time <u>Statistical analysis:</u> standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m <sup>3</sup> -year): 0.13 <sup>b</sup>  Cumulative exposure quartiles for respirable c-silica (mg/m <sup>3</sup> -year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SMR for deaths that listed the presence of arthritis (including RA) was elevated: <ul style="list-style-type: none"> <li>- Number of cases at death: 23</li> <li>- SMR (95% CI): 4.36 (2.76, 6.54)</li> <li>- SRR (number of deaths) by quartile (95% CI not reported):               <ul style="list-style-type: none"> <li>Q1: 1.00 (1) (referent)</li> <li>Q2: 1.73 (3)</li> <li>Q3: 3.73 (7)</li> <li>Q4: 6.91 (7)</li> </ul> </li> <li>- A positive trend over exposure quartiles:                Slope [change in rate per 1 mg/m<sup>3</sup>-year increase (95% CI)]: 0.00018 (0.00017, 0.00019)</li> </ul>

Note: Of the death certificates mentioning arthritis, 12/23 specified RA. A SMR specific for RA was not reported.

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**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Turner and Cherry 2000	<p><u>Study design</u>: historical cohort study with nested case-referent analysis</p> <p><u>Industry</u>: pottery, sandstone, and refractory material (aluminosilicate or c-silica) industries</p> <p><u>Location</u>: United Kingdom</p>	<p><u>Cohort</u>: 8,325 workers (6,353 men, 1,972 women) born in 1916–1945 and employed in pottery or related industries</p> <p><u>Cases</u>: 58 workers (43 men, 15 women) who responded “yes” to the question on RA on the medical survey administered during routine occupational exam (administered every 2 years)</p> <p><u>Referents</u>: 232 workers (172 men, 60 women); 4 referents matched to each case based on sex and as closely as possible to date of birth and date of first exposure to pottery</p> <p><u>Adjustments</u>: smoking, employment in the coal mining industry, number of pregnancies</p> <p><u>Statistical analysis</u>: conditional logistic regression</p>	<p>Mean cumulative exposure to respirable c-silica (mg/m<sup>3</sup>-year):</p> <ul style="list-style-type: none"> <li>- Cases: 2.525</li> <li>- Referents: 2.872</li> </ul> <p>Mean (±SD) exposure concentration to respirable c-silica (mg/m<sup>3</sup>):</p> <ul style="list-style-type: none"> <li>- Cases: 0.1329±0.0769</li> <li>- Referents: 0.1329±0.0741</li> </ul>	<p>There was no increased risk of RA based on analysis of mean c-silica concentrations, cumulative exposure, or duration of employment.</p> <p>ORs (95% CI):</p> <p>Mean c-silica concentration/100 (µg/m<sup>3</sup>):</p> <ul style="list-style-type: none"> <li>- Men: 0.79 (0.40, 1.57)</li> <li>- Women: 1.56 (0.36, 6.75)</li> <li>- Combined: 0.97 (0.56, 1.70)</li> </ul> <p>Cumulative exposure/1,000 (µg/m<sup>3</sup>-year):</p> <ul style="list-style-type: none"> <li>- Men: 0.71 (0.52, 0.97)</li> <li>- Women: 1.13 (0.73, 1.73)</li> <li>- Combined: 0.80 (0.64, 1.02)</li> </ul> <p>Duration/1 (year):</p> <ul style="list-style-type: none"> <li>- Men: 0.29 (0.11, 0.76)</li> <li>- Women: 0.61 (0.18, 2.02)</li> <li>- Combined: 0.31 (0.16, 0.61)</li> </ul> <p>The prevalence of RA in this cohort (58/8325; 0.7%) is equal to the prevalence in the general United Kingdom population for individuals aged 45–64 years (0.7%).</p>

## 3. HEALTH EFFECTS

**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
<b>Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE)</b>				
Conrad et al. 1996	<u>Study design:</u> historical cohort study <u>Industry:</u> uranium miners <u>Location:</u> Germany	<u>Cohort:</u> 15,000 “heavily-exposed” workers with silicosis <u>Adjustments:</u> none <u>Statistical analysis:</u> none	Estimated exposure: >20 mg/m <sup>3</sup>	Uranium workers had a “higher than expected” prevalence of SLE.  Number of cases: - Definite (4+ diagnostic criteria): 28 - Probable (2–3 diagnostic criteria): 15  Estimated prevalence in uranium workers: - 93 in 100,000  Background incidence in male population: - Male population: 3.6 in 100,000 - Caucasian population: 20–50 in 100,000
Steenland and Brown 1995b	<u>Study design:</u> historical cohort study <u>Industry:</u> gold miners <u>Location:</u> South Dakota, United States	<u>Cohort:</u> 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years) <u>Adjustments:</u> see statistical analysis <u>Statistical analysis:</u> life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with $\chi^2$ tests	Median cumulative exposure (mg/m <sup>3</sup> -year): 0.23 <sup>c</sup>	The SMRs for deaths that listed the presence of “other” musculoskeletal diseases (including SLE and SSc) and “other” skin diseases (including SSc and SLE) were increased:  Other musculoskeletal diseases: - Number of cases at death: 10 - SMR (95% CI): 2.14 (1.03, 3.94)  Other diseases of the skin: - Number of cases at death: 10 - SMR (95% CI): 2.45 (1.17, 4.51)  Note: The number of individual SLE or SSc cases was not specified.

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**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Steenland et al. 2001b	<p><u>Study design:</u> historical cohort study</p> <p><u>Industry:</u> industrial sand workers</p> <p><u>Location:</u> United States (11 different states)</p>	<p><u>Cohort:</u> 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure</p> <p><u>Adjustments:</u> age, race, sex, calendar time</p> <p><u>Statistical analysis:</u> standard life-table analysis</p>	<p>Mean cumulative exposure to respirable c-silica (mg/m<sup>3</sup>-year): 0.13<sup>b</sup></p> <p>Cumulative exposure quartiles for respirable c-silica (mg/m<sup>3</sup>-year):</p> <p>Q1: &lt;0.10 (referent)</p> <p>Q2: 0.10–&lt;0.51</p> <p>Q3: 0.51–&lt;1.28</p> <p>Q4: ≥1.28</p>	<p>The SMR for deaths that listed the presences of “other” musculoskeletal diseases (including SLE and SSc) was not increased:</p> <ul style="list-style-type: none"> <li>- Number of cases at death: 8</li> <li>- SMR (95% CI): 2.18 (0.93, 4.28)</li> </ul> <p>Note: Among the eight deaths reporting musculoskeletal diseases, three deaths reported SSc and one death reported SLE.</p>
<b>Sarcoidosis</b>				
Rafnsson et al. 1998	<p><u>Study design:</u> case-referent study</p> <p><u>Industry:</u> diatomaceous earth plant</p> <p><u>Location:</u> Husavik, Iceland</p>	<p><u>Cases:</u> eight cases of sarcoidosis (four men, four women) diagnosed either at the healthcare center in the town of Husavik or at a routine occupational health examination at the a diatomaceous earth plant in the district; diagnoses occurred between 1974 and 1993</p> <p><u>Referents:</u> 70 individuals selected randomly from the population of the district served by the Husavik health center/hospital</p>	<p>Mean exposure to respirable cristobalite in 1978 (mg/m<sup>3</sup>):</p> <ul style="list-style-type: none"> <li>- Loading: 0.3</li> <li>- Packers: 0.6</li> <li>- Over operators: 0.3</li> <li>- Maintenance men: 0.2</li> <li>- Cleaners: 0.1</li> </ul> <p>Mean exposure to respirable cristobalite in 1981 (mg/m<sup>3</sup>):</p> <ul style="list-style-type: none"> <li>- Loading: 0.02</li> <li>- Packers: 0.05</li> <li>- Over operators: 0.002</li> <li>- Maintenance men: 0.01</li> <li>- Cleaners: 0.06</li> </ul>	<p>Number of total sarcoidosis cases with a history of exposure (employed at diatomaceous earth plant): 6/8</p> <p>Number of incidental sarcoidosis cases diagnoses at the healthcare center (not part of routine occupational health exam) with a history of exposure: 4/6</p> <p>Number of referents with a history of exposure (employed at diatomaceous earth plant): 13/70</p> <p>The risk of both total and incidental sarcoidosis cases were increased in exposed individuals.</p>

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**Table 3-11. Autoimmune Disease in Workers Exposed to Respirable c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
		<u>Adjustments:</u> the study authors did stratify for age; however, the age range of the cases determined the age section of the population register that was used to draw the referents <u>Statistical analysis:</u> Fisher's Exact Test		ORs (95% CI): - Total: 13.2 (2.0, 140.9) - Incidental: 8.8 (1.1, 102.5)  Estimated annual incidence of sarcoidosis: - Population of Husavik region: 9.3/100,000 - Total population of Iceland: 0.5–2.7/100,000  Note: The six cases with c-silica exposure were distributed into different job categories; therefore, increased risk was not associated with a specific job.

<sup>a</sup>Exposures were estimated by Mannelje et al. (2002a, 2002b) (not reported in original publication), based on data provided by the original investigators.

<sup>b</sup>Exposures were estimated by Mannelje et al. (2002a, 2002b) (not reported in original publication) for Steenland and Sanderson. (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.

<sup>c</sup>Exposures were estimated by Mannelje et al. (2002a, 2002b) (not reported in original publication), based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; OR = odds ratio; SD = standard deviation; SMR – standard mortality ratio; SRR = standardized rate ratio

## 3. HEALTH EFFECTS

et al. 1985). However, a meta-analysis of 16 studies in c-silica-exposed workers (see Table 3-12 for study details) reported an increased combined estimator of relative risk (CERR) for SSc of 3.20 (95% CI: 1.89, 5.43) (McCormic et al. 2010). The risk was increased in males (CERR: 3.02; 95% CI: 1.24, 7.35), but not females (CERR: 1.03; 95% CI: 0.74, 1.44). Additional analysis indicated that increased risk was predominantly due to studies published prior to 2000 (CERR: 4.22; 95% CI: 1.64, 10.86), with more recent studies not showing an increased risk for SSc (CERR: 1.96; 95% CI: 0.95, 4.07). Location of study was also an important factor, with an increased risk of SSc in c-silica-exposed individuals in European studies (CERR: 5.91; 95% CI: 3.06, 11.42), but not U.S. studies (CERR: 1.23; 95% CI: 0.97, 1.56). Results of this meta-analysis indicate that c-silica exposure may increase the risk of SSc in men; however, available data are inadequate to determine the exposure-response relationship.

*Rheumatoid arthritis (RA)*. Two studies providing exposure data have evaluated the risk of RA in c-silica-exposed workers (see Table 3-11 for study details). The incidence of RA was significantly ( $p < 0.001$ ) increased in a cohort of male granite workers exposed to quartz particles ( $< 5 \mu\text{m}$  diameter) at a geometric mean exposure concentration of 0.82–1.47  $\text{mg}/\text{m}^3$ , with an incidence rate of 1.69/1,000 (0.2%) compared with that of the general population (0.24/1,000; (0.02%)) (Klockars et al. 1987; Koskela et al. 1987b). However, the risk of RA was not increased in a cohort of male and female workers from pottery or related industries exposed to mean air levels of respirable c-silica of 0.1329  $\text{mg}/\text{m}^3$  (Turner and Cherry 2000). A nested case-referent study in the same cohort showed that mean cumulative exposure to respirable c-silica did not differ between cases (2.525  $\text{mg}/\text{m}^3\text{-year}$ ) and referents (2.872  $\text{mg}/\text{m}^3\text{-year}$ ).

Two additional occupational studies with exposure information evaluated the risk of arthritis (including RA) in c-silica-exposed workers; however, these studies are of limited usefulness based on methods of analysis (e.g., grouping RA with osteoarthritis); study details are provided in Table 3-11. Steenland and Brown (1995b) reported a 2.19-fold (95% CI: 1.27, 3.50) increase in the presence of arthritis (including RA) at death in gold miners exposed to mean cumulative respirable c-silica levels of 11.37  $\text{mg}/\text{m}^3\text{-year}$ , and Steenland et al. (2001b) reported a 4.36-fold (95% CI: 2.76, 6.54) increase in the presence of arthritis (including RA) at death in industrial sand workers exposed to mean cumulative respirable c-silica levels of 0.13  $\text{mg}/\text{m}^3\text{-year}$  (exposure estimates calculated by Mannetje et al. 2002b). When analyzed by exposure quartile, a positive trend was observed for arthritis (including RA) in the sand workers cohort (slope: 0.00018; 95% CI: 0.00017, 0.00019); exposure by quartile was not assessed in gold miners. The numbers of arthritis cases were 17 in gold miners and 23 in sand workers. Steenland et al. (2001b) also reported the specific number of RA cases (12) in sand workers; however, SMR analysis was not conducted specifically for RA. Additionally, a study lacking exposure information reported a 2.01-fold



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**Table 3-12. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies**

Studies	Methods	Outcomes for meta-analysis
<p>Bonvenzi et al. 1995 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 5 males, 16 females</li> <li>- Controls: 10 males, 32 females (age- and sex-matched)</li> <li>- Location: Trento, Italy</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 5.20 (0.48, 74.1)</li> </ul> <p>Bonvenzi et al. 2004 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 9 males, 46 females</li> <li>- Controls: 18 males, 153 females (age- and sex-matched)</li> <li>- Location: Verona, Italy</li> <li>- Exposure: occupational history</li> <li>- RR (95% CI): 1.7 (0.4, 7.6)</li> </ul> <p>Burns et al. 1996 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 274 females</li> <li>- Controls: 1184 females (age-, race-, and region-matched)</li> <li>- Location: Michigan, United States</li> <li>- Exposure: self-reported past exposure (job/hobby history), c-silica exposure in abrasive grinding/sandblasting, pottery making, and dental laboratories</li> <li>- OR (95% CI): 1.50 (0.76, 2.93)</li> </ul> <p>Diot et al. 2002 (case-control)</p>	<p>Silman and Jones 1992 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 56 males</li> <li>- Controls: 86 males (age-matched)</li> <li>- Location: United Kingdom</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 1.40 (0.12, 16.1)</li> </ul> <p>Brown et al. 1997 (cohort)</p> <ul style="list-style-type: none"> <li>- Silicosis patients: 1,130 men</li> <li>- Location: Sweden</li> <li>- Exposure: diagnosis of silicosis as proxy for c-silica exposure</li> <li>- Number of scleroderma cases: 5</li> <li>- RR (95% CI): 37 (11.9, 86.3)</li> </ul> <p>Mehlhorn et al. 1999 (cohort)</p> <ul style="list-style-type: none"> <li>- Uranium mine workers: 243,900 men with "high" exposure and 50,000 men with "low" exposure</li> <li>- Location: Germany</li> <li>- Exposure: "high" versus "low;" levels not reported</li> <li>- Number of scleroderma cases: not available</li> <li>- RR (95% CI): 7.41 (6.14, 8.93)</li> </ul> <p>Rosenman et al. 1999 (cohort)</p>	<p><u>Selection of studies:</u> Medline, Toxline, BIOSIS, and Embase searches were performed to identify studies evaluating the association between c-silica exposure and SSc published between 1949 and November 2009. Of the 20 studies identified, only 16 studies had measures of RR (OR, SIR, SMR, or PMR) or sufficient data for calculation of RR for SSc in c-silica-exposed workers. A total of 16 studies including 1,030,152 subjects were selected (781,882 men, 233,324 women, 14,946 sex not specified).</p> <p><u>Data analysis:</u> Measures of RRs and 95% CIs were abstracted from data presented in primary reports. A meta-analysis was conducted using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group's recommendations. Heterogeneity of the studies were analyzed using Cochran Q and I<sup>2</sup> statistics. The</p> <p><u>All studies:</u> An increased risk of SSc with c-silica exposure was identified; studies showed significant heterogeneity.</p> <p>CERR (95% CI):</p> <ul style="list-style-type: none"> <li>- Both sexes: 3.20 (1.89, 5.43)</li> </ul> <p><u>Stratified by sex:</u> An increased risk of SSc with c-silica exposure was identified in men, but not in women; male data showed significant heterogeneity and female data showed nonsignificant heterogeneity.</p> <p>CERR (95% CI):</p> <ul style="list-style-type: none"> <li>- Men: 3.02 (1.24, 7.35)</li> <li>- Men (two studies excluded): 2.06 (1.04, 4.08)</li> <li>- Females: 1.03 (0.74, 1.44)</li> </ul> <p><u>Stratified by location:</u> An increased risk of SSc with c-silica exposure was identified in European studies, but not in studies conducted in the United States. Data for both locations showed</p>

## 3. HEALTH EFFECTS

**Table 3-12. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies**

Studies	Methods	Outcomes for meta-analysis	
<ul style="list-style-type: none"> <li>- Cases: 11 males, 69 females</li> <li>- Controls: 22 males, 138 females (age-, sex-, and smoking-habit-matched)</li> <li>- Location: France</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 5.57 (1.69, 18.37)</li> </ul>	<ul style="list-style-type: none"> <li>- Silicosis patients: 583 men and women</li> <li>- Location: United States</li> <li>- Exposure estimate: diagnosis of silicosis as proxy for c-silica exposure</li> <li>- Number of scleroderma cases: 1</li> <li>- RR (95% CI): 15.65 (0.21, 87.03)</li> </ul> <p>Calvert et al. 2003 (mortality)</p> <ul style="list-style-type: none"> <li>- 17,238 deaths</li> <li>- Location: United States</li> <li>- Exposure estimate: job title (high c-silica exposure in drillers, crushing and grinding machinists, miners, pottery workers, and foundry workers)</li> <li>- Number of scleroderma cases: 976 males, 1,899 females</li> <li>- OR (95% CI): 2.00 (0.39, 10.31)</li> </ul>	<p>CERR and 95% CI were calculated using fixed or random effect models. Further analysis were conducted on studies stratified by sex, location, publication date, and study design.</p> <p>An additional analysis in men only was conducted with two studies excluded (Mehlhorn et al. 1999 and Ziegler et al. 1997) in order to reduce bias. These studies were excluded because they did not use a typical cohort or case-control design; rather, they started historically with a case series and tried to construct a study post-hoc.</p>	<p>significant heterogeneity.</p> <p>CERR (95% CI):</p> <ul style="list-style-type: none"> <li>- Europe: 5.91 (3.06, 11.42)</li> <li>- United States: 1.23 (0.97, 1.56)</li> </ul> <p><u>Stratified by publication date:</u> An increased risk of SSc with c-silica exposure was identified in studies published prior to 2000, but not in 2000 or later. Data for both time periods showed significant heterogeneity.</p> <p>CERR (95% CI):</p> <ul style="list-style-type: none"> <li>- Pre-2000: 4.22 (1.64, 10.86)</li> <li>- Since 2000: 1.96 (0.95, 4.07)</li> </ul> <p><u>Stratified by study design:</u> An increased risk of SSc with c-silica exposure was identified in in case-control studies and cohort studies, but not the case-series study. Cohort studies showed significant heterogeneity; case-control and case-series studies showed nonsignificant heterogeneity.</p>
<p>Englert et al. 2000 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 160 males</li> <li>- Controls: 83 males (age- and region-matched)</li> <li>- Location: Australia</li> <li>- Exposure: occupational history (c-silica exposure in construction, mining, and manufacturing)</li> <li>- OR (95% CI): 2.51 (1.28, 4.98)</li> </ul>	<p>Gold et al. 2007 (mortality)</p> <ul style="list-style-type: none"> <li>- 72,732 male and 197,479 female deaths</li> <li>- Location: United States</li> <li>- Exposure estimate: job title</li> <li>- Number of scleroderma cases: 1,298 males, 4,344 females</li> <li>- OR (95% CI): 1.02 (0.92, 1.13)</li> </ul>		
<p>Lacey et al. 1997 (case-control)</p> <ul style="list-style-type: none"> <li>- Cases: 189 females</li> <li>- Controls: 1,043 females (age-, race-, and region-matched)</li> <li>- Location: Ohio, United States</li> <li>- Exposure: self-reported past exposure (job/hobby history)</li> <li>- OR (95% CI): 0.87 (0.19, 4.0)</li> </ul>	<p>Walsh 1999 (mortality)</p>		

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**Table 3-12. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies**

Studies	Methods	Outcomes for meta-analysis
Maître et al. 2004 (case-control) - Cases: 10 men, 83 women - Controls: 40 men, 166 women (age- and sex-matched) - Location: France - Exposure: based on job title - RR (95% CI): 0.89 (0.26, 3.2)	- 411,404 male and 30,563 female deaths - Location: United States - Exposure estimate: job title (c-silica exposure in mining machine operators and numerous non-mining jobs such as brick/stone mason, grinders/polishers, various construction workers)	CERR (95% CI): - Case-control: 2.24 (1.65, 3.31) - Cohort: 15.49 (4.54, 52.87) - Mortality studies: 1.01 (0.94, 1.08)
Rodnan et al. 1967 (case-control) - Cases: 60 males - Controls: 86 males (age- and race-matched) - Location: United States - Exposure: based on job title (c-silica exposure in coal miners, sandblasters, rock drillers, brick molders, and foundry, enamel, pottery, and cement factory workers) - RR (95% CI): 3.34 (1.59, 7.05)	- Number of scleroderma cases: 128 males, 32 females - PMR (95% CI): 1 (0.80, 1.10)	
	Ziegler et al. 1997 (case series) - Cases: 54 males - Location: Germany - Exposure: occupational history - RR (95% CI): 10.40 (6.10, 17.8)	

CERR = combined estimator of relative risk; CI = confidence interval; OR = odds ratio; PMR = proportionate mortality ratio; RR = relative risk or risk ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Source: McCormic et al. (2010)

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(95% CI: 1.17–3.21) increase in the presence of arthritis (including RA) at death for male granite workers in a mortality cohort (Steenland et al. 1992). The number of arthritis cases in this cohort was 17.

Several additional studies reported a 2–8-fold increase in risk or incidence of RA in cohorts of men with occupational exposure to c-silica, the majority of which were diagnosed with silicosis; however, these studies did not provide quantitative estimates of exposure (Brown et al. 1997; Makol et al. 2011; Rosenman and Zhu 1995; Rosenman et al. 1999; Stolt et al. 2005, 2010). A case-referent study of c-silica-exposed miners showed an increased risk of RA in miners with silicosis compared with c-silica-exposed miners without silicosis, although these findings could not be accounted for based on estimates of cumulative exposure (c-silica exposure levels not reported) (Sluis-Cremer et al. 1986). Results of cohort mortality yielded conflicting results; Calvert et al. (2003) reported an increased OR for RA in c-silica-exposed workers with “high silica exposure,” including miners, crushing and grinding machine workers, pottery workers, and foundry workers, while no increase was observed in workers with potential c-silica exposure from various industries (based on work history and job-exposure matrix) (Gold et al. 2002).

Taken together, available evidence indicates that c-silica exposure may increase the risk of RA; however, available data are inadequate to determine an exposure-response relationship.

*Systemic lupus erythematosus (SLE)*. Two studies providing exposure data have evaluated the risk of SLE in c-silica-exposed workers (Steenland and Brown 1995b; Steenland et al. 2001b); see Table 3-11 for study details. However, these studies are of limited usefulness based on methods of analysis (e.g., grouping SLE with related disorders, statistical analysis not conducted). The incidence of SLE was “higher than expected” in a 15,000 group of “heavily exposed” ( $>20$  mg/m<sup>3</sup>) uranium miners with silicosis, with 28 definite cases (4+ American Rheumatism Association [ARA] criteria) and an additional 15 probable cases (2–3 ARA criteria) (Conrad et al. 1996). Based on these findings, the estimated prevalence of SLE was 93 in 100,000 in uranium workers, compared with the background incidence of 3.6 in 100,000 in the male population and 20–50 in 100,000 in the general Caucasian population (Conrad et al. 1996). In gold miners exposed to mean cumulative respirable c-silica levels of 11.37 mg/m<sup>3</sup>-year, the incidences of “other musculoskeletal diseases” and “other diseases of the skin” at death (including SLE) were increased by 2.14-fold (95% CI: 1.03, 3.94) and 2.45-fold (95% CI: 1.17, 4.51), respectively (Steenland and Brown 1995b; exposure estimates calculated by Mannetje et al. 2002b). However, the incidence of SLE, specifically, was not reported or analyzed. In industrial sand workers exposed to lower cumulative levels of respirable c-silica (0.13 mg/m<sup>3</sup>-year), the incidence of “other musculoskeletal

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diseases” (including SLE) was not increased (Steenland et al. 2001b; exposure estimates calculated by Mannelje et al. 2002b).

Other available case-control and cohort studies reported inconsistent findings; however, these studies did not provide quantitative cumulative exposure estimates or exposure-response data. Two population-based case-control studies reported a 1.6–4-fold increase in risk of SLE diagnosis in individuals with a history of occupational exposure to c-silica (Cooper et al. 2010; Finckh et al. 2006). Women exposed for >5 years had an increased risk (OR: 4.9; 95% CI: 1.1, 21.9) compared to women exposed for 1–5 years (OR: 4.0; 95% CI: 1.2, 12.9); these findings showed a significant duration-related trend ( $p=0.01$ ) (Finckh et al. 2006). Additionally, the relative risk for SLE was increased 24-fold in a cohort of men with silicosis (Brown et al. 1997). In this cohort, a 6-fold excess mortality from musculoskeletal diseases, including RA, SLE, and Sjogren’s syndrome, was identified (6/1130 deaths, 0.5%) (Brown et al. 1997). However, the incidence of SLE was not elevated in other cohorts of patients with silicosis (Makol et al. 2011; Rosenman et al. 1999) and the incidence of SLE at death was not elevated in c-silica-exposed individuals (Calvert et al. 2003; Gold et al. 2007).

Taken together, available data are inadequate to determine if there is an association between c-silica exposure and increased risk of SLE.

*ANCA-associated vasculitis (AAV)*. Studies evaluating the potential association between AAV and c-silica exposure did not report quantitative exposure data. Using studies with qualitative measures of exposure (e.g., occupational history), a meta-analysis of six case-referent studies showed increased ORs for AAV (OR: 2.57; 95% CI: 1.15, 4.36) and AAV with renal involvement (OR: 3.13; 95% CI: 1.63, 5.84) in c-silica-exposed workers (Gomez-Puerta et al. 2013; study details provided in Table 3-13). Additional analysis showed that ORs for specific AAV-associated diseases were also increased, including GPA (OR: 3.56; 95% CI: 1.85, 6.82) and MPA (OR: 3.95; 95% CI: 1.89, 8.24). However, when studies were stratified into those that adjusted for smoking status and occupational risk ( $n=2$ ) and those that did not ( $n=4$ ), studies with unadjusted ORs showed an increase in risk of AAV with c-silica exposure (OR: 2.99; 95% CI: 1.43, 6.25), but studies with adjusted ORs did not (OR: 2.24; 95% CI: 0.74, 6.80). Individually, four of the case-control studies used in the meta-analysis reported an increase in AAV risk in c-silica exposed individuals (Gregorini et al. 1993; Hogan et al. 2001; Nuyts et al. 1995; Stratta et al. 2001b), while the other two did not (Hogan et al. 2007; Lane et al. 2003). After adjustment for smoking status and occupational risk factors, risk was no longer increased in the study by Hogan et al. (2001). Additional studies not included in the meta-analysis also reported an increase in the incidence of AAV or

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**Table 3-13. Meta-Analysis of Relative Risk for ANCA-Associated Vasculitis (AAV) in a Pooled Analysis of Six Case-Control Studies**

Studies	Methods	Outcomes for meta-analysis
<p>Gregorini et al. 1993</p> <ul style="list-style-type: none"> <li>- Cases: 16 patients with ANCA-positive glomerulonephritis</li> <li>- Controls: 32 patients with nephropathy without vasculitis (age- and date-of-admission-matched)</li> <li>- Location: Italy</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 14.0 (1.7, 113.8)</li> <li>- Quality score: S2/C1/E1</li> </ul>	<p>Lane et al. 2003</p> <ul style="list-style-type: none"> <li>- Cases: 75 patients with primary systemic vasculitis</li> <li>- Controls: 220 patients with non-inflammatory musculoskeletal disease (age- and sex-matched)</li> <li>- Location: United Kingdom</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 1.4 (0.7, 2.7)</li> <li>- Adjusted OR (95% CI): 1.4 (0.73, 6.79)</li> <li>- Quality score: S2/C2/E2</li> </ul>	<p>The risk of AAV and AAV with renal involvement was increased in c-silica-exposed individuals.</p> <p>OR (95% CI):</p> <ul style="list-style-type: none"> <li>- All studies: 2.57 (1.15, 4.36)</li> <li>- AAV with renal involvement: 3.13 (1.68, 5.84)</li> <li>- GPA<sup>a</sup>: 3.56 (1.85, 6.82)</li> <li>- MPA<sup>b</sup>: 3.95 (1.89, 8.24)</li> </ul>
<p>Hogan et al. 2001</p> <ul style="list-style-type: none"> <li>- Cases: 65 patients with ANCA-associated vasculitis</li> <li>- Controls: 65 patients with nephropathy without vasculitis (age-, sex-, and region-matched)</li> <li>- Location: United States</li> <li>- Exposure: occupational history</li> <li>- Adjusted OR (95% CI): 4.43 (1.36, 14.4)</li> <li>- Quality score: S3/C1/E1</li> </ul>	<p>Nuyts et al. (1995)</p> <ul style="list-style-type: none"> <li>- Cases: 16 patients with granulomatosis with polyangiitis (formerly called Wegener's granulomatosis)</li> <li>- Controls: 32 randomly selected age-, sex-, and region-matched individuals</li> <li>- Location: Belgium</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 5.0 (1.4, 11.6)</li> <li>- Quality score: S3/C1/E2</li> </ul>	<p>Studies reporting unadjusted estimates of association showed an increased risk of AAV in c-silica-exposed individuals, but studies that adjusted for smoking and occupational risk factors did not.</p> <p>OR (95% CI):</p> <ul style="list-style-type: none"> <li>- Unadjusted studies: 2.99 (1.43, 6.25)</li> <li>- Adjusted studies: 2.24 (0.74, 6.80)</li> </ul>
<p>Hogan et al. 2007</p> <ul style="list-style-type: none"> <li>- Cases: 129 patients with ANCA-positive glomerulonephritis</li> <li>- Controls: 109 randomly selected age-, sex-, and state-matched individuals</li> <li>- Location: United States</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 1.6 (0.9, 2.8)</li> <li>- Quality score: S3/C1/E1</li> </ul>	<p>Stratta et al. 2001b</p> <ul style="list-style-type: none"> <li>- Cases: 31 patients with renal vasculitis</li> <li>- Controls: 58 patients with nephropathy without vasculitis</li> <li>- Location: Italy</li> <li>- Exposure: occupational history</li> <li>- OR (95% CI): 2.4 (1.02, 6.5)</li> <li>- Quality score: S2/C1/E1</li> </ul>	<p><u>Selection of studies:</u> EMBASE and MEDLINE searches were performed to identify case-control and cohort studies evaluating the association between c-silica exposure and ANCA-associated vasculitis published between January 1965 and April 2013. Studies were assessed for quality using the Newcastle-Ottawa Scale; quality scores were assigned based on selection of comparison groups (S; 0–4 points), comparability between the two groups (C; 0–2 points), and exposure ascertainment (E; 0–3 points).</p> <p><u>Data analysis:</u> ORs were abstracted from published reports. Two studies reported adjusted ORs (adjusted for smoking status and occupational risk factors). Heterogeneity of the studies was analyzed using <math>Q</math> and <math>I^2</math> statistics. Data showed significant heterogeneity, so ORs and 95% CI were calculated using random effect models. Further analyses were conducted on studies stratified by OR adjustment and renal involvement. Comprehensive meta-analysis software</p>

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**Table 3-13. Meta-Analysis of Relative Risk for ANCA-Associated Vasculitis (AAV) in a Pooled Analysis of Six Case-Control Studies**

Studies	Methods	Outcomes for meta-analysis
	(www.meta-analysis.com; ©Biostat, Inc.) was used for statistical analysis.	

<sup>a</sup>GPA = granulomatosis with polyangiitis (formerly Wegener granulomatosis).

<sup>b</sup>MPA = microscopic polyangiitis.

ANCA = antineutrophil cytoplasmic autoantibodies; CI = confidence interval; OR = odds ratio

Source: Gomez-Puerta et al. (2013)

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ANCA-positivity with a history of c-silica exposure, including two silicosis cohort studies (Bartunkova et al. 2006; Makol et al. 2011) and two case-referent studies (Beaudreuil et al. 2005; Rihova et al. 2005).

Based on the meta-analysis, evidence suggests that c-silica exposure may increase the risk of AAV; however, the lack of exposure-response data and the lack of increased risk following adjustments for smoking and occupational risk factors preclude the ability to determine if there is an association between c-silica exposure and increased risk of AAV.

*Sarcoidosis.* In a case-referent study, the risk of sarcoidosis was increased 13-fold (95% CI: 2.0, 140.9) in men and women exposed to c-silica at a diatomaceous earth plant in the Husavik region of Iceland; mean exposure levels to respirable cristobalite at the plant ranged from 0.002 to 0.06 mg/m<sup>3</sup>; see study details in Table 3-11 (Rafnsson et al. 1998). The annual incidence of sarcoidosis in the Husavik region was estimated to be 9.3 per 100,000, compared to the national average of 0.5–2.7 per 100,000 (Rafnsson et al. 1998). A study evaluating the potential association between c-silica exposure and sarcoidosis found a decreased risk of sarcoidosis in c-silica-exposed individuals in a mortality cohort (OR: 0.66; 95% CI: 0.54, 0.80) (Calvert et al. 2003), and a statistically significant decrease in the risk of sarcoidosis-related mortality was observed in silica workers in the United States (mortality OR: 0.65; 95% CI: 0.42, 0.74; p<0.05) (Liu et al. 2016). Available data are inadequate to determine if there is an association between c-silica exposure and increased risk of sarcoidosis.

*Amorphous Silica.* No studies evaluating immunological or lymphoreticular effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in immune organ weight or histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No changes in spleen or lymph node histology were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

#### 3.2.1.4 Neurological Effects

*Amorphous Silica.* No studies evaluating neurological effects in humans following inhalation exposure to a-silica were identified.



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No changes in brain weight or central or peripheral nervous tissue histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

**3.2.1.5 Reproductive Effects**

*Amorphous Silica.* No studies evaluating reproductive effects in humans following inhalation exposure to a-silica were identified.

No changes in male or female reproductive organ weight or histology were observed in rats exposed to fumed or precipitated a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No changes in testicular or prostate histology were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

**3.2.1.6 Developmental Effects**

*Amorphous Silica.* No studies evaluating developmental effects in humans or animals following inhalation exposure to a-silica were identified.

**3.2.1.7 Cancer**

*Crystalline Silica.* Well over 100 studies examining the relationship between occupational exposure to c-silica and lung cancer have been published, including several recent reviews (Brown 2009; Checkoway and Franzblau 2000; Cox 2011; Gamble 2011; IARC 2012; NIOSH 2002; Soutar et al. 2000; Steenland 2005; Steenland and Ward 2014). The information reviewed in this section focuses on studies published after the 1997 IARC evaluation of c-silica.

Carcinogenicity Classifications Based on Lung Cancer. In 1997, IARC revised the classification of c-silica from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) citing sufficient evidence for carcinogenicity in humans and animals (IARC 1997). The IARC working group noted that “carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the c-silica or on external factors affecting its biological activity or distribution of its polymorphs.” In 2012, IARC conducted a re-evaluation of the carcinogenicity of c-silica, incorporating data available after the 1997 assessment.

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IARC retained the Group 1 classification for c-silica, concluding that “there is sufficient evidence in humans for the carcinogenicity of c-silica in the form of quartz or cristobalite. c-Silica in the form of quartz or cristobalite dust causes cancer of the lung. There is sufficient evidence in experimental animals for the carcinogenicity of quartz dust.” IARC (2012) also noted that c-silica is carcinogenic to rats following exposure by inhalation or intratracheal instillation, but no evidence of lung cancer has been observed in c-silica-exposed mice or hamsters; the basis of these species differences has not been established. NIOSH (2002) and the NTP 13<sup>th</sup> Report on Carcinogens (NTP 2014) also have concluded that c-silica (respirable size) is a human carcinogen.

Issues and Confounding Factors for Lung Cancer. The IARC (1997) Group 1 classification for c-silica was considered controversial due, in part, to inconsistent results of occupational exposure studies and the lack of exposure-response data (Brown 2009; Cox 2011; Gamble 2011; NIOSH 2002; Pelucchi et al. 2006; Soutar et al. 2000; Steenland 2005; Steenland and Ward 2014). The IARC working group acknowledged that some occupational exposure studies did not show an association between c-silica exposure and lung cancer, possibly due to the characteristics of c-silica in different occupational settings or other factors affecting its biological activity. However, other confounding factors and biases may influence study results, including errors in estimating c-silica exposure levels, absence of (or presence and severity of) silicosis, adequate control of confounding from smoking, and unaccounted occupational co-exposures that may have contributed to lung cancer risk. In addition, compared to other occupational lung carcinogens, such as asbestos, the risk of c-silica-induced lung cancer is low, requiring large study populations to achieve adequate power to detect c-silica-related cancer risk. Therefore, pooled and meta-analyses provide the strongest support of the carcinogenicity of c-silica in the lung. Several pooled and meta-analyses have been published since the IARC (1997) evaluation, providing information on the exposure-response relationship between c-silica and lung cancer and the relationship between silicosis status and lung cancer.

Exposure-Response Data for Lung Cancer. Pooled and meta-analyses of the relationship between cumulative exposure to c-silica and lung cancer are summarized in Table 3-14 (Finkelstein 2000; Lacasse et al. 2009; Steenland et al. 2001a, 2005). Steenland et al. (2001a, 2005) conducted a pooled exposure-response analysis of 65,980 c-silica exposed workers from diatomaceous earth, granite, pottery, and mining industries. Silicosis status of each worker was undefined in the analysis. For the pooled cohort (mean cumulative exposure: 4.27 mg/m<sup>3</sup>-year), the SMR for lung cancer was 1.2 (95% CI: 1.1, 1.3), indicating a 20% increase in the risk of lung cancer. Increasing exposure was significantly associated with increased lung cancer risk. The exposure-response relationship for the pooled cohort stratified by

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**Table 3-14. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica**

Reference	Studies in analysis	Methods and exposure	Outcomes
Finkelstein 2000	<p>Hnizdo and Sluis-Cremer 1993</p> <ul style="list-style-type: none"> <li>- Nested case-control study (data from Hnizdo and Sluis-Cremer 1991)</li> <li>- South Africa; gold miners</li> </ul> <p>Checkoway et al. 1997</p> <ul style="list-style-type: none"> <li>- Cohort study</li> <li>- United States; diatomaceous earth workers</li> </ul>	<p><u>Study type:</u> meta-analysis on lung cancer in c-silica-exposed workers with undefined silicosis status</p> <p><u>Literature search dates:</u> not reported</p> <p><u>Adjustments:</u> no adjustment for exposure to radon daughters in gold mining cohorts</p> <p><u>Statistical analysis:</u> weighted least squares estimate of the regression slope of the logarithm of the OR (or RR) versus exposure was computed for each study; inverse of the variance of log (OR) used as the regression weight; regression slopes were combined using an inverse variance-weighted average</p> <p><u>Exposure:</u> not reported</p>	<p><u>Slope (95% CI) of log (RR) versus lagged cumulative exposure (mg/m<sup>3</sup>-year):</u></p> <ul style="list-style-type: none"> <li>- Hnizdo et al. 1997: 0.48 (0.18, 0.78); lagged 20 years</li> <li>- Checkoway et al. 1997: 0.10 (0.01, 0.20); lagged 15 years</li> <li>- Weighted average: 0.14 (0.05, 0.23)</li> </ul> <p><u>Estimated RR of lung cancer relative to cumulative exposure for lifetime exposure to respirable c-silica:</u></p> <ul style="list-style-type: none"> <li>- 1 mg/m<sup>3</sup>-year: 1</li> <li>- 2 mg/m<sup>3</sup>-year: 1.15 (1.09, 1.20)</li> <li>- 3 mg/m<sup>3</sup>-year: 1.32 (1.26, 1.38)</li> <li>- 4 mg/m<sup>3</sup>-year: 1.51 (1.44, 1.59)</li> <li>- 5 mg/m<sup>3</sup>-year: 1.74 (1.65, 1.82)</li> </ul>
Lacasse et al. 2009	<p><u>Cohort studies:</u> Checkoway et al. 1997 (United States; diatomaceous earth workers); Steenland and Sanderson 2001 (United States; industrial sand workers); Brown and Rushton 2005 (United Kingdom; industrial sand workers); Pukkala et al. 2005 (Finland; miscellaneous)</p> <p><u>Case-control studies:</u> Ulm et al. 1999 (Germany; miners, foundry and quarry workers); Bruske-Hohlfeld et al. 2000 (China; miners and pottery workers); Cocco et al. 2001 (China; miners and pottery workers); Chen et al. 2007 (China; miners and pottery workers); Westberg and Bellander 2003 (Sweden; aluminum foundry workers); Hughes et al. 2001 [updated by McDonald et</p>	<p><u>Study type:</u> dose-response meta-analysis examining the relationship between cumulative exposure (mg/m<sup>3</sup>-year) to c-silica and lung cancer in workers with undefined silicosis status</p> <p><u>Literature search dates:</u> 1966–December 2007</p> <p><u>Statistical analysis:</u> data from all studies were pooled into a joint analysis; spline regression models were used; heterogeneity between different studies was modeled by an additional random component of variance; responses were evaluated for no lag time; post-hoc analysis of subset of more homogenous studies</p>	<p>Number of c-silica-exposed workers in all cohort studies: 1,608,635<sup>a</sup></p> <p>Number of workers in all case control studies: 1,726 cases; 4,746 controls</p> <p><u>Results including all studies:</u> Heterogeneity was observed across studies.</p> <p>The risk of lung cancer increased with increasing exposure to c-silica. Estimated RR (95% CI) for cumulative exposures of:</p> <ul style="list-style-type: none"> <li>- 1.0 mg/m<sup>3</sup>-year: 1.22 (1.01, 1.47)</li> <li>- 6.0 mg/m<sup>3</sup>-year: 1.84 (1.48, 2.28)</li> </ul> <p>Estimated threshold for lung cancer:</p>

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**Table 3-14. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica**

Reference	Studies in analysis	Methods and exposure	Outcomes
	al. 2005] (United States; industrial sand workers)	was conducted <u>Exposure</u> : not reported for overall cohort or individual studies	>1.84 mg/m <sup>3</sup> -year  Post-hoc analysis of a subset of more homogenous studies (n=8; excluding Ulm et al. 1999 and Hughes et al. 2001) revealed similar results (numeric data not reported).  Study authors note that interpretation of results "is however limited by the wide range of exposure to respirable c-silica reported in the original studies, the heterogeneity across studies, and the confounding effect of silicosis that cannot be fully assessed."
Steenland 2005; Steenland et al. 2001a	<u>10 Cohorts (C)</u> - C1: Checkoway et al. 1997; United States; diatomaceous earth workers (non-mine) - C2: Koskela et al. 1994; Finland; granite workers (non-mine) - C3: Costello and Graham (1998); United States; granite workers (non-mine) - C4: Steenland et al. 2001a; United States; industrial sand workers (non-mine) - C5: Chen et al. 1992; China; pottery workers (non-mine) - C6: Chen et al. 1992; China; tin miners - C7: Chen et al. 1992; China; tungsten miners - C8: Hnizdo et al. 1997; South Africa; gold miners - C9: Steenland et al. 1995b; United States; gold miners	<u>Study type</u> : pooled exposure-response analysis examining the relationship between cumulative exposure (mg/m <sup>3</sup> -year) to c-silica and lung cancer in workers with undefined silicosis status  <u>Literature search dates</u> : not reported <u>Adjustments</u> : not applicable <u>Statistical analysis</u> : nested case-control analyses using conditional logistic regression; matched for age, race, sex, date of birth; excess lifetime risk estimated by spline model with 15-year lag  <u>Median cumulative exposure (mg/m<sup>3</sup>-year)</u> : C1: 1.05 C2: 4.63	<u>SMRs (95% CI) for lung cancer</u> C1: - Number of workers: 2,342 - Number of lung cancer deaths: 77 - SMR: 1.3 (1.0, 1.6) C2: - Number of workers: 1,026 - Number of lung cancer deaths: 38 - SMR: 1.4 (1.0, 2.0) C3: - Number of workers: 5,408 - Number of lung cancer deaths: 124 - SMR: 1.2 (1.0, 1.3) C4: - Number of workers: 4,027 - Number of lung cancer deaths: 85 - SMR: 1.6 (1.2, 1.98) C5: - Number of workers: 9,017

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**Table 3-14. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica**

Reference	Studies in analysis	Methods and exposure	Outcomes
	- C10: de Klerk and Musk 1998; Australia; gold miners	C3: 0.71 C4: 0.13 C5: 6.07 C6: 5.27 C7: 8.56 C8: 4.23 C9: 0.23 C10: 11.37 Pooled cohort: 4.27  <u>Pooled cohort cumulative (mg/m<sup>3</sup>-year) exposure quintiles:</u> Q1: <0.4 Q2: 0.4–2.0 Q3: 2.0–5.4 Q4: 5.4–12.8 Q5: >12.8	- Number of lung cancer deaths: 68 - SMR: 1.1 (0.84, 1.4) C6: - Number of workers: 7,858 - Number of lung cancer deaths: 97 - SMR: 2.1 (1.7, 2.6) C7: - Number of workers: 28,481 - Number of lung cancer deaths: 135 - SMR: 0.63 (0.53, 0.75) C8: - Number of workers: 2,260 - Number of lung cancer deaths: 77 - SMR: not calculated (no comparison rates available for South Africa) C9: - Number of workers: 3,348 - Number of lung cancer deaths: 156 - SMR: 1.2 (1.0, 1.4) C10 - Number of workers: 2,213 - Number of lung cancer deaths: 135 - SMR: 1.8 (1.5, 2.1)  Pooled cohort (study authors note “that there is considerable heterogeneity of results by study”): - Number of workers: 65,980 - Number of lung cancer deaths: 992 - SMR: 1.2 (1.1, 1.3)  <u>ORs (95% CI) for pooled cohort, not lagged:</u> Q1: 1.0 Q2: 1.0 (0.85, 1.3)

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**Table 3-14. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica**

Reference	Studies in analysis	Methods and exposure	Outcomes
			<p>Q3: 1.3 (1.1, 1.7)            Q4: 1.5 (1.2, 1.9)            Q5: 1.6 (1.3, 2.1)            Spline curve analysis showed an exposure-related monotonic increase in risk of death due to lung cancer.</p> <p><u>ORs (95% CI) for pooled cohort, lagged by 15 years:</u>            Q1: 1.0            Q2: 1.0 (0.83, 1.3)            Q3: 1.3 (1.0, 1.6)            Q4: 1.5 (1.2, 1.8)            Q5: 1.5 (1.2, 1.9)</p> <p><u>ORs (95% CI) for pooled cohort, miners only:</u>            Q1: 1.0            Q2: 0.9 (0.66, 1.2)            Q3: 0.81 (0.59, 1.1)            Q4: 1.2 (0.89, 1.6)            Q5: 1.4 (1.0, 1.9)</p> <p><u>ORs (95% CI) for pooled cohort, non-miners only:</u>            Q1: 1.0            Q2: 1.2 (0.92, 1.6)            Q3: 2.1 (1.6, 2.8)            Q4: 1.7 (1.2, 2.4)            Q5: 1.5 (0.97, 2.4)</p> <p><u>Estimated excess lifetime risk (95% CI), above background risk lifetime risk of 3–6% for death due to lung cancer, for</u></p>

## 3. HEALTH EFFECTS

**Table 3-14. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica**

Reference	Studies in analysis	Methods and exposure	Outcomes
			<u>exposure to 0.1 mg/m<sup>3</sup> respirable c-silica for 45 years, by location:</u> - China: 1.1% (0.1, 2.3) - United States: 1.7% (0.2, 3.6) - Finland: 1.3% (0.1, 2.9)

<sup>a</sup>High number due 1.6 million c-silica-exposed workers participating in the 1970 Finnish national census (Pukkala et al. 2005).

CI = confidence interval; OR = odds ratio; RR = risk ratio; SMR = standardized mortality ratio

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cumulative exposure quintiles (<0.4 [referent]; 0.4–2.0; 2.0–5.4, 5.4–12.8, and >12.8 mg/m<sup>3</sup>-year) showed increased ORs for lung cancer at cumulative exposures >2.0 mg/m<sup>3</sup>-year, based on both no lag time and a 15-year lag time. A significant positive trend was observed using the log of cumulative exposure lagged for 15 years (p=0.015; coefficient=0.062). For a 45-year exposure to 0.1 mg/m<sup>3</sup>, the estimated excess for death due to lung cancer was 1.1–1.7% above a background lifetime risk for death due to lung cancer of 3–6%. A meta-analysis of over 1.6 million c-silica-exposed workers with undefined silicosis status from diatomaceous earth, industrial sand, mining, foundry, quarry, and pottery industries showed an exposure-response relationship between cumulative c-silica exposure and lung cancer (Lacasse et al. 2009). For cumulative exposures of 1.0 and 6.0 mg/m<sup>3</sup>-year, estimated risk ratios (95% CI) were 1.22 (1.01, 1.47) and 1.84 (1.48, 2.28), respectively. The exposure-response relationship between cumulative exposure to c-silica and relative risk of lung cancer (no lag time) is shown in Figure 3-3. The study authors stated that results showed an exposure-response relationship with an estimated exposure threshold for lung cancer of >1.84 mg/m<sup>3</sup>-year. Based on a meta-analysis of two studies, Finkelstein (2000) estimated increased risk ratios for cumulative exposures ≥2.0 mg/m<sup>3</sup>-year, with estimated RRs (95% CI) ranging from 1.15 (1.09, 1.20) to 1.74 (1.65, 1.82) for exposures ranging from 2.0 to 5 mg/m<sup>3</sup>-year, respectively.

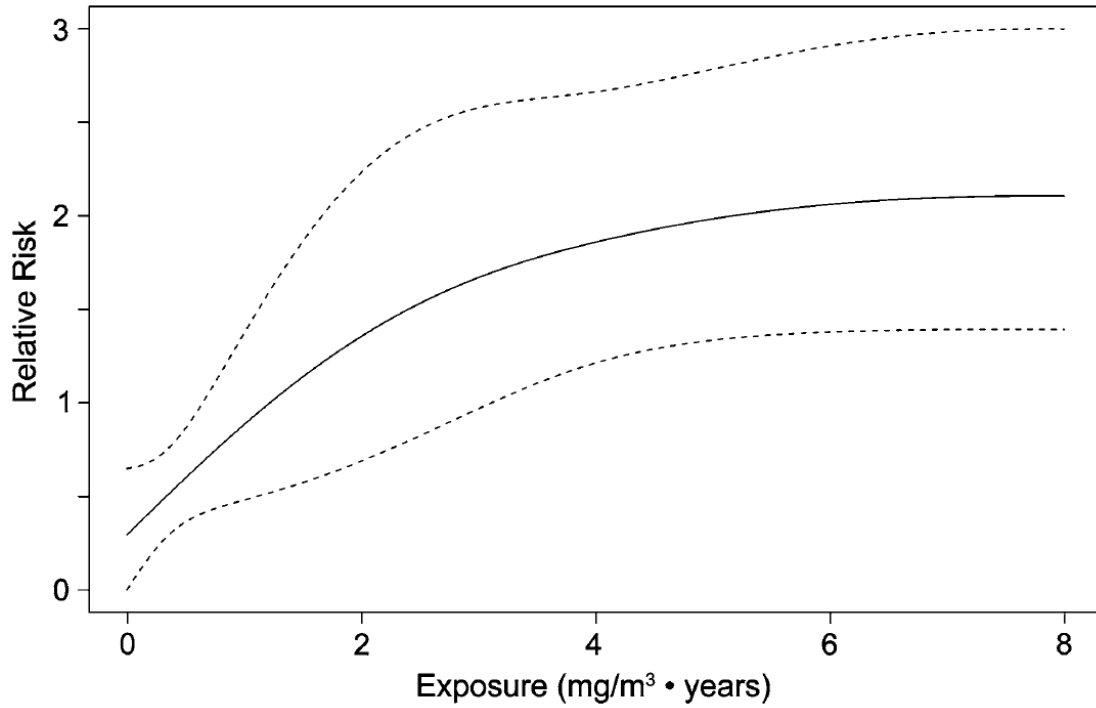
Lung Cancer and the Role of Silicosis. Numerous studies have explored the relationship between silicosis and increased risk of lung cancer (Brown 2009; Checkoway 2000; Checkoway and Franzblau 2000; Cox 2011; NIOSH 2002; Pelucchi et al. 2006; Smith et al. 1995; Soutar et al. 2000; Steenland and Ward 2014). Details of recent meta- or pooled analyses providing information on the relationship between silicosis status and increased risk of lung cancer are provided in Table 3-15 (Erren et al. 2009b; Kurihara and Wada 2004; Pelucchi et al. 2006). In general, studies show that the risk of lung cancer is increased in workers with and without silicosis, but the association between workers with silicosis and lung cancer is stronger than for workers without silicosis. For workers with silicosis, risk ratios and SMRs (95% CI) ranged from 1.52 (1.02, 2.26) to 4.47 (3.17, 6.30), compared to a range of 0.97 (0.69, 1.38) to 1.2 (1.0, 1.4) for workers without silicosis.

Crystalline Silica, Smoking, and Lung Cancer. Adjusting for potential confounding bias from smoking is important in studies examining the association between c-silica and lung cancer, because smoking is a risk factor for lung cancer (Brown 2009; Cox 2011; NIOSH 2012). However, smoking may also interact with silica to produce lung cancer. Results of a retrospective study in China showed increased lung cancer risk in never-smokers in association with c-silica exposure and that the change in risk with increasing exposure was similar in never-smokers and ever-smokers (Table 3-16) (Liu et al. 2013). The



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**Figure 3-3. Dose-Response Relationship Between Exposure to Silica and Relative Risk of Lung Cancer with its 95% Confidence Limit (No Lag Time)**



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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
Erren et al. 2009a, 2009b	<p>A. <u>Workers without silicosis</u></p> <p><u>Cohort studies:</u> Armstrong et al. 1979 (Australia; miners); Puntoni et al. 1988 (Italy; refractory brick workers); Mehnert et al. 1990 (Germany; quarry workers); Amandus and Costello 1991 (United States; miners); Dong et al. 1995 (China; refractory brick workers); Finkelstein 1995 (Canada; miscellaneous industries); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (United States; diatomaceous earth workers)</p> <p><u>Case-control studies:</u> Armstrong et al. 1979 (Australia; miners); Mastrangelo et al. 1988 (Italy; miscellaneous industries); Lagorio et al. 1990 (Italy; ceramic workers); Sherson et al. 1991 (Denmark; foundry workers)</p>	<p><u>Study type:</u> meta-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis, and (B) with undefined silicosis status</p> <p><u>Literature search dates:</u> 1966 through January 2007</p> <p><u>Adjustments:</u> Three studies adjusted for smoking (Dong et al. 1995; Lagorio et al. 1990; Mastrangelo et al. 1988); no smoking adjustment was made for other studies</p> <p><u>Adjustments:</u> except for smoking, adjustments for individual studies were not reported</p> <p><u>Statistical analysis:</u> a multi-stage strategy approach was used to examine heterogeneity between studies (fixed-effect summaries and 95% CI for various combinations of studies were calculated, with individual studies weighted by precision); homogeneity of contributing results was analyzed by <math>\chi^2</math> statistics; interactions with covariates was examined by meta-regression.</p> <p><u>Exposure:</u> Not reported for overall cohort or individual studies</p>	<p>A. <u>For c-silica-exposed workers without silicosis</u></p> <p>Total number of workers included in analysis: not reported</p> <p>Risk ratios (95% CI) for:</p> <ul style="list-style-type: none"> <li>- Entire cohort: 1.2 (1.1, 1.3)</li> <li>- Cohorts adjusted for smoking (three studies): 1.0 (0.8, 1.3)</li> <li>- Cohorts not adjusted for smoking (eight studies): 1.2 (1.1, 1.4)</li> </ul> <p>The increased risk of 20% appears to be influenced by smoking.</p>
	<p>B. <u>Workers with undefined silicosis status</u></p> <p><u>Cohort studies:</u> Armstrong et al. 1979 (Australia; miners); Neuberger et al. 1986 (Austria; miscellaneous); Westerholm et al. 1986 (Sweden; miscellaneous); Finkelstein et al. 1987 (Canada; miners); Zambon et al. 1987 (Italy; miscellaneous); Puntoni et al. 1988 (Italy; refractory brick); Infante-Rivard et al. 1989 (Canada; miscellaneous); Mehnert et al. 1990 (Germany; quarry workers); Ng et al. 1990 (China; miscellaneous); Tornling et al. 1990 (Sweden; miscellaneous); Amandus and Costello 1991 (United States, miners); Amandus et al. 1991 (miscellaneous); Chen et al. 1992 (China; miscellaneous); Dong et al. 1995 (China; refractory brick workers);</p>		<p>B. <u>For c-silica-exposed workers with undefined silicosis status</u></p> <p>Total number of workers included in analysis: not reported</p> <p>Risk ratios (95% CI) for:</p> <ul style="list-style-type: none"> <li>- All studies combined: 2.1 (1.9, 2.3)</li> <li>- Cohort studies: 2.0 (1.7, 2.3)</li> <li>- Case-control studies: 2.3 (1.8, 2.9)</li> <li>- SIR studies: 2.6 (2.1, 3.3)</li> <li>- Mortality OR studies: 1.8 (1.3, 2.7)</li> <li>- Studies adjusted for smoking (nine studies): 2.2 (1.8, 2.7)</li> <li>- Studies not adjusted for smoking: 2.0 (1.8, 2.3)</li> </ul>

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
	<p>Goldsmith et al. 1995 (miscellaneous); Meijers et al. 1996 (Netherlands; ceramic workers); Starzynski et al. 1996 (Poland; miscellaneous); Wang et a; 1996 (China; metal workers); de Klerk and Musk 1998 (Australia; gold miners); Checkoway et al. 1999 (United States; diatomaceous earth workers); Chan et al. 2000 (China; miscellaneous); Carta et al. 2001 (Italy; metal miners); Berry et al. 2004 (Australia; miscellaneous); Ulm et al. 2004 (Germany; quarry)</p> <p><u>Case-control studies:</u> Steenland and Beaumont 1986 (United States; granite workers); Mastrangelo et al. 1988 (Italy; miscellaneous); Cocco et al. 1990 (Italy; miscellaneous); Lagorio et al. 1990 (Italy; miscellaneous); Hnzido et al. 1997 (South Africa; gold miners); Finkelstein 1998 (Canada; miscellaneous); Cocco et al. 2001 (China; miscellaneous); Tsuda et al. 2002 (Japan; refractory brick)</p> <p><u>SIR studies:</u> Chia et al. 1991 (Singapore; miscellaneous); Sherson et al. 1991 (Denmark; foundry workers); Partanen et al. 1994 (Finland; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous).</p> <p><u>Mortality OR studies:</u> Schuler et al. 1986 (Switzerland; miscellaneous); Forastiere et al. 1989 (Italy; ceramic workers)</p>		Homogeneity statistics indicated a substantial difference between studies, although tests for publication bias were negative.

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
Kurihara and Wada 2004	<p>A. <u>Workers without silicosis</u></p> <p><u>Cohort studies</u>: Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1995 (United States; dusty trade workers); Dong et al. 1995 (China; brick workers); Finkelstein 1995 (Canada; miners and other workers); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (California; diatomaceous earth miners)</p> <p><u>Case-control studies</u>: Mastrangelo et al. 1988 (Italy; miscellaneous industries); Forastiere et al. 1986 (Italy; quarry workers; ceramic workers)</p> <p>B. <u>Workers with undefined silicosis status</u></p> <p><u>Cohort studies</u>: Costello and Graham 1988 (Vermont; granite workers); Guenel et al. 1989 (Denmark; stone workers); Mehnert et al. 1990 (Germany; quarry workers); Merlo et al. 1991 (Italy; brick workers); Sherson et al. 1991 (Denmark; foundry workers); Cocco et al. 1994 (Italy; miners); Costello et al. 1995 (United States; stone crushers); Dong et al. 1995 (China; brick workers); Steenland and Brown 1995b (South Dakota; gold miners); Meijers et al. 1996 (Netherlands; ceramic workers); Rafnsson and Gunnarsdottir 1997 (Iceland; diatomaceous earth workers); Cherry et al. 1998 (United Kingdom; pottery workers); de Klerk and Musk 1998 (Australia; gold miners); Checkoway et al. 1999 (California; diatomaceous earth workers); McDonald et al. 2001 (United States and</p>	<p><u>Study type</u>: meta-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis; (B) with undefined silicosis status; (C) with silicosis; and (D) with silicosis by smoking status</p> <p><u>Literature search dates</u>: 1966–2001</p> <p><u>Adjustments</u>: adjustments in individual studies included, age, sex, calendar period, race, region, smoking; individual studies may not have included all adjustments listed</p> <p><u>Statistical analysis</u>: random effects model; publication bias assessed by funnel plot and Kendall rank correlation test; association between standardized effects and precision assessed by linear regression test intercept analysis</p> <p><u>Exposure</u>: not reported for overall cohort or individual studies</p>	<p>A. <u>Workers without silicosis</u> Risk ratios (95% CI) for lung cancer (combined cohort and case-control studies): 0.96 (0.81, 1.15)</p> <p>B. <u>Workers with undefined silicosis status</u> Risk ratios (95% CI) for lung cancer: - Cohort studies: 1.29 (1.20, 1.40) - Case-control studies: 1.42 (1.22, 1.65) - All studies: 1.32 (1.23, 1.41)</p> <p>C. <u>Workers with silicosis</u> Risk ratios (95% CI) for lung cancer: - Cohort studies: 2.49 (2.08, 2.99) - Case-control studies: 1.89 (1.45, 2.48) - All studies: 2.37 (1.98, 2.84)</p> <p>D. <u>Workers with silicosis by smoking status</u> - Risk ratio (95% CI) for lung cancer in smokers with silicosis: 4.47 (3.17, 6.30) - Risk ratio (95% CI) for lung cancer in nonsmokers with silicosis: 2.24 (1.46, 3.43)</p>

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
	Canada; sand workers); Steenland et al. 2001a (United States; sand workers); Stern et al. 2001 (plasterers and masons)		
	<u>Case-control studies:</u> Forastiere et al. 1986 (Italy; quarry workers; ceramic workers); McLaughlin et al. 1992 (China; iron-copper miners; potteries workers; tin miners; tungsten miners); De Stefani et al. 1996 (Uruguay; miscellaneous); Cherry et al. 1998 (United Kingdom; pottery and sandstone workers); Ulm et al. 1999 (Germany; ceramic workers; quarry workers); Bruske-Hofeld et al. 2000 (Germany; miscellaneous); Martin et al. 2000 (France; miscellaneous); Szadkowska-Stanczyk and Szymczak 2001 (Poland; pulp and paper workers)		
	C. <u>Workers with silicosis</u>		
	<u>Cohort studies:</u> Infante-Rivard et al. 1989 (Canada; miscellaneous); Ebihara et al. 1990 (Japan; miscellaneous); Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1995 (United States; dusty trade workers); Dong et al. 1995 (China; brick workers); Meijers et al. 1996 (Netherlands; ceramic workers); Brown et al. 1997 (Sweden; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous); Finkelstein 1998 (Canada; miners); Checkoway et al. 1999 (California; diatomaceous earth workers); Chan et al. 2000 (Hong Kong; miscellaneous)		

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
	<p><u>Case-control studies:</u> Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1992 (North Carolina; dusty trade workers); Dong et al. 1995 (China; brick workers); Finkelstein 1995 (Canada; miners and other workers); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (California; diatomaceous earth miners)</p> <p>D. <u>Workers with silicosis by smoking status</u></p> <p><u>Cohort studies with silicosis based on smoking:</u> Dong et al. 1995 (China; brick workers); Amandus et al. 1995 (United States; dusty trade workers); Ebihara et al. 1990 (Japan; miscellaneous); Ebihara and Kawami 1998 (Japan; miscellaneous); Infante-Rivard et al. 1989 (Canada; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous)</p> <p><u>Case-control studies:</u> Mastrangelo et al. 1988 (Italy; miscellaneous industries); Hnizido et al. 1997 (South Africa; gold miners)</p>		

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
Pelucci et al. 2006	<p>A. <u>Workers without silicosis</u></p> <p><u>Cohort studies</u>: Checkoway et al. 1999 (United States; diatomaceous earth workers);</p> <p><u>Case-control studies</u>: Ulm et al. 1999 (Germany; stone, quarry, and ceramic workers)</p> <p>B. <u>Workers with undefined silicosis status</u></p> <p><u>Cohort studies</u>: Brown and Rushton 2005 (United Kingdom; industrial sand workers); Checkoway et al. 1997 (United States; diatomaceous earth workers); Checkoway et al. 1996 (United States; phosphate industry); Cherry et al. 1998 (United Kingdom; pottery refractory and sandstone workers); Chiazzie et al. 1997 (United States; filament glass workers); Coggiola et al. 2003 (Italy; talc miners and millers); de Klerk and Musk 1998 (Australia; gold miners); Finkelstein and Verma 2005<sup>a</sup> (Canada; brick workers); Graham et al. 2004 (United States; granite workers); Kauppinen et al. 2003 (Finland; asphalt workers); McDonald et al. 2005 (United States; industrial sand workers); Merlo et al. 2004 (Italy; graphite electrode manufacturing); Moshhammer and Neuberger 2004 (Austria; miscellaneous); Moulin et al. 2000 (France; stainless steel workers); Ogawa et al. 2003 (stone cutters); Pukkala et al. 2005<sup>a</sup> (Finland; miscellaneous); Rafnsson and Gunnarsdottir 1997 (Iceland; diatomaceous earth workers); Smailyte et al. 2004 (Lithuania; cement production);</p>	<p><u>Study type</u>: pooled-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis; (B) with undefined silicosis status; and (C) with silicosis</p> <p><u>Literature search dates</u>: 1996–July 2005 (studies published after the IARC 1997 assessment)</p> <p><u>Adjustments</u>: not reported for overall cohort; some adjustments reported for individual studies</p> <p><u>Statistical analysis</u>: pooled relative risks calculated according to study design, using fixed and random effect models</p> <p><u>Exposure</u>: not reported for overall cohort</p>	<p>A. <u>Workers without silicosis</u> Relative risks (95% CI) (random effects model)</p> <ul style="list-style-type: none"> <li>- Cohort studies: 1.19 (0.87, 1.57)</li> <li>- Case-control studies: 0.97 (0.68, 1.38)</li> </ul> <p>B. <u>Workers with undefined silicosis status</u> Relative risks (95% CI) (random effects model)</p> <ul style="list-style-type: none"> <li>- Cohort studies: 1.25 (1.18, 1.33)</li> <li>- Case-control studies: 1.41 (1.18, 1.70)</li> </ul> <p>C. <u>Workers with silicosis</u> Relative risks (95% CI) (random effects model)</p> <ul style="list-style-type: none"> <li>- Cohort studies: 1.69 (1.32, 2.16)</li> <li>- Case-control studies: 3.27 (1.32, 8.2)</li> </ul> <p><u>All cohort studies, for any silicosis status</u></p> <ul style="list-style-type: none"> <li>- Relative risk (95% CI) (random effects model): 1.34 (1.25, 1.45)</li> <li>- Relative risk (95% CI) (fixed effects model): 1.19 (1.16, 1.21)</li> </ul> <p><u>All case-control studies, for any silicosis status</u></p> <ul style="list-style-type: none"> <li>- Relative risk (95% CI) (random effects model): 1.41 (1.18, 1.67)</li> <li>- Relative risk (95% CI) (fixed effects model): 0.99 (0.98, 1.00)</li> </ul> <p><u>By occupational setting</u> Cohort studies (number of cohorts) and relative risks (95% CI)</p>

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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
	Steenland and Greenland 2004 (United States; industrial sand workers); Stone et al. 2004 (United States; fiberglass workers)		<ul style="list-style-type: none"> <li>- Miners (3): 1.17 (1.03, 1.32)</li> <li>- Sand workers (3) 1.29 (1.03, 1.61)</li> <li>- Ceramic, diatomaceous earth, and refractory brick workers (4): 1.40 (1.11, 1.75)</li> </ul>
	<p><u>Case-control studies:</u> Bruske-Hohlfeld et al. 2000 (Germany; miscellaneous); Calvert et al. 2003 (United States; miscellaneous); Chen and Chen 2002<sup>a</sup> (China; tin miners); Cocco et al. 2001<sup>a</sup> (miners and pottery factory workers); De Stefani et al. 1996 (Uruguay; miscellaneous); Hnizdo et al. 1997<sup>a</sup> (South Africa; cold miners); Martin et al. 2000 (France; electricity and gas workers); Menvielle et al. 2003 (New Caledonia; miscellaneous); Rodriguez et al. 2000<sup>a</sup> (Spain; iron and steel foundry workers); Szadkowska-Stanczyk and Szymczak 2001 (Poland; pulp and paper workers); Tsuda et al. 2002 (China; refractory brick workers); Watkins et al. 2002<sup>a</sup> (United States; roofing manufacturing and asphalt production workers); Westberg and Bellander 2003<sup>a</sup> (Sweden; foundry workers)</p> <p>C. <u>Workers with silicosis</u></p> <p><u>Cohort studies:</u> Berry et al. 2004 (South New Wales; miscellaneous); Brown et al. 1997 (Sweden; miscellaneous); Carta et al. 2001 (Italy; miners and quarry workers); Chan et al. 2000 (China; miscellaneous); Checkoway et al. 1999 (United States; diatomaceous earth workers); Starzynski et al. 1996 (Poland, miscellaneous); Ulm et al. 2004 (Germany; stone and quarry workers)</p>		<ul style="list-style-type: none"> <li>- Miscellaneous exposure (10): 1.17 (1.12, 1.22)</li> </ul> <p>Case-control studies (number of cohorts and relative risks (95% CI))</p> <ul style="list-style-type: none"> <li>- Miners (4): 1.47 (1.19, 1.82)</li> <li>- Sand workers (0): –</li> <li>- Ceramic, diatomaceous earth, and refractory brick workers (3): 1.26 (0.99, 1.62)</li> <li>- Miscellaneous exposure (10): 1.24 (1.02, 1.52)</li> </ul>



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**Table 3-15. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status**

Reference	Studies in analysis	Exposure and methods	Outcomes
	<u>Case-control studies</u> : Finkelstein 1998 (Canada; miscellaneous)		

<sup>a</sup>Studies included in analysis by occupational setting.

CI = confidence interval; OR = odds ratio; SIR = standardized incidence ratio

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**Table 3-16. Lung Cancer Risk in Smokers and Nonsmokers Exposed to c-Silica**

Reference	Study design and industry	Cohort and methods	Exposure	Outcome
Liu et al. 2013	<p><u>Study design:</u> retrospective cohort</p> <p><u>Industry:</u> metal miners, pottery workers in China</p>	<p><u>Cohort:</u> 34,018 Chinese workers (86% male) not likely exposed to other lung carcinogens; employed during 1960–1974, with follow-up to 2003</p> <p><u>Methods:</u> To investigate the joint effect of silica and smoking, hazard ratios were estimated by crossed dichotomized silica exposure (exposed = A+, unexposed = A-) and smoking (ever smokers = B+, never smokers = B-)</p> <p><u>Adjustments:</u> facility, sex, year of birth, smoking amount</p>	<p><u>Exposure quartiles (Q) (mg/m<sup>3</sup>-year):</u></p> <ul style="list-style-type: none"> <li>- Q1: 0</li> <li>- Q2: &gt;0</li> <li>- Q3: &lt;1.12</li> <li>- Q4: ≥1.12</li> </ul>	<p><u>Nonsmokers</u></p> <p>Lung cancer/nonsmokers in quartile:</p> <ul style="list-style-type: none"> <li>- Q1: 27/4960</li> <li>- Q2: 50/7211</li> <li>- Q3: 34/7285</li> <li>- Q4: 43/4886</li> </ul> <p>HRs (95% CI):</p> <ul style="list-style-type: none"> <li>- Q1: 1</li> <li>- Q2: 1.10 (0.68-1.78)</li> <li>- Q3: 1.0</li> <li>- Q4: 1.60 (1.01, 2.55)</li> </ul> <p><u>Smokers</u></p> <p>Lung cancer deaths in smokers/smokers in quartile:</p> <ul style="list-style-type: none"> <li>- Q1: 101/5430</li> <li>- Q2: 368/16,417</li> <li>- Q3: 199/10,850</li> <li>- Q4: 270/10,997</li> </ul> <p>HRs (95% CI) in smokers:</p> <ul style="list-style-type: none"> <li>- Q1: 2.75 (1.74, 4.35)</li> <li>- Q2: 3.83 (2.48, 5.90)</li> <li>- Q3: 3.42 (2.32, 5.05)</li> <li>- Q4: 5.07 (3.41, 7.52)</li> </ul> <p>Study authors stated that “the joint effect of [c]-silica and smoking was more than additive and close to multiplicative.”</p>

CI = confidence interval; HR = hazard ratio

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study authors stated that “the joint effect of [*c*-]silica and smoking on lung cancer was more than additive and close to multiplicative.”

Other Cancers. Cancers of the esophagus, stomach, intestine, and kidney have been reported in *c*-silica-exposed workers; however, associations between *c*-silica and these cancers have not been thoroughly studied or established (IARC 2012; NIOSH 2002). In general, findings of these studies have been inconsistent and studies often include co-exposures to other risk factors (Brown 2009). In many cases, observations of cancers other than lung were made in studies investigating the association between *c*-silica exposure and lung cancer, and appropriate adjustments for confounding factors were not considered (Chen and Tse 2012; NIOSH 2002).

***Amorphous Silica.*** A limited number of human studies have reported an increased risk of lung cancer or mesothelioma in industries with occupational exposure to *a*-silica; however, the usefulness of these studies is limited due to potential co-exposure to *c*-silica and lack of quantitative exposure data.

The mortality from lung cancer was increased in workers exposed to silica (both amorphous and quartz) (SMR: 1.43; 95% CI: 1.09, 1.84) in a cohort of 2,570 diatomaceous earth workers (Checkoway et al. 1993). However, the contribution of *a*-silica to increased mortality is unknown, as a separate analysis for the population of workers exposed only to *a*-silica (n=129) was not conducted. Similarly, an increased risk for lung cancer was observed in a cohort of 231 refractory brick workers exposed to a mixture of *a*-silica and *c*-silica; however, only *c*-silica levels were measured (McLaughlin et al. 1997; Merget et al. 2002).

A limited number of reports from the sugarcane industry suggest a potential increased risk for lung cancer and/or mesothelioma in sugarcane farmers, although available data are inconclusive. Since sugarcane farmers are exposed to biogenic *a*-silica fibers (IARC 1997), this suggests a possible association between biogenic *a*-silica fiber exposure and lung cancer and/or mesothelioma; however, exposure levels to *a*-silica were not available in these studies, and sugarcane workers are also exposed to *c*-silica during the harvesting process when sugarcane plants are burned (Le Blond et al. 2010). A case-series report from India suggested that five observed cases of mesothelioma in sugarcane workers with no known exposure to asbestos could have been due to biogenic *a*-silica fiber exposure (Das et al. 1976). In a case-control study, an increased risk of lung cancer was observed in sugarcane farmers in Southern Louisiana (RR: 2.3; 95% CI: 1.8–3.0) (Rothschild and Mulvey 1982). When stratified by smoking, the association was only observed in farmers who were also smokers (OR: 2.6; 95% CI 1.8–4.0). However, other case-

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control studies did not find associations between working at, or living near, a sugarcane farm and increased risk for lung cancer or mesothelioma (Brooks et al. 1992; Sinks et al. 1994).

No treatment-related tumors were reported in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel  $\alpha$ -silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981) or rats, guinea pigs, or rabbits following exposure to precipitated  $\alpha$ -silica at 126 mg/m<sup>3</sup> for 8 hours/day, 7 days/week for 12–24 months (Schepers 1981).

#### 3.2.2 Oral Exposure

Studies in humans and animals have evaluated potential health effects associated with silica levels in drinking water (Aschengrau et al. 1989; Dobbie and Smith 1982; Gillette-Guyonnet et al. 2005; Jacquemin-Gadda et al. 1996; Öner et al. 2005, 2006; Radovanovic et al. 1991); however, little information regarding the potential adverse health effects following oral exposure to silica is available. For most human drinking water studies, the silica species is not identified; thus, for the purposes of this assessment, it is assumed that exposure is to forms of  $\alpha$ -silica. Information on oral  $\alpha$ -silica exposure includes a series of dietary studies in animals reported by Lewinson et al. (1994) and a 2-year dietary bioassay in rats and mice with 6- and 12-month interim sacrifices (Takizawa et al, 1988).

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Table 3-17 and plotted in Figure 3-4.

##### 3.2.2.1 Death

**Crystalline Silica.** No studies evaluating mortality in humans following oral exposure to  $\alpha$ -silica were identified.

No mortalities were observed in 3-month-old albino rats exposed to 50 mg  $\alpha$ -silica/kg/day as sodium metasilicate in drinking water for 8 days (Öner et al. 2005, 2006). No mortalities were observed in guinea pigs exposed to 51 mg  $\alpha$ -silica/kg/day as crushed quartz or granite in drinking water for 5 days/week for 4 months (Dobbie and Smith 1982).

**Amorphous Silica.** In an LD<sub>50</sub> study in Sprague-Dawley rats, no deaths were observed during the 4-week observation period following single oral doses of  $\alpha$ -silica up to 7,900 mg/kg in the precipitated

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
<b>ACUTE EXPOSURE</b>									
<b>Death</b>									
1	Rat (Wistar)	2 wk (F)				16000	(20% mortality)	Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	The same animals were used in each dose group (dose was increased in step-wise manner every 2 wks).
<b>Systemic</b>									
2	Rat (Sprague-Dawley)	once (GO)	Bd Wt	5000				Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	
3	Rat (Sprague-Dawley)	once (GO)	Bd Wt	7900				Lewinson et al. 1994 Amorphous (precipitated Sipernat D 17)	
4	Rat (albino)	8 d (W)	Renal	50 M				Oner et al. 2005, 2006 Crystalline (sodium metasilicate)	No treatment-related change in renal function (glomerular filtration rate, urine output).
			Bd Wt	50 M					

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
5	Rat (Wistar)	5-8 wk (F)	Hemato	7500		Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	High-dose group used step-wise increases from 2000-16,000 mg/kg/day (doubling every 2 wks).
			Hepatic		7500 (severe atrophy of liver epithelium)		
			Renal	7500			
			Bd Wt	1000	7500 (decreased body weight)		
6	Rat (Wistar)	6 mo (F)	Resp	500		Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No treatment-related changes in organ weight or histology.
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Endocr	500			
			Bd Wt	500			
7	Gn Pig (NS)	5 d/wk 4 mo (W)	Renal	51 M		Dobbie and Smith 1982 Crystalline (Granite)	

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
8	Gn Pig (NS)	5 d/wk 4 mo (W)	Renal	51 M			Dobbie and Smith 1982 Crystalline (Quartz)	
<b>Immuno/ Lymphoret</b>								
9	Rat (Wistar)	6 mo (F)		500			Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No treatment-related changes in immune organ weight or histology.
<b>Neurological</b>								
10	Rat (Wistar)	6 mo (F)		500			Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No treatment-related changes in brain weight or histology.
<b>Reproductive</b>								
11	Rat (Wistar)	6 mo (F)		500			Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No treatment-related changes in reproductive organ weight or histology.

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
<b>CHRONIC EXPOSURE</b>								
<b>Systemic</b>								
12	Rat (Fischer- 344)	26 wk (F)	Cardio	2220 M 1160 F	2410 F (14% decrease in heart weight)		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	Organ system NOAELs indicate no treatment-related changes in organ weight, histology, or clinical chemistry.
			Hemato	2220 M 2410 F				
			Hepatic	2220 M 2410 F				
			Renal	2220 M 2410 F				
			Bd Wt	2220 M 2410 F				



## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
13	Rat (Fischer- 344) (F)	52 wk (F)	Cardio	2030 M			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in organ weight, histology, or clinical chemistry.
				2220 F				
			Hemato	2030 M				
				2220 F				
			Hepatic	2030 M				
				2220 F				
			Renal	2030 M				
				2220 F				
			Bd Wt	2030 M				
				2220 F				

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
14	Rat (Fischer- 344) (F)	103 wk (F)	Cardio	1900 M			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	Organ system NOAELs indicate no treatment-related changes in organ weight, histology, or clinical chemistry.
				2020 F				
			Hemato	1900 M				
				2020 F				
			Hepatic	1900 M	980 F (14% decrease in liver weight)			
	480 F							
Renal	1900 M							
	2020 F							
Bd Wt	1900 M							
	2020 F							

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
15	Mouse (B6C3F1)	26 wk (F)	Cardio	6700 M 2070 F	3780 F (19% decrease in heart weight)		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	Organ system NOAELs indicate no treatment-related changes in organ weight, histology, or clinical chemistry.
			Hemato	6700 M 9810 F				
			Hepatic	6700 M 3780 F	9810 F (16% decrease in liver weight)			
			Renal	6700 M 2070 F	3780 F (15% decrease in kidney weight)			
			Bd Wt	6700 M 9810 F				

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
16	Mouse (B6C3F1)	52 wk (F)	Cardio	6100 M	2970 F (13% decrease in heart weight)		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	Organ system NOAELs indicate no treatment-related changes in organ weight, histology, or clinical chemistry.
				1640 F				
			Hemato	6100 M				
				7560 F				
			Hepatic	6100 M				
				7560 F				
			Renal	6100 M				
				7560 F				
			Bd Wt	6100 M				
				7560 F				

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
17	Mouse (B6C3F1)	93 wk (F)	Cardio	5910 M			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in organ weight, histology, or clinical chemistry.
				6010 F				
			Hemato	5910 M				
				6010 F				
			Hepatic	5910 M				
				6010 F				
Renal	5910 M							
	6010 F							
Bd Wt	5910 M							
	6010 F							
<b>Immuno/ Lymphoret</b>								
18	Rat (Fischer- 344)	26 wk (F)		2220 M	2410 F (18% decrease in spleen weight)		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in spleen histology.
				1160 F				
19	Rat (Fischer- 344)	52 wk (F)		2030 M			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in spleen weight or histology.
				2220 F				
20	Rat (Fischer- 344)	103 wk (F)		1900 M			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in spleen weight or histology.
				2020 F				

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
21	Mouse (B6C3F1)	26 wk (F)		3280 M 9810 F	6700 M (20% decrease in spleen weight)	Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	
22	Mouse (B6C3F1)	52 wk (F)		6100 M 7560 F		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in spleen weight or histology.
23	Mouse (B6C3F1)	93 wk (F)		5910 M 6010 F		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in spleen weight or histology.
<b>Neurological</b>							
24	Human	NS (W)		0.13 F		Gillette-Guyonnet et al. 2005 Unspecified	Cognitive function did not decline with increasing silica content in drinking water.
25	Human	NS (W)		0.15		Jacqmin-Gadda et al. 1996 Unspecified	Cognitive function did not decline with increasing silica content in drinking water.

## 3. HEALTH EFFECTS

Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
26	Rat (Fischer- 344)	26 wk (F)		2220 M		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
				2410 F			
27	Rat (Fischer- 344)	52 wk (F)		2030 M		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
				2220 F			
28	Rat (Fischer- 344)	103 wk (F)		1900 M		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
				2020 F			
29	Mouse (B6C3F1)	26 wk (F)		6700 M		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
				9810 F			
30	Mouse (B6C3F1)	52 wk (F)		6100 M		Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
				7560 F			

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Table 3-17 Levels of Significant Exposure to Silica - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
31	Mouse (B6C3F1)	93 wk (F)		5910 M 6010 F			Takizawa et al. 1988 Amorphous (Syloid 244 silicon dioxide)	No treatment-related changes in brain weight or histology.
<b>Reproductive</b>								
32	Human	NS (W)		0.04 F	0.23 F (spontaneous abortion)	Aschengrau et al. 1989 Unspecified	Analysis was adjusted for other trace elements and water characteristics in tap water.	
33	Rat (Wistar)	1 gen (F)		500		Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No changes in reproductive function.	
<b>Developmental</b>								
34	Rat (Wistar)	1 gen (F)		500		Lewinson et al. 1994 Amorphous (fumed Aerosil R 972)	No gross anomalies, no changes in pup growth or survival.	

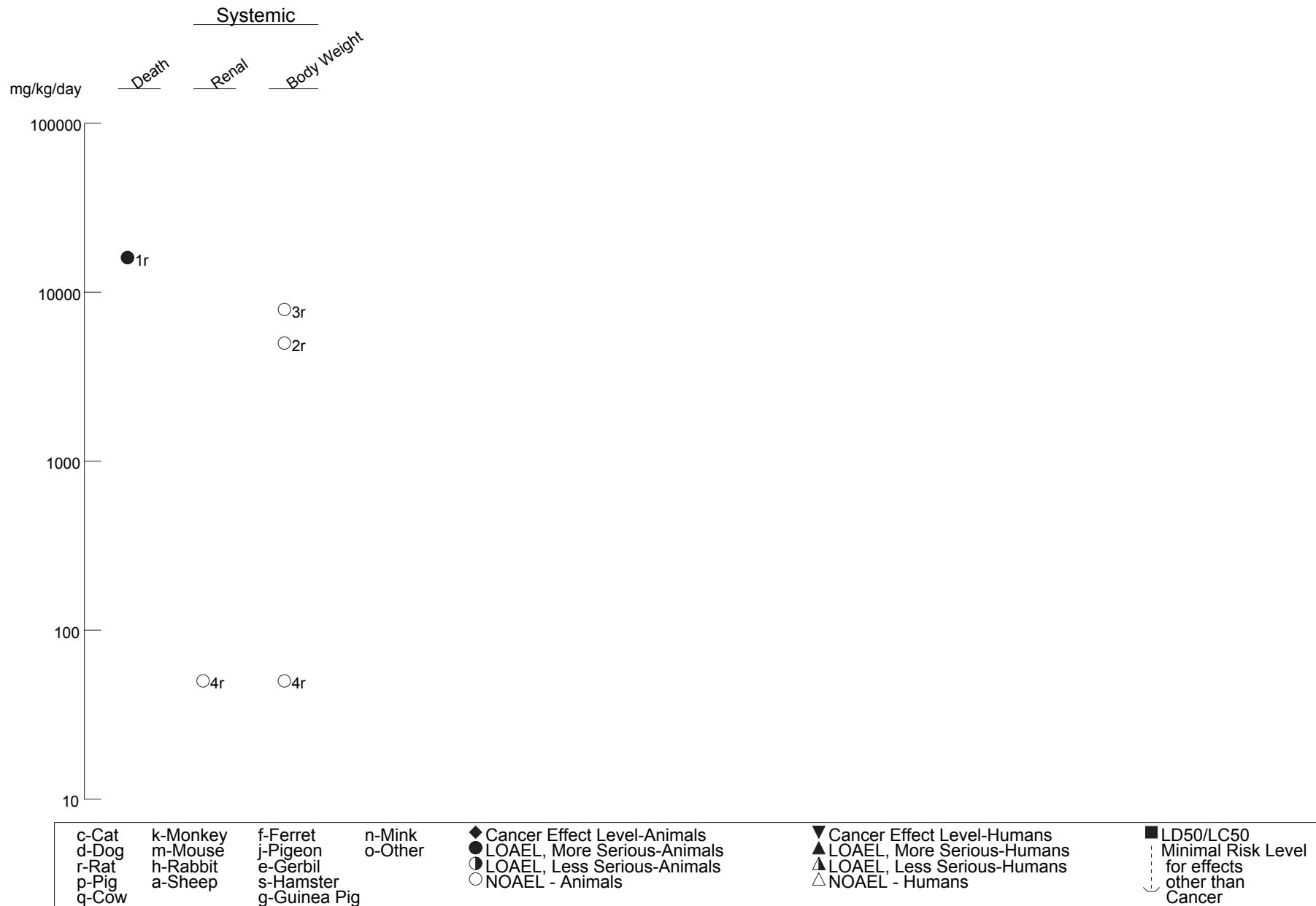
a The number corresponds to entries in Figure 3-4.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation; (GO) = gavage in oil; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)



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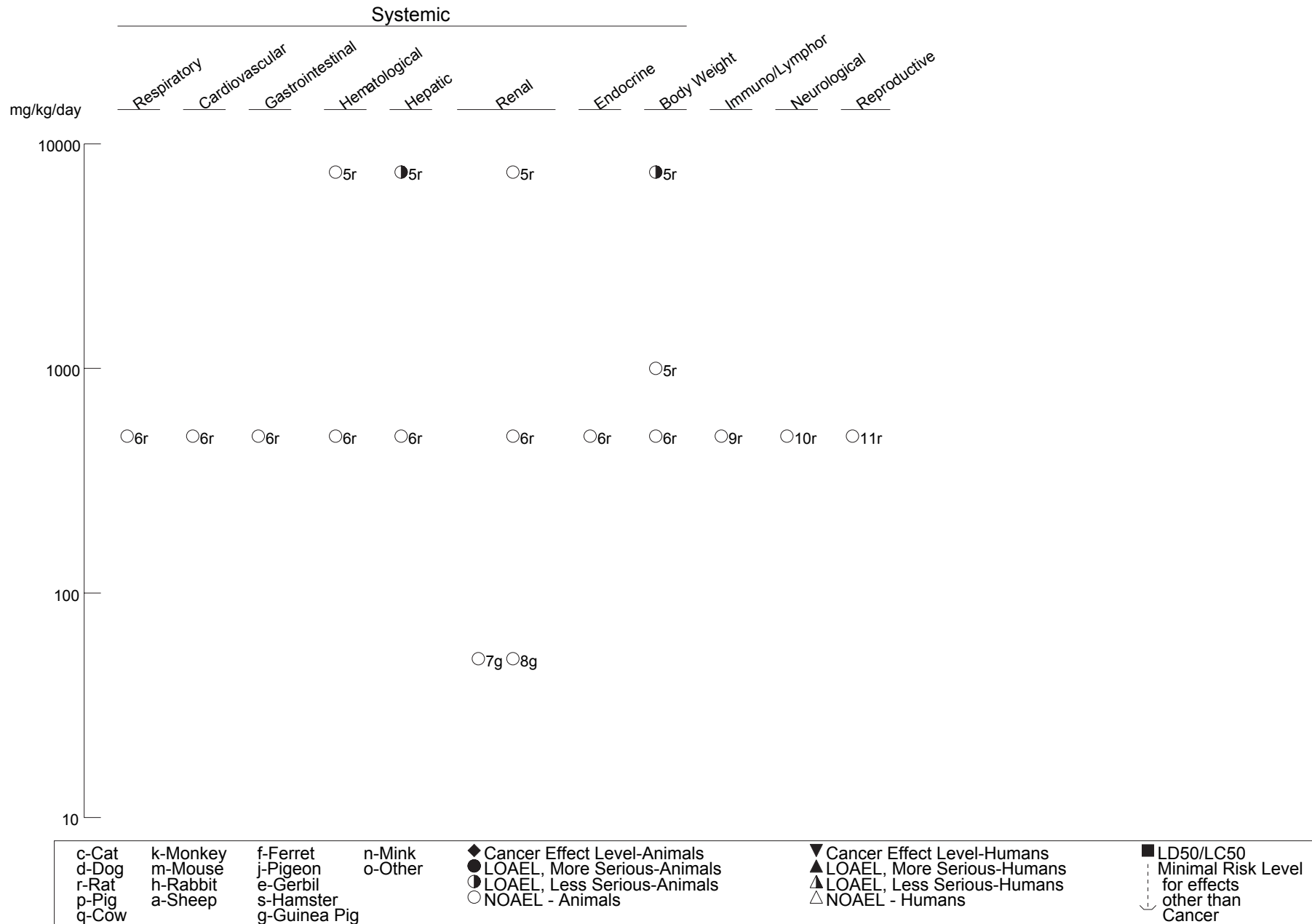
Figure 3-4 Levels of Significant Exposure to Silica - Oral  
Acute (≤14 days)



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Figure 3-4 Levels of Significant Exposure to Silica - Oral (Continued)

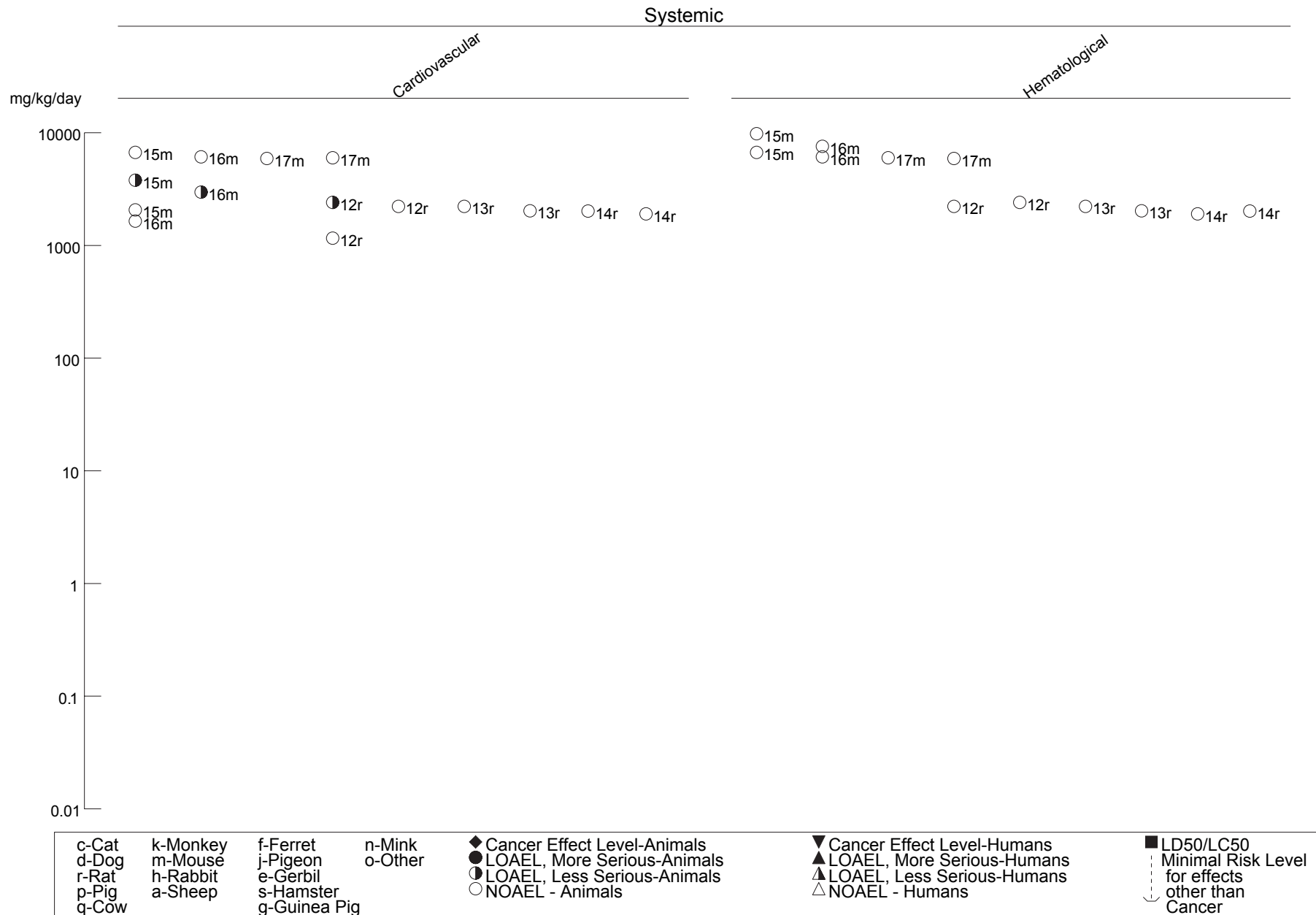
Intermediate (15-364 days)



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Figure 3-4 Levels of Significant Exposure to Silica - Oral (Continued)

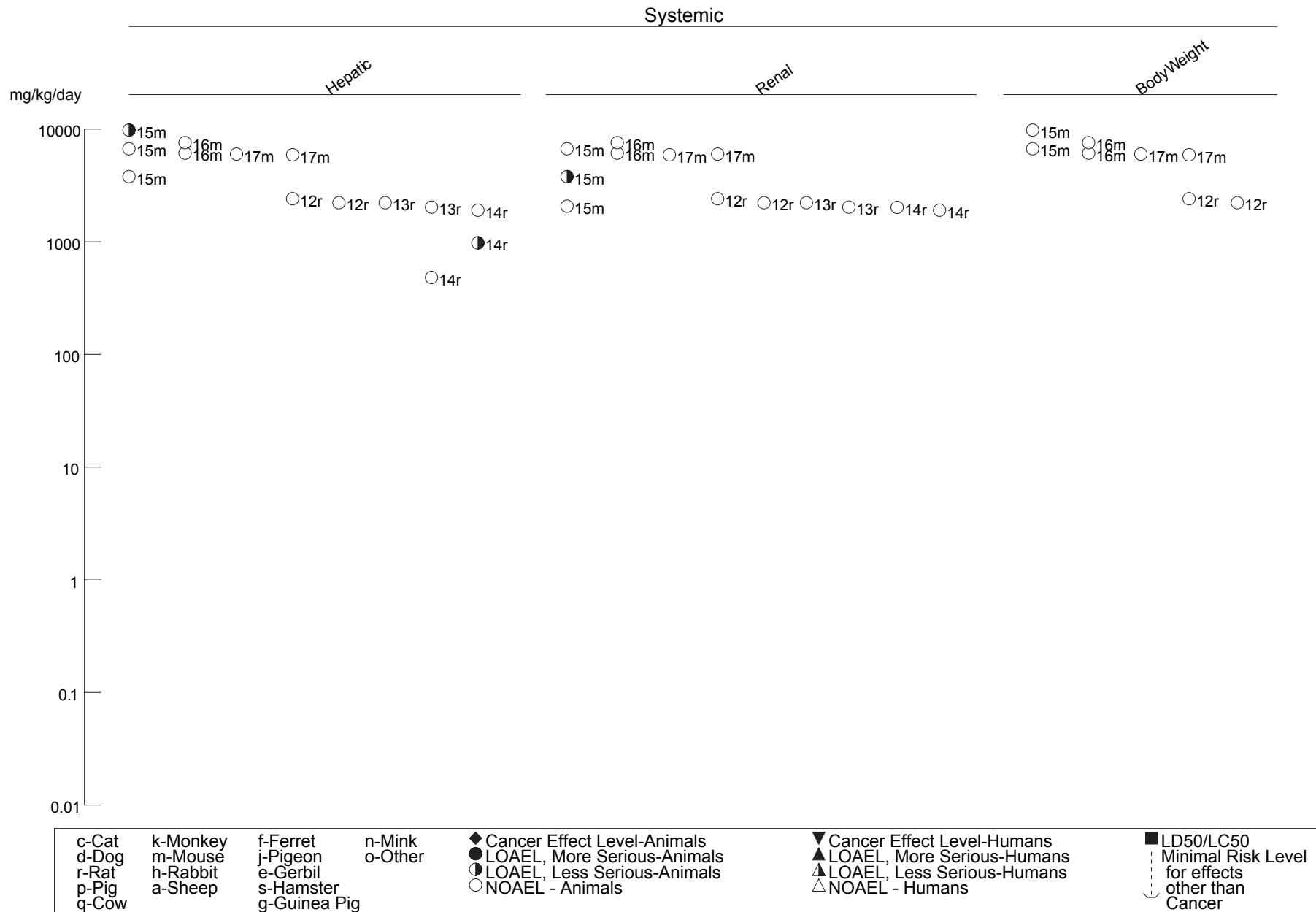
Chronic (≥365 days)



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Figure 3-4 Levels of Significant Exposure to Silica - Oral (Continued)

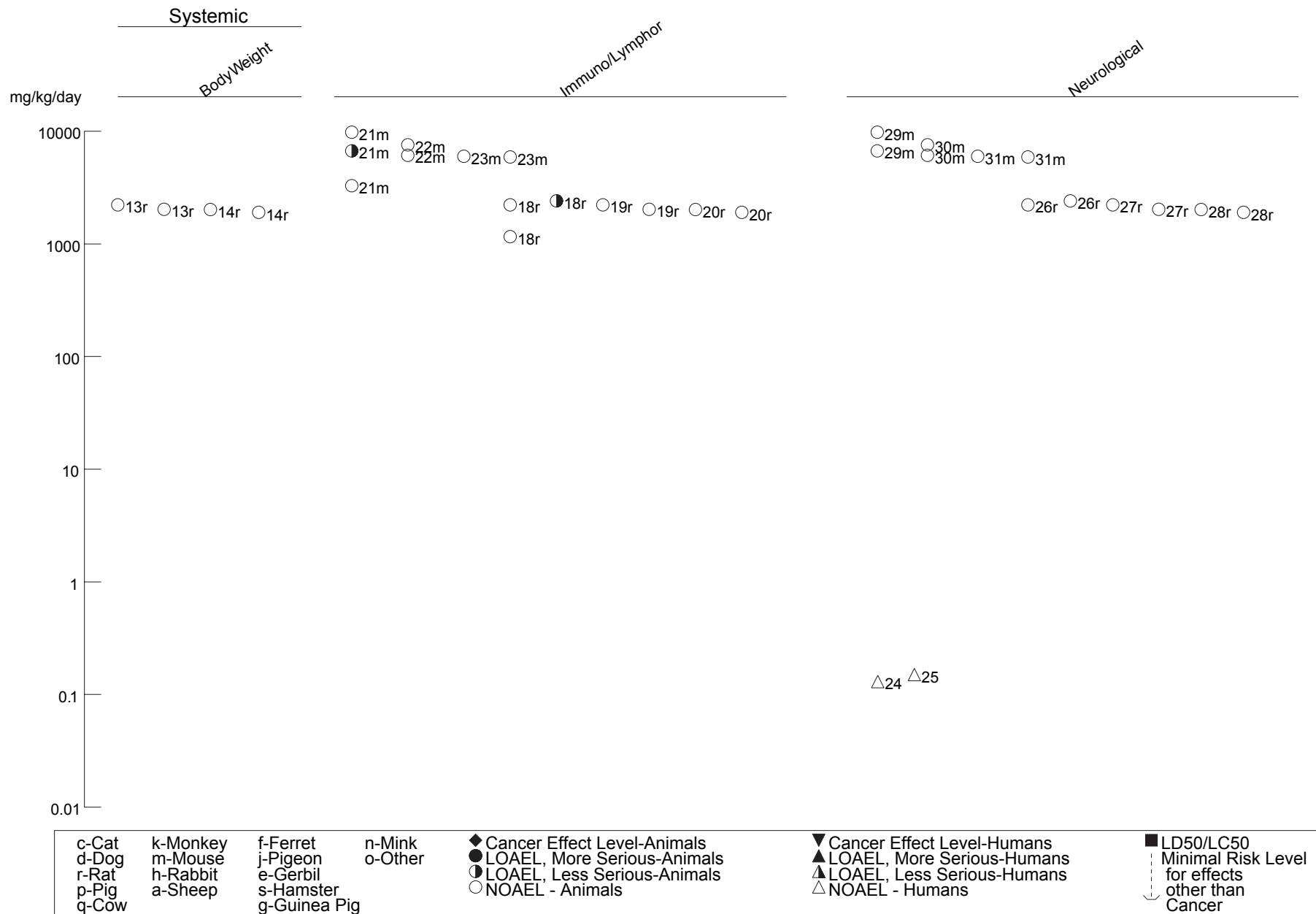
Chronic (≥365 days)



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Figure 3-4 Levels of Significant Exposure to Silica - Oral (Continued)

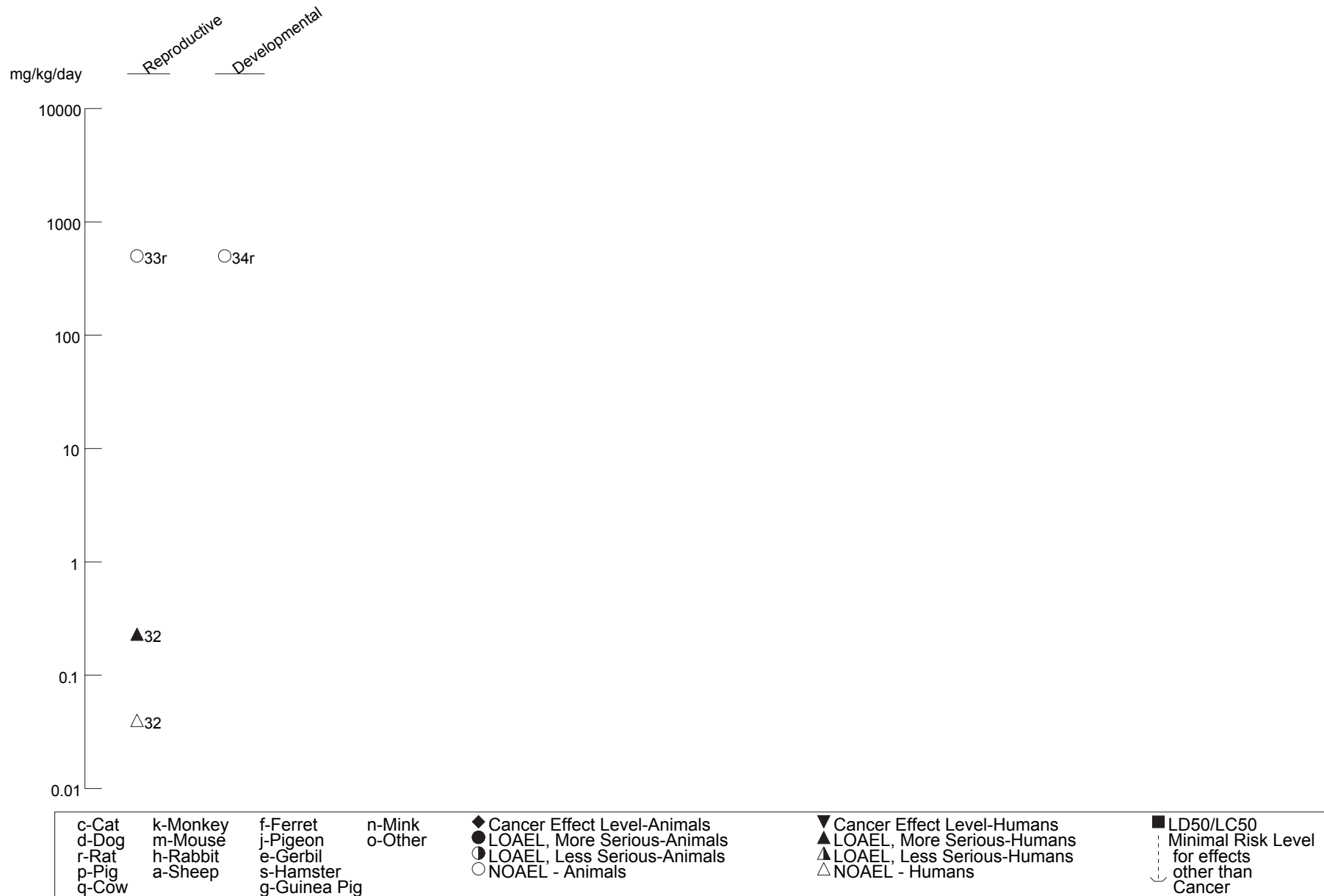
Chronic (≥365 days)



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Figure 3-4 Levels of Significant Exposure to Silica - Oral (Continued)

Chronic (≥365 days)



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hydrophobic silica (PHS) form via gavage in olive oil or 5,000 mg/kg in the fumed hydrophobic silica form (FHS) via gavage in peanut oil (Lewinson et al. 1994).

In an intermediate-duration dietary study in Wistar rats, 2/10 males and 2/10 females died during the 8<sup>th</sup> (and final) week of exposure to time-weighted average (TWA) a-silica (FHS) doses of 7,500 mg/kg/day (Lewinson et al. 1994). Daily doses were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Mortalities were attributed to acute exposure to the highest administered dose of 16,000 mg/kg/day. Clinical signs of toxicity observed during weeks 6–8 included shyness, dirty fur, reduced activity, cachexia, and hemorrhage in the mucous membranes of the eyes and nose. No deaths were observed in rats exposed to dietary a-silica (FHS) at doses up to 1,000 mg/kg/day for 5 weeks or 500 mg/kg/day for 6 months (Lewinson et al. 1994). Mortality in F344 rats and B6C3F1 mice exposed to dietary a-silica (silicon dioxide) for 6 months was comparable to controls at doses up to 2,413 and 9,810 mg/kg/day, respectively (Takizawa et al. 1988)

In a 2-year bioassay, mortality in animals exposed to dietary a-silica (silicon dioxide) was similar to controls at doses up to 2,010 mg/kg/day in F344 rats and 6,010 mg/kg/day in B6C3F1 mice (Takizawa et al. 1988). Similarly, mortality in Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months was comparable to historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

#### 3.2.2.2 Systemic Effects

The systemic effects reported in a limited number of human and animal studies evaluating oral exposure to c-silica and a-silica are described below.

#### Respiratory Effects.

**Crystalline Silica.** No studies evaluating respiratory effects in humans or animals following oral exposure to c-silica were identified.

**Amorphous Silica.** No significant changes in lung weight or histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). No changes in lung histology were observed in Wistar rats exposed to dietary a-silica (FHS) at

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100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

**Cardiovascular Effects.**

**Crystalline Silica.** No studies evaluating cardiovascular effects in humans following oral exposure to c-silica were identified.

Changes in endothelial vasoactivity of the aorta were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg-day as sodium metasilicate in drinking water for 8 days, compared with controls; baseline c-silica content in drinking water was 267 µg/L (Öner et al. 2006). Observed changes included significantly ( $p < 0.05$ ) increased *ex vivo* contractile responses to phenylephrine and dilation responses to acetylcholine, sodium nitroprusside, and the calcium ionophore A-23187 in aortic rings isolated from exposed rats, compared with aortic rings isolated from controls. The toxicological significance of these findings is not known.

**Amorphous Silica.** No significant changes in heart weight or histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). A significant 19% decrease in heart weight was observed in female B6C3F1 mice exposed to dietary a-silica (silicon dioxide) at  $\geq 3,780$  mg/kg/day for 26 weeks; heart weights were not decreased in female B6C3F1 mice at 2,070 mg/kg/day, male B6C3F1 mice at doses up to 6,700 mg/kg/day, or F344 rats at doses up to 2,410 mg/kg/day (Takizawa et al. 1988). In the same study, no treatment-related changes in heart histology were reported in rats or mice exposed for 26 weeks at doses up to 2,410 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988)

In a 2-year dietary bioassay with a-silica (silicon dioxide), no significant changes in heart weight or histology were observed at doses up to 2,010 mg/kg/day in F344 rats or 6,010 mg/kg/day in B6C3F1 mice (Takizawa et al. 1988). However, in the 12-month interim sacrifice, a significant 13–18% decrease in heart weight was observed in female mice at  $\geq 2,970$  mg/kg/day; heart weights were not decreased in female mice at 1,640 mg/kg/day, male mice at doses up to 6,100 mg/kg/day, or rats at doses up to 2,220 mg/kg/day (Takizawa et al. 1988). No histopathological changes were observed in the heart at the 12-month interim sacrifice at doses up to 2,220 in rats or 7,560 mg/kg/day in mice (Takizawa et al. 1988).



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**Gastrointestinal Effects.**

*Crystalline Silica.* No studies evaluating gastrointestinal effects in humans or animals following oral exposure to c-silica were identified.

*Amorphous Silica.* No histopathological changes were observed in the stomach, small intestine, or large intestine of Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994).

**Hematological Effects.**

*Crystalline Silica.* No studies evaluating hematological in humans or animals following oral exposure to c-silica were identified.

*Amorphous Silica.* No significant changes in hemoglobin, erythrocytes, leukocytes, or differential leukocyte counts were observed in Wistar rats exposed to dietary a-silica (FHS) at doses up to 1,000 mg/kg/day for 5 weeks, TWA doses of 7,500 mg/kg/day for 8 weeks, or 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). In F344 rats, no biologically relevant changes in hemoglobin, hematocrit, erythrocytes, leukocytes, or differential leukocyte counts were observed following exposure to dietary a-silica (silicon dioxide) at doses up to 2,410 mg/kg/day for 26 weeks, 2,220 mg/kg/day for 52 weeks, or 2,020 mg/kg/day for 103 weeks, compared with controls (Takizawa et al. 1988). Similarly, no biologically relevant changes in hemoglobin, hematocrit, erythrocytes, leukocytes, or differential leukocyte counts were observed in B6C3F1 mice exposed to dietary a-silica (silicon dioxide) at doses up to 9,810 mg/kg/day for 26 weeks, 7,560 mg/kg/day for 52 weeks, or 6,010 mg/kg/day for 93 weeks, compared with controls (Takizawa et al. 1988).

No significant changes in bone marrow histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994).

**Musculoskeletal Effects.** No studies evaluating musculoskeletal effects in humans or animals following oral exposure to c-silica or a-silica were identified.

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**Hepatic Effects.**

**Crystalline Silica.** No studies evaluating hepatic effects in humans or animals following oral exposure to c-silica were identified.

**Amorphous Silica.** Severe atrophy of the hepatic epithelium was observed in male and female Wistar rats following dietary exposure to TWA a-silica (FHS) doses of 7,500 mg/kg/day for 8 weeks; incidence data were not provided (Lewinson et al. 1994). Daily concentrations were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Liver cells showed condensation of the cytoplasm, loss of basophilic structure, and hyperchromatic and contracted nuclei. These changes were seen sporadically in females (2/10) exposed to dietary a-silica (FHS) at 1,000 mg/kg/day for 5 weeks, but not males at 1,000 mg/kg/day or either sex at  $\leq 500$  mg/kg/day (Lewinson et al. 1994).

No significant changes in liver weight or histology were observed in Wistar or F344 rats exposed to dietary a-silica (FHS or silicon dioxide) at doses up to 2,410 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994; Takizawa et al. 1988). In B6C3F1 mice, a significant 16% decrease in liver weight was observed in females exposed to dietary a-silica (silicon dioxide) at a dose of 9,810 mg/kg/day; liver weights were not decreased in female mice at 3,780 mg/kg/day or male mice at doses up to 6,700 mg/kg/day (Takizawa et al. 1988). No treatment-related changes in liver histology were reported in male or female B6C3F1 mice exposed to dietary a-silica (silicon dioxide) for 26 weeks at doses up to 6,700 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

A significant 14–15% decrease in liver weight was observed in female F344 female rats exposed to dietary a-silica (silicon dioxide) at doses  $\geq 980$  mg/kg/day for 103 weeks; liver weights were not decreased in females at 480 mg/kg/day for 103 weeks, males at doses up to 910 mg/kg/day for 103 weeks, or males or females at doses up to 2,220 mg/kg/day for 52 weeks (Takizawa et al. 1988). No treatment-related histopathological lesions in the liver were observed in rats exposed to dietary a-silica (silicon dioxide) for 52 or 103 weeks at doses up to 2,220 mg/kg/day (Takizawa et al. 1988). Similarly, no histopathological changes in the liver were observed in Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). In B6C3F1 mice, no significant changes in liver weight or histology were observed following exposure to dietary a-silica (silicon dioxide) at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

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**Renal Effects.**

**Crystalline Silica.** The relationship between Balkan nephropathy (BN; an endemic chronic kidney disease of the Balkan Peninsula) and well water chemical composition and characteristics was evaluated in 366 inhabitants of Petka, Serbia, a village affected by BN, from January 1974 to December 1985 (Radovanovic et al. 1991). Silicon dioxide and nitrate content of the 85 wells used by study subjects were measured during June and August 1974. Wells used by each study subject for at least 1 year during the 12-year period, as well as during the 30 preceding years, were identified, and the data were analyzed as “person/wells”. A total of 28 individuals using 24 wells were diagnosed with BN. Using a multiple logistic regression model, silicon dioxide levels were significantly positively correlated with developing BN (regression coefficient  $\pm$  standard error:  $0.0611 \pm 0.023$ ; standardized regression coefficient = 2.63;  $p = 0.008$ ). The mean ( $\pm$  standard deviation) well water silicon dioxide levels in the BN-affected group ( $33.79 \pm 6.09$  mg/L) was 11% greater than the mean ( $\pm$  standard deviation) silicon dioxide levels in the BN-spared group ( $30.52 \pm 8.02$  mg/L). Additionally, well altitude was significantly negatively correlated with developing BN (regression coefficient  $\pm$  standard deviation:  $-0.4075 \pm 0.016$ ; standardized regression coefficient:  $-2.97$ ;  $p = 0.001$ ). While significant findings suggest a correlation between silicon dioxide content in well water and BN, Radovanovic et al. (1991) suggested that the magnitude of change is too small to be a biologically plausible cause-effect mechanism. Additionally, silicon dioxide content of well water only explained 6.9% of the total variability. The study authors proposed that it is more likely that the silicon dioxide content in well water is correlated with the disease, rather than the underlying cause of the BN. Although the etiology of BN remains unknown, several possible causes have been proposed including viral, environmental, and genetic risk factors. Exposure to trace elements, including silica, are included in the list of potential risk factors, but current research has been more focused on mycotoxins, phytotoxins (particularly aristolochic acid), and genetic predisposition (reviewed by Schiller et al. 2008; Voice et al. 2006). Additionally, lower silica content (unspecified form, assumed to be c-silica) has been reported in wells from BN-endemic villages, compared to higher silica content in well water of the control villages (reviewed by Voice et al. 2006).

Focal nephritis in the distal tubule and collecting duct was observed in two of six male guinea pigs exposed to 51 mg c-silica/kg/day as crushed quartz in drinking water for 5 days/week for 4 months; no kidney lesions were observed in the six control animals (Dobbie and Smith 1982). Observed renal lesions were most evident in the subcapsular and corticomedullary regions, and included dilation, cystic changes, chronic inflammatory infiltrate, increased collagen fibers, and proteinaceous material. No renal lesions

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were observed in animals similarly exposed to 51 mg c-silica/kg/day as crushed granite (Dobbie and Smith 1982). This study indicates that the form of c-silica is important with regard to the degree and extent of renal toxicity.

No significant changes in glomerular filtration rate or urine output were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg-day as sodium metasilicate in drinking water for 8 days, compared with controls; the baseline c-silica content in drinking water was 267 µg/L (Öner et al. 2005, 2006). After exposure, rats were sacrificed and renal cortical slices were obtained for culture. Total ammonia levels, ammonia secretion rate, and gamma-glutamyl transpeptidase ( $\gamma$ -GT) were significantly ( $p < 0.05$ ) elevated and total glutamine content was significantly ( $p < 0.05$ ) decreased in renal slices from exposed rats, compared with controls. Ammoniogenesis associated with c-silica exposure could potentially lead to altered function of renal proximal tubule cells. The toxicological significance of these findings is not established.

***Amorphous Silica.*** No histopathological changes in the kidney were observed in Wistar rats exposed to dietary a-silica (FHS) at doses up to 1,000 mg/kg/day for 5 weeks or at TWA doses of 7,500 mg/kg/day for 8 weeks, compared with controls (Lewinson et al. 1994).

No significant changes in liver weight or histology were observed in Wistar or F344 rats exposed to dietary a-silica (FHS or silicon dioxide) at doses up to 2,410 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). In B6C3F1 mice, a significant 15–22% decrease in kidney weight was observed in females exposed to dietary a-silica (silicon dioxide) at  $\geq 3,780$  mg/kg/day; kidney weights were not decreased in female mice at 2,070 mg/kg/day or male B6C3F1 mice at doses up to 6,700 mg/kg/day (Takizawa et al. 1988). No treatment-related changes in kidney histology were reported in male or female B6C3F1 mice exposed to dietary a-silica (silicon dioxide) for 26 weeks at doses up to 6,700 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

No changes in kidney histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant changes in kidney weight or histology were observed in F344 rats exposed to dietary a-silica at doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant changes in kidney weight or histology were observed following exposure to dietary a-silica at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

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**Endocrine Effects.**

*Crystalline Silica.* No studies evaluating endocrine effects in humans or animals following oral exposure to c-silica were identified.

*Amorphous Silica.* No significant changes in adrenal, pituitary, ovary, or testes weights or histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the thyroid (thyroid weights not recorded). No changes in testes or ovary histology were observed in male and female Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

**Dermal Effects.** No studies evaluating dermal effects in humans or animals following oral exposure to c-silica or a-silica were identified.

**Ocular Effects.** No studies evaluating ocular effects in humans or animals following oral exposure to c-silica or a-silica were identified.

**Body Weight Effects.**

*Crystalline Silica.* No studies evaluating changes in body weight in humans following oral exposure to c-silica were identified.

No significant body weight effects were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg/day as sodium metasilicate in drinking water for 8 days, compared with controls (Öner et al. 2005, 2006); the baseline c-silica content in drinking water was 267 µg/L.

*Amorphous Silica.* In an LD<sub>50</sub> study in Sprague-Dawley rats, no effects on body weight were observed during the 4-week observation period following single oral doses of silicon dioxide at PHS doses up to 7,900 mg/kg or FHS doses up to 5,000 mg/kg (Lewinson et al. 1994).

In an intermediate-duration study, mean body weight was decreased in male and female Wistar rats exposed to TWA a-silica (FHS) doses of 7,500 mg/kg/day for 8 weeks, compared with controls

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(Lewinson et al. 1994). Dose concentrations were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Body weight effects were observed during weeks 4–8. No body weight effects were observed in Wistar rats exposed to dietary  $\alpha$ -silica (FHS) at doses up to 1,000 mg/kg/day for 5 weeks or 500 mg/kg/day for 6 months (Lewinson et al. 1994). Similarly, no significant effects on body weight were observed in F344 rats or B6C3F1 mice exposed to dietary  $\alpha$ -silica (silicon dioxide) at doses up to 2,410 or 9,810 mg/kg/day, respectively, for 26 weeks (Takizawa et al. 1988).

In a chronic-duration study, body weights in Wistar rats exposed to dietary  $\alpha$ -silica (FHS) at 100 mg/kg/day for 24 months were comparable to historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant body weight effects were observed in F344 rats exposed to dietary  $\alpha$ -silica (silicon dioxide) at doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant body weight effects were observed following exposure to dietary  $\alpha$ -silica (silicon dioxide) at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

#### 3.2.2.3 Immunological and Lymphoreticular Effects

**Crystalline Silica.** No studies evaluating immunological or lymphoreticular effects in humans or animals following oral exposure to  $\alpha$ -silica were identified.

**Amorphous Silica.** A significant 18% decrease in spleen weight was observed in female F344 rats exposed to dietary  $\alpha$ -silica (silicon dioxide) at 2,410 mg/kg/day for 26 weeks (Takizawa et al. 1988). Spleen weights were not decreased in female F344 rats at  $\leq 1,160$  mg/kg/day or male F344 rats at doses up to 2,220 mg/kg/day, and no treatment-related histopathological lesions were reported (Takizawa et al. 1988). No significant changes in thymus or spleen weight or histology were observed in Wistar rats exposed to dietary  $\alpha$ -silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the lymph nodes. In B6C3F1 mice, a significant 20% decrease in spleen weight was observed in males exposed to dietary  $\alpha$ -silica (silicon dioxide) at 6,700 mg/kg/day for 26 weeks (Takizawa et al. 1988). Spleen weights were not decreased in male B6C3F1 mice at  $\leq 3,280$  mg/kg/day or female B6C3F1 mice at doses up to 2,220 mg/kg/day, and no treatment-related histopathological lesions were reported (Takizawa et al. 1988).

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No changes in spleen histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant changes in spleen weight or histology were observed in F344 rats exposed to dietary a-silica (silicon dioxide) at doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant changes in spleen weight or histology were observed following exposure to dietary a-silica (silicon dioxide) at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

**3.2.2.4 Neurological Effects**

**Crystalline Silica.** Silica levels in drinking water were not associated with cognitive impairment using the Mini-Mental State Examination (MMSE) in 3,777 French subjects >65 years of age; median silica (form not specified, assumed to be c-silica) levels in drinking water were 11.2 mg/L (range 4.2–22.4 mg/L) (Jacqmin-Gadda et al. 1996). Using a reference water intake of 1.046 L for populations >65 years of age and a reference body weight of 80 kg (EPA 2011), estimated mean daily intakes were calculated to be 0.15 mg/kg/day (range 0.05–0.29 mg/kg/day). These findings were supported by a second study, which found a negative association between silica (form not specified, assumed to be c-silica) levels in drinking water and cognitive impairment in the Short Portable Mental Status Questionnaire in 7,598 French females  $\geq$ 75 years of age; the average daily intake was of 10.17 mg/day (Gillette-Guyonnet et al. 2005). Using reference body weight of 80 kg (EPA 2011), daily intakes were calculated to be 0.13 mg/kg/day for this study. A 5-year follow-up study in this cohort indicated that women with low silica intake ( $\leq$ 4 mg/day) had a 2.7-fold increased risk of Alzheimer's disease (OR: 2.74; 95% CI: 1.09, 6.86), while high silica intake (9–12 mg/day) was not associated with Alzheimer's disease (OR: 2.00; 95% CI: 0.56, 7.07) (Gillette-Guyonnet et al. 2005).

No studies evaluating neurological effects in animals following oral exposure to c-silica were identified.

**Amorphous Silica.** No clinical signs of neurotoxicity or significant changes in brain weight or histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Similarly, no clinical signs of neurotoxicity or significant changes in brain weight or histology were observed in F344 rats or B6C3F1 mice exposed to dietary a-silica (silicon dioxide) at doses up to 2,410 or 9,810 mg/kg/day, respectively, for 26 weeks (Takizawa et al. 1988).

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No clinical signs of neurotoxicity were observed in Wistar rats exposed to dietary  $\alpha$ -silica (FHS) at 100 mg/kg/day for 24 months (Lewinson et al. 1994). No clinical signs of neurotoxicity or significant changes in brain weight or histology were observed in F344 rats exposed to dietary  $\alpha$ -silica (silicon dioxide) at doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no clinical signs of neurotoxicity or significant changes in brain weight or histology were observed following exposure to dietary  $\alpha$ -silica (silicon dioxide) at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

**3.2.2.5 Reproductive Effects**

**Crystalline Silica.** The risk of spontaneous abortion in a case-control study of 286 women with spontaneous abortions through 27 weeks of gestation and 1,391 women with live births was correlated with high silica (form not specified, assumed to be  $\alpha$ -silica) content in drinking water in Boston (Aschengrau et al. 1989). The adjusted OR for the highest silica tertile (3.7–32.0 mg/L) was increased compared to the lowest tertile (0–2.7 mg/L); OR: 1.9, 95% CI: 1.1, 3.2. The risk of spontaneous abortion was not increased in the middle tertile (2.8–3.6 mg/L); OR: 0.5; 95% CI: 0.3, 0.8. The ORs were adjusted for other trace elements (arsenic, chromium, lead, mercury, sodium, potassium, iron, sulfate, chloride, nitrate, and copper) and water characteristics (pH, alkalinity, hardness, Langelier index, and water source). Using a reference water intake of 1.043 L for populations  $\geq 21$  years of age and a reference body weight of 80 kg (EPA 2011), estimated daily intakes for exposure in the lowest, middle, and highest tertiles were 0–0.035, 0.036–0.047, and 0.048–0.42 mg/kg/day, respectively. Other trace elements associated with increased risk of spontaneous abortion in this study included any detectable levels of mercury and high levels of arsenic or potassium. Limitations of this study include lack of actual water consumption data and lack of control for unmeasured water quality parameters (e.g., organic contaminants, groundwater treatment) and other environmental exposures.

No studies evaluating reproductive effects in animals following oral exposure to  $\alpha$ -silica were identified.

**Amorphous Silica.** Reproductive performance was not impaired during the generation of two litters in male and female Wistar rats exposed to dietary  $\alpha$ -silica (FHS) at 500 mg/kg/day for a total of 6 months; mating for the first litter occurred after 8 weeks of exposure and mating for the second litter occurred after 17 weeks of exposure (Lewinson et al. 1994). There were no significant changes in the breeding rate, number of pregnant females, number of live and dead pups, or mean litter size in exposed rats, compared with controls.



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No significant changes in testes or ovary weight or histology were observed in Wistar male and female rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the uterus (uterus weight not recorded). No changes in testes, ovary, or uterus histology were observed in Wistar rats exposed to dietary a-silica (FHS) at 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

**3.2.2.6 Developmental Effects**

*Crystalline Silica.* No studies evaluating developmental effects in humans or animals following oral exposure to c-silica were identified.

*Amorphous Silica.* There were no significant changes in mean birth weight, number of runts, gross pup abnormalities at birth, growth or survival during lactation, or gross pathological findings at the postnatal week 4 sacrifice from the first or second litter produced by male and female Wistar rats exposed to dietary a-silica (FHS) at 500 mg/kg/day for a total of 6 months, compared with controls (Lewinson et al. 1994). Mating for the first litter occurred after 8 weeks of exposure, and mating for the second litter occurred after 17 weeks of exposure.

**3.2.2.7 Cancer**

*Crystalline Silica.* No studies evaluating cancer in humans or animals following oral exposure to c-silica were identified.

*Amorphous Silica.* In a 2-year bioassay that utilized small animal groups (18–21/sex/group per species), neoplastic lesions attributable to dietary a-silica (silicon dioxide) exposure were not observed at doses up to 2,010 mg/kg/day in F344 rats or doses up to 6,010 in B6C3F1 mice (Takizawa et al. 1988). In another study, neoplastic lesions attributable to dietary a-silica (FHS) exposure were not observed in Wistar rats exposed to 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). However, the reliability of this study is low because it utilized small animal groups (20/sex/group), lacked a concurrent control, and used a single dose level that did not approach the maximum tolerable dose (MTD) (e.g., no systemic toxicity was observed).

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**3.2.3 Dermal Exposure**

No association between dermal exposure to c-silica or a-silica and adverse health effects has been reported.

**3.3 GENOTOXICITY**

**Crystalline Silica.** Available evidence indicates that c-silica is a genotoxic agent in mammalian cells, with the ability to cause mutagenicity, clastogenicity, and DNA damage. Results of *in vivo* human studies, *in vivo* animal studies, and *in vitro* studies evaluating the genotoxicity of c-silica are summarized below and in Tables 3-18, 3-19, and 3-20, respectively.

Human Occupational Studies. Chromosomal and DNA damage have been reported in a limited number of studies evaluating workers with occupational exposure to c-silica.

DNA strand breaks were significantly increased ( $p < 0.001$ ) in peripheral lymphocytes from a cohort of foundry and pottery workers exposed to c-silica for an average of 14–15 years, compared with unexposed referents (Basaran et al. 2003). The mean occupational exposure levels to respirable dust and respirable quartz in foundry workers were  $16.7 \pm 1.01$  and  $0.72 \pm 0.35$  mg/m<sup>3</sup>, respectively; exposure levels were not reported for pottery workers (et Basaran al. 2003).

Chromosomal aberrations and sister chromatid exchanges were significantly increased ( $p < 0.01$ ) by 1.5–2-fold in whole-blood samples (cell types not specified) from a cohort of stone crushers exposed to c-silica, compared with unexposed referents (Sobti and Bhardwaj 1991). Findings remained significant when workers were stratified by alcohol use and smoking status. Exposure levels and duration of exposure were not reported. Micronuclei frequency was significantly ( $p < 0.001$ ) increased by 2–3-fold in peripheral lymphocytes and nasal epithelial cells from a cohort of glass industry workers, sand blasters, and stone grinders exposed to c-silica for an average of 7 years, compared with unexposed referents (Demircigil et al. 2010). The cumulative exposure to c-silica was significantly associated with micronuclei frequencies in both cell types (regression coefficient [95% CI] = 6.71 [5.06–8.37] for peripheral lymphocytes and 5.47 [4.56–6.37] for nasal epithelial cells;  $p < 0.001$ ); however, cumulative exposure levels were not reported (Demircigil et al. 2010).

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**Table 3-18. Genotoxicity of c-Silica in Occupational Studies**

Exposure group	Silica species	End point	Results	Reference
Patients diagnosed with lung cancer and silicosis <sup>a</sup>	c-Silica (not specified)	Gene mutation frequency of p53 gene	+	Liu et al. 2000
Foundry and pottery workers <sup>b</sup>	Quartz	DNA strand breaks in peripheral lymphocytes	+	Basaran et al. 2003
Stone crushers <sup>b</sup>	c-Silica (not specified)	Chromosomal aberrations in peripheral whole-blood samples	+	Sobti and Bhardwaj 1991
Stone crushers <sup>b</sup>	c-Silica (not specified)	Sister chromatid exchanges in peripheral whole-blood samples	+	Sobti and Bhardwaj 1991
Glass industry workers, sand blasters, and stone grinders <sup>c</sup>	c-Silica (not specified)	Micronuclei in peripheral lymphocytes	+	Demircigil et al. 2010
Glass industry workers, sand blasters, and stone grinders <sup>c</sup>	c-Silica (not specified)	Micronuclei in nasal epithelial cells	+	Demircigil et al. 2010

<sup>a</sup>Diagnosis of silicosis as a proxy for c-silica exposure.

<sup>b</sup>It was not reported whether or not exposed workers had silicosis.

<sup>c</sup>Silicosis was diagnosed in 50% of former workers (n=10) and 24% of current workers (n=40); micronuclei were increased in both current and former worker populations.

+ = positive result; DNA = deoxyribonucleic acid

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**Table 3-19. Genotoxicity of c-Silica *In Vivo* Animal Studies**

Species	Silica species	End point	Results	Reference
Rat (inhalation)	Cristobalite	Gene mutation at <i>hprt</i> locus in alveolar type II epithelial cells	+	Johnston et al. 2000
Rat (intratracheal)	Quartz	Gene mutation at <i>hprt</i> locus in alveolar type II epithelial cells	+	Driscoll et al. 1997
Rat (intratracheal)	Quartz	DNA strand breaks in lung epithelial cells	+	Knaapen et al. 2002
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001a
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001b
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001c
Hamster (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	-	Seiler et al. 2001c

+ = positive result; - = negative result; 8-OHdG = 8-hydroxydeoxyguanosine; DNA = deoxyribonucleic acid

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**Table 3-20. Genotoxicity of c-Silica *In Vitro***

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
<i>Bacillus subtilis</i> (H17 Rec <sup>+</sup> , M45 Rec <sup>-</sup> )	c-Silica (not specified)	DNA repair	NT	–	Kada et al. 1980
<i>B. subtilis</i> (H17 Rec <sup>+</sup> , M45 Rec <sup>-</sup> )	c-Silica (not specified)	DNA repair	NT	–	Kanematsu et al. 1980
Mammalian cells:					
RLE-6TN rat alveolar epithelial cells	BAL cells from quartz-exposed rats <sup>a</sup>	Mutation at <i>hprt</i> locus	NT	+	Driscoll et al. 1997
Muta <sup>TM</sup> Mouse lung epithelial cells	Quartz	<i>cII</i> and <i>lacZ</i> mutant frequency	NT	–	Jacobsen et al. 2007
Human small airway epithelial cells	Quartz	DNA strand breaks	NT	+	Msiska et al. 2010
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Msiska et al. 2010
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Fanizza et al. 2007
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Cakmak et al. 2004
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002a
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002b
Hel 299 human embryonic lung cells	Quartz	DNA strand breaks	NT	+	Zhong et al. 1997b
RLE-6TN rat alveolar epithelial cells	Quartz	DNA strand breaks	NT	+	Li et al. 2007
RLE-6TN rat alveolar epithelial cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002b
Rat alveolar macrophages	c-Silica (not specified)	DNA strand breaks	NT	+	Zhang et al. 2000
Rat alveolar macrophages	c-Silica (not specified)	DNA strand breaks	NT	+	Zhang et al. 1999
Muta <sup>TM</sup> Mouse lung epithelial cells	Quartz	DNA strand breaks	NT	–	Jacobsen et al. 2007
V79 Chinese hamster lung fibroblasts	Quartz	DNA strand breaks	NT	+	Zhong et al. 1997b
Muta <sup>TM</sup> Mouse lung epithelial cells	Quartz	Oxidative DNA damage	NT	±	Jacobsen et al. 2007
A549 human bronchial epithelial cancer cells	Quartz	8-OHdG modified DNA	NT	+	Schins et al. 2002
RLE-6TN rat alveolar epithelial cells	Quartz	8-OHdG modified DNA	NT	+	Li et al. 2007

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**Table 3-20. Genotoxicity of c-Silica *In Vitro***

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
RLE-6TN rat alveolar epithelial cells <sup>a</sup>	Quartz	8-OHdG modified DNA	NT	+	Schins et al. 2002a
Hel 299 human embryonic lung cells	Quartz	Chromosomal aberrations	NT	-	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Chromosomal aberrations	NT	-	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Chromosomal aberrations	NT	-	Price-Jones et al. 1980
SHE cells	Quartz	Chromosomal aberrations	NT	+	Elias et al. 2006
SHE cells	Quartz	Chromosomal aberrations	NT	-	Oshimura et al. 1984
SHE cells	Diatomaceous earth (~50% cristobalite)	Chromosomal aberrations	NT	+	Elias et al. 2006
Hel 299 human embryonic lung cells	Quartz	Micronuclei	NT	+	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Zhong et al. 1997a
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Liu et al. 1996b
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	-	Price-Jones et al. 1980
CHO cells	Quartz	Micronuclei	NT	+	Hart and Hesterberg 1998
CHO cells	Cristobalite	Micronuclei	NT	+	Hart and Hesterberg 1998
CHO cells	Diatomaceous earth (42% c-silica)	Micronuclei	NT	+	Hart and Hesterberg 1998
SHE cells	Quartz	Micronuclei	NT	-	Oshimura et al. 1984
Human peripheral lymphocytes and monocytes	Quartz	Sister chromatid exchanges	NT	±	Pairon et al. 1990
Human peripheral lymphocytes	Quartz	Sister chromatid exchanges	NT	-	Pairon et al. 1990
Human peripheral lymphocytes and monocytes	Tridymite	Sister chromatid exchanges	NT	+	Pairon et al. 1990
Human peripheral lymphocytes	Tridymite	Sister chromatid exchanges	NT	-	Pairon et al. 1990

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**Table 3-20. Genotoxicity of c-Silica *In Vitro***

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
BALB/3T3 mouse embryo cells	Quartz	Cell transformation	NT	+	Keshava et al. 1999
SHE cells	Quartz	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Quartz	Cell transformation	NT	+	Elias et al. 2006
SHE cells	Quartz	Cell transformation	NT	+	Hesterberg and Barret 1984
SHE cells	Quartz	Cell transformation	NT	-	Oshimura et al. 1984
SHE cells	Cristobalite	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (>50% c-silica)	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (~50% c-silica)	Cell transformation	NT	+	Elias et al. 2006
Isolated DNA					
Herring sperm genomic DNA	Quartz	DNA damage	NT	+	Daniel et al. 1993
$\lambda$ HindIII-digested DNA	Quartz	DNA damage	NT	+	Shi et al. 1994
$\lambda$ HindIII-digested DNA	Quartz	DNA damage	NT	+	Daniel et al. 1993
$\lambda$ HindIII-digested DNA	Quartz	DNA damage	NT	+	Daniel et al. 1995
$\lambda$ HindIII-digested DNA	Tridymite	DNA damage	NT	+	Daniel et al. 1995
$\lambda$ HindIII-digested DNA	Cristobalite	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Quartz	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Tridymite	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Cristobalite	DNA damage	NT	+	Daniel et al. 1995
Calf thymus DNA	Quartz	DNA binding	NT	+	Mao et al. 1994

<sup>a</sup>RLE-6TN cells were incubated with BAL cells collected from rat lungs 15 months after a single intratracheal exposure to 10 or 100 mg/kg of  $\alpha$ -quartz.

+ = positive result; - = negative result;  $\pm$  = marginal result; 8-OHdG = 8-hydroxydeoxyguanosine; BAL = bronchoalveolar lavage; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested; SHE = Syrian hamster embryo

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Animal Studies. Evidence from a limited number of animal studies indicates that c-silica is a mutagenic and DNA damaging agent *in vivo*; however, the susceptibility appears to differ between species, with effects observed in rats but not hamsters.

The number of mutations at the *hprt* locus was significantly increased ( $p < 0.05$ ) in alveolar type II epithelial cells isolated from rat lungs following exposure to cristobalite via inhalation at concentrations of 3 mg/m<sup>3</sup> for 6 hours/day, 5 days/week, for 13 weeks (Johnston et al. 2000). Similarly, the number of gene mutations at the *hprt* locus was significantly increased ( $p < 0.05$ ) in a dose-related manner in alveolar type II epithelial cells isolated from rat lungs 15 months after a single intratracheal instillation of 10 or 100 mg/kg of quartz, compared with controls (Driscoll et al. 1997).

DNA strand breaks were significantly increased ( $p < 0.05$ ) in lung epithelial cells isolated from rats 3 days after a single intratracheal instillation of 2 mg/rat (9 mg/kg, based on reported body weights) of quartz, compared with controls (Knaapen et al. 2002). When the quartz samples were pretreated with the surface modifying compounds, polyvinylpyridine-*N*-oxide or aluminium lactate, DNA damage was inhibited, suggesting a critical role of the reactive particle surface in quartz-induced DNA damage *in vivo*. 8-Hydroxydeoxyguanosine (8-OHdG) modified DNA was increased in a time- and dose-dependent manner in alveolar cells isolated from rat lungs 3, 21, or 90 days after a single intratracheal instillation of quartz at doses  $\geq 1.2$  mg/rat (6 mg/kg, based on reported body weights), indicating oxidative DNA damage; modified DNA was not significantly elevated at doses  $\leq 0.6$  mg/rat (3 mg/kg, based on reported body weights) (Seiler et al. 2001a, 2001b, 2001c). However, 8-OHdG modified DNA was not significantly elevated in alveolar cells isolated from hamster lungs 90 days after a single intratracheal instillation of quartz at doses up to 12 mg/kg (Seiler et al. 2001c).

In vitro Studies. Evidence from the numerous *in vitro* studies provides consistent evidence that c-silica is a DNA damaging agent. Evidence also suggests that c-silica is mutagenic and clastogenic; however, there are some inconsistencies in the results between different test systems.

The number of gene mutations at the *hprt* locus was significantly increased in rat alveolar epithelial cells incubated with bronchoalveolar lavage (BAL) cells collected from rat lungs 15 months after a single intratracheal instillation of quartz particles at a dose of 10 or 100 mg/kg; mutations were significantly increased in a dose-related manner when the BAL cell:epithelial cell ratio was 50:1, but not 10:1 (Driscoll et al. 1997). However, *cII* and *lacZ* mutant frequencies were not elevated in Muta<sup>TM</sup> Mouse lung epithelial cells exposed to quartz particles *in vitro* (Jacobsen et al. 2007).



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DNA repair was not induced in the Rec-assay in *Bacillus subtilis* (Kada et al. 1980; Kanematsu et al. 1980). However, DNA strand breaks and/or 8-OHdG modified DNA were consistently observed in various human, rat, and hamster lung cell lines exposed to quartz particles *in vitro* (Cakmak et al. 2004; Fanizza et al. 2007; Li et al. 2007; Msiska et al. 2010; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000; Zhong et al. 1997b). Oxidative DNA damage was reported as “marginally” increased ( $p=0.05$ ) in Muta<sup>TM</sup> Mouse lung epithelial cells exposed to quartz particles *in vitro*, compared with control; however, the number of DNA strand breaks was not significantly increased following quartz exposure (Jacobsen et al. 2007). Generation of reactive oxygen species (ROS) following c-silica exposure was associated with DNA damage in several of these studies (Li et al. 2007; Msiska et al. 2010; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000), and surface modifications of quartz that decrease hydroxyl-radical generation and reduce cell uptake led to reductions in quartz-mediated DNA damage (Schins et al. 2002a). In various isolated DNA samples, DNA damage was consistently observed following incubation with c-silica (quartz, tridymite, cristobalite) (Daniel et al. 1993, 1995; Shi et al. 1994) and DNA binding to c-silica particles was observed (Mao et al. 1994).

Available data indicate that c-silica can cause clastogenic effects; however, evidence is not conclusive. Both chromosomal aberrations and cytotoxicity were significantly increased in Syrian hamster embryo (SHE) cells following *in vitro* exposure to quartz and calcined diatomaceous earth (approximately 50% crystallization) (Elias et al. 2006). Chromosomal aberrations were not observed in SHE cells at lower, non-cytotoxic concentrations of quartz (Oshimura et al. 1984). Additionally, chromosomal aberrations were not induced in human embryonic lung cells or Chinese hamster lung fibroblasts following *in vitro* exposure to quartz (Nagalakshmi et al. 1995; Price-Jones et al. 1980). In contrast, several studies reported micronuclei induction following exposure to quartz or calcined diatomaceous earth in various cell lines, including human embryonic lung cells, Chinese hamster fibroblasts, and Chinese hamster ovary (CHO) cells (Hart and Hesterberg 1998; Nagalakshmi et al. 1995; Zhong et al. 1997a). Low concentrations of quartz did not induce micronuclei in Chinese hamster fibroblasts or SHE cells (Oshimura et al. 1984; Price-Jones et al. 1980). Sister chromatid exchanges were induced in mixed human peripheral lymphocyte and monocyte cultures following exposure to tridymite at cytotoxic concentrations, but results with quartz were inconclusive (only significant in 1/3 replicates at cytotoxic concentration); neither tridymite nor quartz induced sister chromatid exchanges in purified human peripheral lymphocyte cultures (Pairon et al. 1990).

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Quartz induced cell transformation in mouse embryo cells, and transformed cells showed significant genomic instability compared with non-transformed cells (Keshava et al. 1999). Cell transformation and cytotoxicity were induced in a concentration-related manner in SHE cells following exposure to various crystalline species, including quartz, cristobalite, and heated diatomaceous earth samples with some crystallization (Elias et al. 2000, 2006; Hesterberg and Barret 1984). The extent of cytotoxicity of various c-silica samples and the induction of cell transformation was not correlated; however, transforming potency was well-correlated with the amount of hydroxyl radicals generated (Elias et al. 2000, 2006). Cell transformation was not observed in SHE cells at lower, noncytotoxic concentrations of quartz (Oshimura et al. 1984).

***Amorphous Silica.*** a-Silica has been shown to cause DNA damage and chromosomal aberrations *in vitro*; however, concentrations producing these effects are approximately 2–4-fold higher than c-silica under similar experimental conditions. The *in vivo* database is too limited to draw conclusions. *In vivo* and *in vitro* genotoxicity studies evaluating a-silica are summarized in Table 3-21.

**Animal Studies.** No significant increases in the number of mutations at the *hprt* locus were observed in alveolar type II epithelial cells isolated from rat lungs following exposure to a-silica via inhalation at concentrations of 50 mg/m<sup>3</sup> for 6 hours/day, 5 days/week, for 13 weeks (Johnston et al. 2000). As discussed above, exposure to c-silica under the same conditions resulted in a significant increase in mutations. The only other available *in vivo* study showed no induction of micronuclei in peripheral blood erythrocytes from mice following oral or intraperitoneal exposure to silicon dioxide at doses up to 5,000 mg/kg (Morita et al. 1997).

**In vitro Studies.** Available evidence from *in vitro* studies show that a-silica is capable of causing DNA and chromosomal damage at concentrations 2–4-fold higher than c-silica; however, findings are inconsistent between studies. DNA strand breaks were significantly elevated in human embryonic lung cells and Chinese hamster lung fibroblasts following exposure to a-silica *in vitro*; however, the concentration of a-silica required to induce micronuclei was 4-fold higher than the concentration of c-silica (quartz) required to induce micronuclei under the same experimental conditions (Zhong et al. 1997b). Some evidence of DNA strand breaks was observed in human lung epithelial cells exposed to a-silica at noncytotoxic concentrations up to 80 µg/mL; however, the results did not exhibit concentration-dependence (Guidi et al. 2013). In murine macrophage cells, DNA strand breaks were only observed at a-silica particle concentrations that caused cytotoxicity (≥5 µg/mL) (Guidi et al. 2013).

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**Table 3-21. Genotoxicity of  $\alpha$ -Silica**

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
<b><i>In vivo</i></b>					
Rat (inhalation)	$\alpha$ -Silica	Gene mutation at <i>hprt</i> locus in alveolar type II epithelial cells		–	Johnston et al. 2000
Mouse (oral)	Silicon dioxide	Micronuclei in peripheral erythrocytes		–	Morita et al. 1997
Mouse (intraperitoneal)	Silicon dioxide	Micronuclei in peripheral erythrocytes		–	Morita et al. 1997
<b><i>In vitro</i></b>					
Mammalian cells:					
A549 human lung epithelial cells	$\alpha$ -Silica	DNA strand breaks	NT	±	Guidi et al. 2013
Hel 299 human embryonic lung cells	$\alpha$ -Silica	DNA strand breaks	NT	+	Zhong et al. 1997b
RAW264.7 murine macrophages	$\alpha$ -Silica	DNA strand breaks	NT	+	Guidi et al. 2013
V79 Chinese hamster lung fibroblasts	$\alpha$ -Silica	DNA strand breaks	NT	+	Zhong et al. 1997b
SHE cells	Diatomaceous earth (0% c-silica)	Chromosomal aberrations	NT	+	Elias et al. 2006
SHE cells	$\alpha$ -Silica	Chromosomal aberrations	NT	+	Elias et al. 2006
A549 human lung epithelial cells	$\alpha$ -Silica	Micronuclei	NT	–	Guidi et al. 2013
RAW264.7 murine macrophages	$\alpha$ -Silica	Micronuclei	NT	+	Guidi et al. 2013
V79 Chinese hamster lung fibroblasts	$\alpha$ -Silica	Micronuclei	NT	+	Liu et al. 1996b
CHO cells	Diatomaceous earth (4% crystalline)	Micronuclei	NT	+	Hart and Hesterberg 1998
SHE cells	Diatomaceous earth ( $\leq$ 6% c-silica)	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (0% c-silica)	Cell transformation	NT	–	Elias et al. 2006
SHE cells	$\alpha$ -Silica	Cell transformation	NT	–	Elias et al. 2000
SHE cells	$\alpha$ -Silica	Cell transformation	NT	–	Elias et al. 2006

+ = positive result; - = negative result; ± = inconclusive result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested; SHE = Syrian hamster embryo

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Both chromosomal aberrations and cytotoxicity were significantly increased in exposures to natural, non-crystalline diatomaceous earth; however, exposure to vitreous  $\alpha$ -silica did not induce chromosomal aberrations (Elias et al. 2006).  $\alpha$ -Silica did not induce micronuclei in human lung epithelial cells; however,  $\alpha$ -silica and non-crystalline diatomaceous earth induced micronuclei in murine macrophage cells, Chinese hamster lung fibroblasts, and CHO cells (Guidi et al. 2013; Hart and Hesterberg 1998; Liu et al. 1996b). The concentration of  $\alpha$ -silica required to induce micronuclei was 2-fold higher than the concentration of quartz required to induce micronuclei in Chinese hamster lung fibroblasts (Liu et al. 1996b).

Both cell transformation and cytotoxicity were induced in a concentration-related manner in SHE cells exposed to natural diatomaceous earth samples with minimal (up to 6%) crystallization (Elias et al. 2000, 2006). However, neither cell transformation nor cytotoxicity was observed in SHE cells exposed to unheated diatomaceous earth samples (0% crystallization) or pyrogenic or vitreous  $\alpha$ -silica samples (Elias et al. 2000, 2006).

## 3.4 TOXICOKINETICS

Throughout this section, the term silica refers to all types of silica particles. Information that is specific to  $c$ -silica or  $\alpha$ -silica is indicated as such.

### 3.4.1 Absorption

#### 3.4.1.1 Inhalation Exposure

Inhaled silica particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption by blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, kidney). The above processes apply to all forms of deposited silica, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size) and biological reactivity (e.g., macrophage recruitment, activation, and cytotoxicity).

Particles having diameters  $>5 \mu\text{m}$  deposit in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract (Bailey et al. 2007; ICRP 1994). Smaller particles ( $\leq 5 \mu\text{m}$ ) are deposited primarily in the pulmonary

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region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow. Dissolution, which contributes to absorptive clearance of some types of particles, is negligible for c-silica because of the low solubility of c-silica particles. Dissolution may play a larger role in clearance of a-silica, and may contribute to its faster pulmonary clearance compared to c-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981).

The various processes that contribute to the clearance of silica from the respiratory tract give rise to multiphasic lung retention kinetics (Katsnelson et al. 1992; Stober et al. 1999; Vacek et al. 1991). In most studies of lung retention, at least two kinetic components are evident. The faster phase is thought to be contributed by relatively rapid mechanical clearance mechanisms (e.g., mucociliary transport) and, for more soluble forms (e.g., a-silica), absorption to blood of soluble or relatively rapidly dissolved insoluble material deposited in the lung. The slower phase is contributed by physical transformation and dissolution and/or mechanical clearance of highly insoluble particles by phagocytosis and macrophage migration.

Rates for slow-phase clearance vary with the type of silica particle inhaled, inhaled dosage, and animal species (Kreyling 1990). In humans, slow-phase clearance of highly insoluble particles occurs with half-lives of several years (Bailey et al. 2007; ICRP 1994). The slow phase of clearance of silica particles explains the accumulation of particles in the human lung that can occur with repeated exposures to airborne silica as well as its detection in lung tissue years after cessation of exposure (Borm et al. 2002; Case et al. 1995; Dobrev et al. 1975; Dufresne et al. 1998; Loosereewanich et al. 1995).

Studies conducted in rodents found that clearance of c-silica (quartz) was >10 times slower than a-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981). A contributing factor to the slower clearance of c-silica may be its greater cytotoxic potency, related to its surface structure. In rats, clearance following inhalation of an aerosol of pure cristobalite was slower than following inhalation of aerosols of quartz, and rats showed a more pronounced lung inflammatory response to cristobalite compared to quartz (Hemenway et al. 1990). Macrophages play an important role in the mechanical clearance of silica particles (Absher et al. 1992; Brody et al. 1982). A more intense inflammatory response to macrophage cytotoxicity induced by c-silica results in slow particle clearance (Donaldson and Borm 1998; Fenoglio et al. 2000; Warheit et al. 2007). In general, mechanical clearance of deposited particles appears to have a limited capacity. Macrophage-mediated clearance of respirable particles is inhibited at high particle loads. This phenomenon has been referred to as *particle overload* (Mauderly et

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al. 1990; Morrow 1992). The inhaled dose required to achieve particle overload is not the same in all animal species and may be lower in small mammals (Snipes 1996). Rats exhibit lower particle overload thresholds than hamsters (Saffiotti et al. 1993). Above the particle overload threshold, differences in clearance between c-silica and a-silica become less pronounced (Pratt 1983). Particle overload is an important consideration in low-dose extrapolation of dose-response relationships and in extrapolation across animal species because it may result in a nonlinear relationship between the inhaled dosages and particle burden in the lung (Lippmann and Timbrell 1990; McClellan 1990). Particle overload may also render the respiratory tract more vulnerable to other airborne particulates as a result of depressed particle clearance (Morrow 1992).

#### **3.4.1.2 Oral Exposure**

Little information regarding the gastrointestinal absorption of silica was identified. In rats, six gavage doses of 50 mg c-silica did not result in detectable silica particles in gastrointestinal submucosa or region lymph nodes, suggesting little or no transfer out of the gastrointestinal tract lumen (Gonzalez Huergo 1991).

#### **3.4.1.3 Dermal Exposure**

Studies of dermal absorption of silica have not been reported and, given the solubility of silica dusts, dermal exposure is likely to be a minor pathway of absorption of silica. Skin samples collected from patients with progressive systemic scleroderma (PSS) and who were also exposed to c-silica (quartz dusts) showed evidence of quartz crystals in chorionic fibers, blood vessel walls, corneas, epidermal keratinocytes, and collagen fiber, based on detection of birefringent particles (Mehlhorn et al. 1990). This finding could indicate dermal absorption or dermal deposition of inhaled or ingested silica. Quartz crystals were not observed in skin tissue of patients who did not have PSS and were exposed to quartz dust, including silicosis patients.

### **3.4.2 Distribution**

#### **3.4.2.1 Inhalation Exposure**

Few studies of distribution of silica outside of the respiratory tract have been reported (Absher et al. 1992). Evidence for associations between exposure to c-silica dusts and renal disease suggests that c-silica particles may distribute to the kidney (see Section 3.2.1.3, Inhalation, Systemic Effects). Silica

### 3. HEALTH EFFECTS

has been detected in kidney tissue and urine of workers who have been exposed to c-silica, suggesting that systemic distribution can occur in humans following inhalation exposure (Giles et al. 1978; Hauglustaine et al. 1980; Ibrahim et al. 2011; Saldanha et al. 1975). Inhalation exposure of rats to c-silica shows distribution primarily to mediastinal lymph nodes and thymus; silica particles were detected in negligible amounts in the blood, kidney, liver, and spleen (Absher et al. 1992). These studies suggest that lymph may provide a mechanism for systemic distribution of silica particles (Vacek et al. 1991).

#### **3.4.2.2 Oral Exposure**

Studies of the systemic distribution of silica following oral exposures have not been reported.

#### **3.4.2.3 Dermal Exposure**

Studies of the systemic distribution of silica following dermal exposures have not been reported.

#### **3.4.3 Metabolism**

Absorbed silica is not metabolized. Although c-silica particles are highly insoluble, *in vitro* studies have found that silica particles dissolved from slate dust can bind to serum albumin (Singh et al. 1984).

#### **3.4.4 Elimination and Excretion**

##### **3.4.4.1 Inhalation Exposure**

Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that systemic distribution can occur in humans following inhalation exposure (Ibrahim et al. 2011). Urine is an excretory pathway for silica absorbed from the respiratory tract.

##### **3.4.4.2 Oral Exposure**

Ingested silica is excreted in the feces. Absorbed silica, if absorption were to occur, may be excreted in urine; however, no studies of excretion of silica following absorption from the gastrointestinal tract have been reported.

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**3.4.4.3 Dermal Exposure**

Studies of excretion of silica following dermal exposures have not been reported.

**3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.



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The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

If PBPK models for silica exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models for c-silica or a-silica were identified.

## 3.5 MECHANISMS OF ACTION

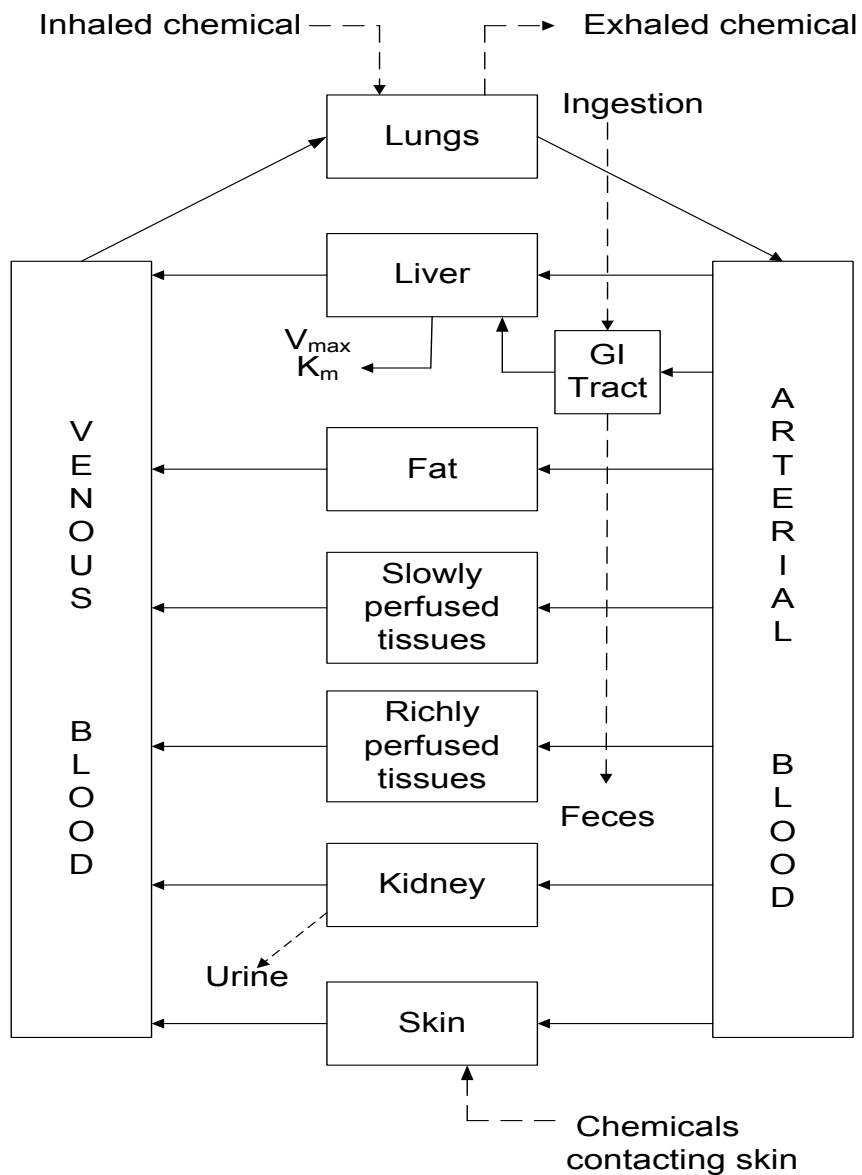
### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** Several mechanisms contribute to the absorption of inhaled particles: (1) physical transformation of particles deposited in the lung, including fragmentation or surface modification; (2) dissolution of particles; and (3) phagocytosis of particles by macrophages (Bailey et al. 2007; ICRP 1994).

The relative contributions of these mechanisms appear to depend on several factors, including: (1) particle size of the inhaled aerosol; (2) water solubility; and (3) surface characteristics of the particles that affect macrophage activation and cytotoxicity. Macrophage phagocytosis and migration is by far the dominant mechanism for absorption of silica particles from the pulmonary region of the respiratory tract.

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**Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

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Phagocytosis of silica particles is mediated by interactions with cell membrane receptors (Hamilton et al. 2008). Following uptake, silica particles trigger cytotoxicity and apoptosis (Hamilton et al. 2008; Hornung et al. 2008; Thibodeau et al. 2004), leading to impaired particle clearance (Donaldson and Borm 1998; Fenoglio et al. 2000). Because of the effect of cytotoxicity on macrophage-mediated clearance, physical characteristics of silica particles that affect cytotoxic potential may contribute to differences in lung clearance of silica particles (Begin et al. 1987; Brown and Donaldson 1996; Fenoglio et al. 2000).

Dissolution, which contributes to absorptive clearance of some types of particles, is negligible for c-silica because of the low solubility of c-silica particles. Dissolution may play a larger role in clearance of a-silica, and may contribute to its faster clearance compared to c-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981).

Studies conducted in Caco-2 cell culture monolayers, a differentiated cell line derived from human small intestine, have found that silica amorphous silica particles 50–200 nm in diameter agglomerate in gastrointestinal fluids (Sakai-Kato et al. 2014). Absorptive transfer across the monolayers was negligible when the monolayers were exposed to silica particles >100 nm.

**Distribution.** Based on observations of silica particles in mediastinal lymph nodes following inhalation, lymph may provide a mechanism for system distribution of silica particles (Absher et al. 1992; Vacek et al. 1991).

**Metabolism.** Absorbed silica is not metabolized. Although silica particles are highly insoluble, *in vitro* studies have found that silica particles dissolved from slate dust can bind to serum albumin (Singh et al. 1984).

**Excretion.** Renal handling of silicon has been studied in clinical studies of healthy adults and in chronic renal failure patients (Alder and Berlyne 1986; Berlyne and Alder 1986). In these studies, silicon was measured in urine and plasma using atomic absorption spectrophotometry, which could not distinguish chemical forms of silicon. The exposure source of the silicon in plasma and urine was not known and exposure may have been to metallic silicon or silicate. Urinary excretion of silicon was correlated with urinary calcium, suggesting that it may be excreted as an orthosilicate complex (Alder and Berlyne 1986; Berlyne and Alder 1986). Clearance studies showed that mechanisms of urinary excretion of silicon involve glomerular filtration and renal tubular secretion (Alder and Berlyne 1986; Berlyne and Alder 1986).

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**3.5.2 Mechanisms of Toxicity**

The mechanisms of toxicity for the main health effects of concern, including silicosis, COPD, lung cancer, autoimmune disease, and renal disease, for c-silica are discussed below.

***Role of Crystalline Silica Surface and Structural Features.*** The ability of different c-silicas (tridymite, cristobalite, and quartz) to induce fibrosis can vary. In addition, c-silica is more fibrogenic than a-silica. Although the underlying mechanism for this variability has not been firmly established, both surface and structural features of silica appear to play a critical role in the fibrogenic activity of silica (Altree-Williams and Sprogis 1982; Cox 2011; Donaldson and Borm 1998; Erdogan and Hasirci 1998; Fujimura 2000; Guthrie 1995; IARC 2012; Leung et al. 2012; Mossman and Churg 1998; Murashov et al. 2006; Rimal et al. 2005; Shi et al. 2001). Freshly fractured c-silica particles (i.e., particles generated during abrasive blasting) are much more cytotoxic than “aged” particles due to the abundance of free radicals on the fresh surface (silanol groups, ionized silanol groups). This increased redox potential leads to increased inflammatory reactions in the lungs. Processing of particles (through heating, grinding, chemical treatment, etc.) can decrease surface reactivity of c-silica. c-Silica particles can readily adsorb other dusts and minerals, which may alter biological activity. Furthermore, the surface density of silanol, which varies between polymorphs, affects *in vitro* biological activity of silica (Murashov et al. 2006). Particle size also is likely to affect toxicity, although the relationship between c-silica particle size and biological activity is still unclear. Studies have come to divergent conclusions, with some suggesting that particles in the 1–2- $\mu\text{m}$  size range are the most fibrogenic, while others indicate that larger particles ( $\geq 5 \mu\text{m}$ ) have the greatest fibrogenic potential. Therefore, exposure conditions, including differences in dust composition, surface reactivity, particle size, and particle age, can alter the exposure-response relationship between c-silica and disease, particularly silicosis, and potentially trigger various response mechanisms.

***Silicosis.*** Lung injury is a well-known effect of c-silica exposure (see Respiratory Effects in Section 3.2.1.2 Systemic Effects of Inhalation Exposure), and the general mechanisms of silicosis have been extensively investigated (reviewed by Chen and Shi 2002; Cox 2011; Ding et al. 2002; Fujimura 2000; Huaux 2007; IARC 2012; Leung et al. 2012; Mossman and Churg 1998; Mossman and Glen 2013; Parks et al. 1999; Rimal et al. 2005; Shi et al. 2001; Weissman et al. 1996). The underlying mechanism of silicosis is considered to be an inflammatory process resulting from c-silica-induced cell death and tissue damage, predominantly mediated through macrophage apoptosis. The general mechanisms

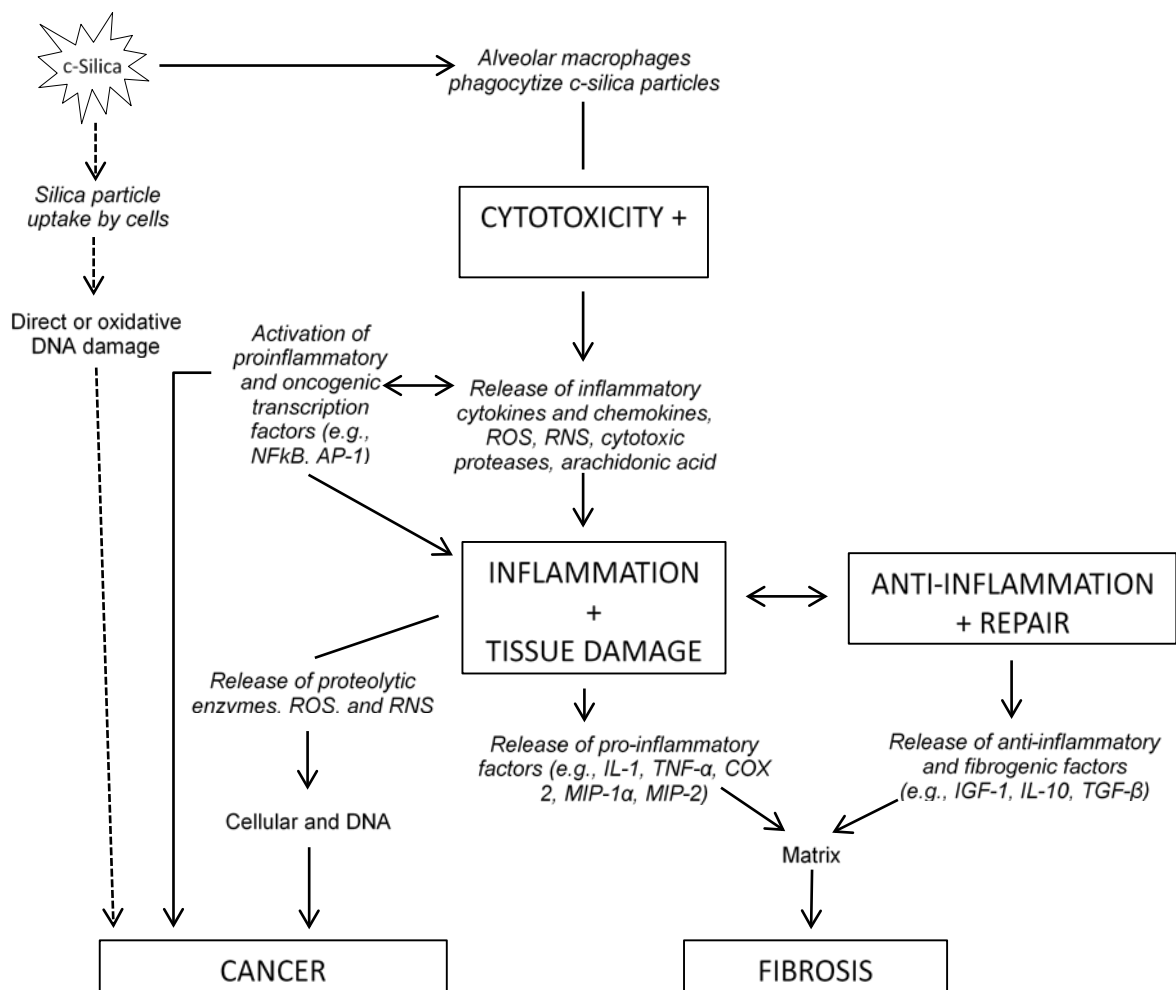
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underlying the development of silicosis are fairly well established (see Figure 3-6). In the lung, inhaled c-silica particles are phagocytized by alveolar macrophages. c-Silica is cytotoxic, leading to cell death and release of intracellular silica, which is taken up by other macrophages. In addition to releasing intracellular c-silica upon cell death, damaged macrophages release a wide array of inflammatory cytokines and chemokines (notably TNF- $\alpha$  and IL-1), ROS and reactive nitrogen species (RNS), and arachidonic acid metabolites. These chemicals damage nearby cells and the extracellular matrix and also recruit additional macrophages to the site of damage. Additionally, various transcription factors, notably the pro-inflammatory and oncogenic factors nuclear factor kappa-B (NF $\kappa$ B) and activator protein (AP-1), are upregulated during this inflammatory response, potentially via reactive species or proteolytic pathways. This recurring cycle of macrophage phagocytosis, death, and release of intracellular contents results in a chronic inflammatory process (alveolitis). Injury to other pulmonary cells (e.g., epithelial cells and fibroblasts) resulting from interactions with c-silica particles may also contribute to alveolitis. However, studies in animal models indicate that apoptosis of macrophages, and subsequent influx of additional macrophages, is the predominant mediator of alveolitis. The inflammatory phase is followed by a reparative phase, which leads to release of anti-inflammatory and fibrogenic factors (e.g., EGF, IGF-1, IL-10, TGF- $\beta$ ) to stimulate recruitment and proliferation of mesenchymal cells, leading to tissue repair and remodeling. Additionally, chronic inflammation damages alveolar type I epithelial cells, which triggers hyperplasia and hypertrophy of type II epithelial cells, which also leads to tissue repair and remodeling. Persistent cycling between the inflammatory and reparative phases leads to excess extracellular matrix deposition, ultimately leading to fibrosis. The inflammatory cytokines TNF- $\alpha$  and IL-1 appear to be critical in the fibrotic process, as these cytokines are required for the development of c-silica-induced fibrosis in animal models, and individuals with certain TNF- $\alpha$  or IL-1 polymorphisms show an increased risk of developing silicosis (see Section 3.10 Populations That Are Unusually Susceptible for more details).

While the major biological processes underlying silicosis have been established and the role of surface and structural properties have been acknowledged, the molecular events mediating the inflammatory response in alveolar macrophages have not been fully elucidated (reviewed by Chen and Shi 2002; Cox 2011; Ding et al. 2002; Huaux 2007; Leung et al. 2012; Mossman and Glenn 2013; Shi et al. 2001). A sequence of events that could potentially lead to the induction of inflammation after phagocytosis of c-silica by macrophages includes: (1) cellular uptake of c-silica into a phagosome via the scavenger receptor MARCO; (2) swelling of phagosome, followed by lysing of phagosome and release of contents into cytosolic compartment; (3) activation of nucleotide-binding domain, leucine-rich repeat protein NALP3; (4) association of NALP3 with intracellular adapter protein ASC and pro-caspase-1, forming the

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**Figure 3-6. Overview of the Major Biological Processes Proposed to Underlie the Pathogenesis of Silicosis and Lung Cancer**



Inhaled c-silica is phagocytized by alveolar macrophages. The phagocytized c-silica causes cytotoxicity and apoptosis, leading to release of intracellular c-silica as well as several chemicals (inflammatory cytokines and chemokines, ROS, and arachidonic acid metabolites). These chemicals damage nearby cells and extracellular matrix, activate transcription factors, and recruit additional macrophages to the site of damage. This cycle repeats, causing a chronic inflammatory process. The inflammatory phase is followed by a reparative phase, which leads to release of anti-inflammatory and fibrogenic factors to stimulate tissue repair and remodeling. Excessive cycling between the inflammatory and reparative phases leads to excess extracellular matrix deposition, ultimately leading to fibrosis. The inflammatory process can also lead to release of proteolytic enzymes and oxidants that cause cellular and DNA damage, resulting in genotoxic events that can trigger a carcinogenic process. This secondary, inflammation-driven genotoxicity pathway is the most likely mechanism underlying c-silica-induced cancer; however, a direct genotoxic of c-silica particles cannot be ruled out (see dashed arrows).

DNA = deoxyribonucleic acid; RNS= reactive nitrogen species; ROS = reactive oxygen species

Sources: Borm et al. (2011); Chen and Shi (2002); Cox (2011); Ding et al. (2002); Fujimura (2000); Huaux (2007); IARC (2012); Leung et al. (2012); Mossman and Chung (1998); Mossman and Glenn (2013); Rimal et al. (2005); Schins (2002); Shi et al. (2001); Weissman et al. (1996)

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NALP3 inflammasome; (5) activation of caspase-1 by inflammasome, leading to activation of proinflammatory interleukins (e.g., IL-1 $\beta$ , IL-18) that were upregulated by activation of NF $\kappa$ B via an unknown mechanism; and (6) activation of downstream mediators of inflammation, such as tumor necrosis factor alpha (TNF- $\alpha$ ) and cyclooxygenase II (COX-2). The activation of the NALP3 inflammasome also requires generation of ROS, which are produced following the stimulation of a respiratory burst in phagocytic cells. c-Silica can produce ROS either directly via chemical interactions on freshly cleaved surfaces (see above) or indirectly via ROS generation in macrophages (oxidative burst).

Following macrophage activation, the innate immune system responds, causing the observed inflammatory responses in the lung. However, the innate immune mechanisms underlying the observed inflammatory responses are complex and not fully understood (reviewed by Fujimura 2000; Huaux 2007; Leung et al. 2012; Weissman et al. 1996). T-lymphocyte responses have been implicated, as there is a predominance of CD4+ T cells (helper/inducer T cells) in both humans diagnosed with silicosis and animal models of silicosis. However, several animal studies have shown that T-lymphocyte responses are not essential for the development of silicosis. Furthermore, the underlying response may not be due to inflammation exclusively, as several studies in mice show a persistent anti-inflammation response subsequent to an acute inflammation response. The anti-inflammatory response is coupled with a pro-fibrogenic response. Interleukin-10 (IL-10) is proposed to play a key role in this process. IL-10 has been shown to increase profibrotic activity via induction of TNF- $\alpha$  expression in conjunction with suppression of the expression of the anti-fibrotic eicosanoid PGE<sub>2</sub>. These events are consistent with the overview shown in Figure 3-6, which proposes that persistent cycling between inflammation and repair processes (including anti-inflammatory processes) leads to pathological fibrogenesis.

***Chronic Obstructive Pulmonary Disease (COPD).*** COPD, characterized by airflow limitation due to chronic bronchitis or emphysema, is associated with exposure to c-silica dust even in the absence of silicosis. Possible mechanisms involved in the development of c-silica-induced COPD include: (1) cellular damage, generation of ROS, and subsequent release of proinflammatory and fibrogenic factors, and (2) injury to epithelial cells, allowing c-silica to penetrate small airway walls and induce localized fibrosis (Hnizdo and Vallyathan 2003).

***Lung Cancer.*** It is generally thought that lung cancer following c-silica exposure results from inflammation-based mechanisms secondary to silicosis; however, a direct genotoxic effect of c-silica particles cannot be ruled out (reviewed by Borm et al. 2011; Brown 2009; Checkoway and Franzblau

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2000; Chen and Shi 2002; Cox 2011; Ding et al. 2002; Huaux 2007; IARC 2012; Leung et al. 2012; Mossman and Glenn 2013; Schins 2002; Shi et al. 2001) (see Figure 3-6).

As discussed above, silicosis is associated with chronic inflammation, which triggers activation of tissue repair, proliferation, and hyperplasia of mesenchymal cells and alveolar epithelial cells. As indicated above, oncogenic transcription factors are also activated during the inflammatory process (e.g., NF $\kappa$ B, AP-1). As in silicosis, it is proposed that TNF- $\alpha$  has a critical role in c-silica-induced lung cancer. While NF $\kappa$ B leads to TNF- $\alpha$  release, TNF- $\alpha$  in turn is capable of activating NF $\kappa$ B, which leads to increased survival of transformed epithelial cells. The increased survival, and subsequent division, could lead to increased pools of preneoplastic cells and ultimately neoplastic transformation. One proposed mechanism for this progression, based on studies in rat models, is epigenetic silencing of the tumor suppressor gene p16 through hypermethylation of the promotor region due to proliferative stress. Additionally, chronic inflammation results in the formation of ROS and RNS. These reactive species are thought to play a major role in DNA and cell damage, resulting in secondary, inflammation-driven genotoxicity that can lead to neoplastic changes. These inflammation-based mechanisms are proposed to have a threshold effect, as chronic inflammation occurs only following c-silica overload in the lung. This inflammation-based mechanism of carcinogenicity is supported by epidemiological data indicating that the association between c-silica and lung cancer is stronger in individuals with silicosis than in individuals without silicosis. However, these findings could merely reflect that c-silica levels high enough to cause silicosis (and inflammation) are also capable of causing cancer, rather than indicating that silicosis is a necessary precursor for cancer development.

As discussed in Section 3.3 Genotoxicity, c-silica is a mutagenic and genotoxic agent both *in vitro* and *in vivo*. Phagocytized c-silica particles could cause DNA damage and cell transformation by directly interacting with DNA, disrupting chromosome segregation during mitosis, generation of ROS on reactive particle surfaces or during oxidative burst by macrophage, and/or depleting antioxidant defenses. This mechanism is proposed to be non-threshold in nature, and therefore does not require c-silica overload in the lung. As discussed above for silicosis, surface properties and particle size, shape, and crystallinity are also important mediators for the genotoxic potential of c-silica. For example, surface modification of quartz (to block reactive surfaces) prevents ROS generation and oxidative DNA damage *in vitro*. This mechanism of carcinogenicity is supported by epidemiological data indicating that lung cancer can occur in individuals who were not diagnosed with silicosis.



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***Autoimmune Disease.*** Information in this section is from the following reviews: Huaux (2007); Lee et al. (2012); Maeda et al. (2010); Otsuki et al. (2007); Parks et al. (1999); Rimal et al. (2005); Rocha-Parise et al. (2014); Steenland and Goldsmith (1995); and Stratta et al. (2001a). c-Silica is a known immune adjuvant that can nonspecifically enhance immune responses via increased antibody production. The inflammatory response induced by c-silica is thought to underlie its adjuvant effect, potentially through IL-1 activation of T-helper cells, which facilitate B-cell production of antibodies. Therefore, c-silica exposure alone may not cause autoimmune dysfunction; rather, c-silica exposure may act as an adjuvant to promote or accelerate autoimmune disease development triggered by another factor (e.g., genetic susceptibility, pathogen or chemical exposure). Thus, the severe inflammatory response following exposure to c-silica is proposed as a common initiating step that could lead to a variety of autoimmune disorders.

Autoimmune disorders following c-silica exposure may occur secondary to silicosis, as chronic immune stimulation in the lungs is capable of causing systemic effects. For example, pulmonary inflammation can lead to release of elastase into systemic circulation, leading to thrombotic events that mildly damage vasculature. Chronic mild damage to vasculature may, in turn, lead to chronic inflammation in blood vessels, triggering vasculitis. Alternatively, autoimmune disorders may occur independently of lung disease due to deposition of c-silica particles in the lymphatic system (transported via macrophages). In this case, macrophage destruction and recruitment cycles would occur in the lymph system (as described above in the lung), leading to stimulation of T-helper cells and B-cell production. Increased B-cell activation would explain elevated levels of autoantibodies observed in c-silica-exposed individuals, including:

- Rheumatoid factor, which is associated with rheumatoid arthritis;
- Anti-nuclear antigen, which is associated with systemic sclerosis;
- Anti-topoisomerase I (anti-Scl-70), which is associated with systemic sclerosis;
- ANCA, which is associated with ANCA-associated vasculitis;
- Anti-CD95/Fas autoantibody, which leads to increased survival of responder T-lymphocytes (autoimmune lymphoproliferative syndrome) and increased immune reactivity with self/non-self antigens, and
- Anti-caspase 8 autoantibody, which is associated with decreased Fas-mediated apoptosis in T-lymphocytes.

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Recent studies have shown that c-silica specifically alters the peripheral CD4+25+ T-cell fraction, particularly the balance between T-responder and T-regulator cells mediated via Fas-dependent apoptosis (see Figure 3-7). This imbalance, in addition to excess autoantibodies produced by activated B-cells, would lead to a dysregulation of autoimmunity. The disruption would likely be subclinical; however, promotion of a pre-existing autoimmune disorder or triggering of an autoimmune disorder in a pre-disposed individual could occur.

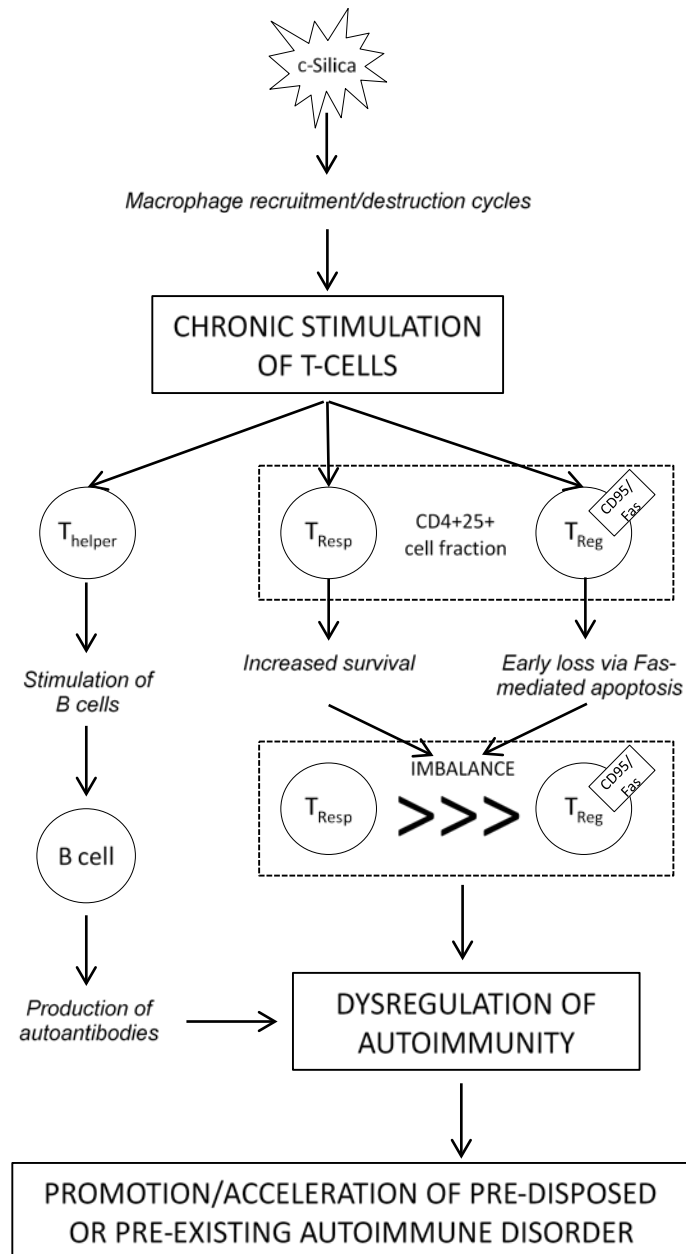
**Renal Disease.** Evidence for elevated risk of renal disease has been observed in c-silica-exposed individuals, both in the presence and absence of silicosis (see Renal Effects in Section 3.2.1.2 Systemic Effects of Inhalation Exposure). Renal damage in c-silica-exposed individuals has been associated with two distinct mechanistic pathways: (1) direct toxic effect of excessive c-silica accumulation in the kidney and (2) indirect toxic effects secondary to autoimmune disease (as reviewed by Parks et al. 1999; Stratta et al. 2001a). In the first proposed pathway, deposition of c-silica particles in the kidney leads to chronic inflammation, which progresses to fibrosis in a process similar to that described above for silicosis. This type of renal damage is most often described in individuals diagnosed with silicosis, and c-silica overload would directly lead to renal failure. In the second proposed pathway, renal complications of autoimmune diseases would occur via different mechanisms depending upon the specific autoimmune disease present. For example, renal damage associated with ANCA-associated vasculitis and systemic sclerosis is associated with vascular pathology in the glomerulus, resulting in glomerulonephritis. Renal pathology associated with systemic lupus erythematosus appears to be due to deposition of autoantibodies in the kidney. It has also been proposed that protein adsorbed onto the surface of c-silica deposited in the kidney may denature, potentially acquiring antigenic properties. Subsequently, excess antibody production from chronic immune stimulation in the lung and/or lymphatic system could cross-react with renal antigens.

#### 3.5.3 Animal-to-Human Extrapolations

Numerous animal studies examining effects of inhaled c-silica have been conducted, and have been particularly useful in investigating pulmonary clearance of particles and mechanisms of toxicity (Cox 2011; EPA 1996; NIOSH 2002). However, results of animal studies may be difficult to extrapolate to humans due to species differences in macrophage overloading, which can affect pulmonary clearance and toxicity (EPA 1996). Rats appear to be more sensitive than hamsters to macrophage overload (Saffiotti et al. 1993). Furthermore, it has been proposed that overload of lung macrophages in rats may not be relevant to humans (Snipes 1996). Regarding use of animal models to investigate the carcinogenic effects

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**Figure 3-7. Proposed Mechanistic Pathway Leading to Autoimmune Dysregulation Following c-Silica Exposure**



c-Silica exposure causes macrophage recruitment/destruction cycles in the lymphatic system, leading to chronic stimulation of T-cells. Helper T-cells stimulate production of B-cells, which leads to increased production of autoantibodies. Both T-responder and T-regulator cells are also stimulated; however, T-regulator cells are lost from the fraction due to Fas-mediated apoptosis. This causes an imbalance in the CD4+25+ cell fraction. Together with increased production of autoantibodies, this imbalance leads to dysregulation of autoimmunity, promoting and/or accelerating autoimmune disease development triggered by another factor (e.g., genetic predisposition or other chemical exposure).

Sources: Huax (2007); Lee et al. (2012, 2014); Maeda et al. (2010); Otsuki et al. (2007); Parks et al. (1999); Rimal et al. (2005); Steenland and Goldsmith (1995); Stratta et al. (2001a)

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of c-silica, c-silica is carcinogenic in rats exposed by inhalation or intratracheal instillation, but not in mice or hamsters (IARC 2012). Thus, not all experimental animals appear to be appropriate for use in extrapolation to humans.

### 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for “...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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No studies were located regarding endocrine disruption in humans and/or animals after exposure to c-silica or a-silica.

**3.7 CHILDREN'S SUSCEPTIBILITY**

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

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However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

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alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information regarding susceptibility of children to c-silica or a-silica has been identified. Silicosis is considered to be an occupational disease that typically occurs with prolonged (years) exposure. The same adverse effects observed in adult workers would be expected to occur in children if sufficiently exposed. However, non-occupational exposure of children to c-silica could occur in rare circumstances (Bhagia 2012; Grobbelaar and Bateman 1991a, 1991b; Norboo et al. 1991a, 1991b; Ranavanya et al. 1992; Rees and Murphy 2007). For example, a mixed-etiology pneumoconiosis (combined exposure to c-silica, heavy dust, and heavy domestic smoke) has been reported in adults engaging in domestic maize hand-grinding activities using quartz rocks in South Africa (Grobbelaar and Bateman 1991). Unique geographical locations and environmental conditions may also result in elevated exposure leading to silicosis. For example, radiographic evidence consistent with silicosis has been reported in older individuals in agricultural villages in the northwest Himalayas in India (Norboo et al. 1991a, 1991b; Ranavanya et al. 1992). This area has frequent dust storms, producing silicogenic rock dust with high c-silica content. However, non-occupational exposure to elevated levels of c-silica that produce silicosis is very rare.

#### **3.8 BIOMARKERS OF EXPOSURE AND EFFECT**

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to

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identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to silica are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by silica are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

#### **3.8.1 Biomarkers Used to Identify or Quantify Exposure to Silica**

***Crystalline Silica and Amorphous Silica.*** Silica has been detected in urine of ceramic factory workers exposed to c-silica, indicating that systemic distribution occurs in humans following inhalation exposure (Ibrahim et al. 2011). Thus, the presence of silica in the urine indicates that exposure has taken place. a-Silica is excreted in the feces. The source of fecal silica is most likely from unabsorbed particles of inhaled silica that are deposited in the oral cavity and swallowed or are cleared from the airway by mucociliary clearance and subsequently swallowed. However, the quantitative relationship between urinary silica and cumulative exposure is unknown. Thus, no biomarkers of exposure to c- or a-silica have been identified.

#### **3.8.2 Biomarkers Used to Characterize Effects Caused by Silica**

No biomarkers have been identified to characterize effects caused by c-silica or a-silica. Several studies have examined the association between biomarkers of oxidative stress and inflammation in blood and urine in small numbers of silica-exposed workers and in laboratory animals. Markers examined include



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lactate dehydrogenase, alkaline phosphatase, tumor necrosis factors, interleukins, Clara cell proteins, and numerous proinflammatory cytokines (Aggarwal 2014; Altindag et al. 2003; Braz et al. 2014; Deb et al. 2012; Jiang et al. 2015; Sauni et al. 2012; Sellamuthu et al. 2011; Slavov et al. 2010; Wang et al. 2007). Although associations have been observed, the biomarkers examined are not specific for exposure to silica or as markers of silicosis or pre-silicosis. Elevation of these markers also may be caused by exposure to many other chemicals and by diseases involving inflammatory processes or oxidative stress. Therefore, at this time, no biomarkers for silica effects or for early detection of silica exposure-induced toxicity have been established.

#### 3.9 INTERACTIONS WITH OTHER CHEMICALS

**Crystalline Silica.** As discussed in Section 3.2.1.7 (Inhalation, Cancer), results of recent studies show that the risk of lung cancer due to c-silica is higher in smokers than in nonsmokers. Results of a retrospective study in China examining lung cancer risk in smoking and nonsmoking c-silica-exposed workers showed a consistent increase (2.75–4.38-fold) in lung cancer risk in smokers versus nonsmokers over stratified exposure quartiles (Liu et al. 2013). The study authors stated that ‘the joint effect of [c-]silica and smoking was more than additive and close to multiplicative.’ In addition, different c-silica industries may involve co-exposures with other chemicals (e.g., radon, metals, trace elements, asbestos, formaldehyde, benz[a]pyrene) that could potentially increase the toxicity of inhaled c-silica.

**Amorphous silica.** No studies on interactions of a-silica with other chemicals were identified.

#### 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to silica than will most persons exposed to the same level of silica in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of silica, or compromised function of organs affected by silica. Populations who are at greater risk due to their unusually high exposure to silica are discussed in Section 6.7, Populations with Potentially High Exposures.

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*Crystalline Silica.*

Underlying Diseases. Progression of silicosis can cause serious decrements in lung function that may result in death due to respiratory failure (see Section 3.2.1.2, Inhalation, Systemic Effects, Respiratory). Thus, individuals with underlying lung disease (e.g., asthma, emphysema, tuberculosis, infection with human immunodeficiency virus) may be more susceptible to adverse respiratory effects of inhaled c-silica. Workers with underlying renal diseases also may be more susceptible to adverse respiratory effects of inhaled c-silica.

Smoking. As discussed in Section 3.2.1.7 (Inhalation, Cancer), results of recent studies show that the risk of lung cancer due to c-silica is higher in smokers than in nonsmokers. Results of a retrospective study in China examining lung cancer risk in smoking and nonsmoking c-silica workers showed a consistent increase (2.75–4.38-fold) in lung cancer risk in smokers versus nonsmokers over stratified exposure quartiles (Liu et al. 2013). The study authors stated that ‘the joint effect of [*c*-]silica and smoking was more than additive and close to multiplicative.’”

Polymorphisms. Information in this section is from the following reviews: Ding et al. 2002; Gomez-Puerta et al. 2013; Iannello et al. 2002; IARC 2012; NIOSH 2002; Parks et al. 1999; Yucesoy et al. 2002.

Specific growth factors and cytokines have been identified as playing a crucial role in the pathogenesis of silicosis, particularly TNF- $\alpha$  or IL-1 (see Section 3.5.2 Mechanisms of Toxicity for more details). Evidence from human studies indicates that certain polymorphisms for TNF- $\alpha$  or IL-1 are associated with increased incidence and/or severity of silicosis following occupational exposure to c-silica. For example, in silicotic patients, the risk of developing severe fibrosis was associated with the HLA-Aw19-B18 TNF- $\alpha$  haplotype in the Caucasian population and the HLA-Bw54 TNF- $\alpha$  haplotype in the Japanese population. In a case-control study, the TNF- $\alpha$  variant (-238) was significantly associated with severe silicosis and the TNF- $\alpha$  (-308), IL-1RA (+2018), and IL-1RA (-208) variants were significantly associated with moderate and severe silicosis.

Allelic variants of TNF- $\alpha$  or IL-1 have also been associated to autoimmune and inflammatory diseases. For example, individuals with the HLA-DR3 TNF- $\alpha$  haplotype or a minor variant of the IL-1RA VNTR in linkage disequilibrium have a genetic predisposition to SLE. Therefore, individuals with polymorphisms in these genes may also have increased susceptibility to autoimmune effects associated with occupational exposure to c-silica. In addition, individuals with other known genetic predispositions

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to autoimmune disease may have an increased risk of autoimmune dysfunction with occupational exposure to c-silica (e.g., genetic alterations in the major histocompatibility complex). For example, only specific strains of mice (NZB and MRL/MpJ) develop autoimmune pathology resembling SLE following exposure to c-silica dust.

Altitude. In a recent review, Vearrier and Greenberg (2011) concluded that workers at high altitude are at risk for more rapid development and progression of silicosis.

*Amorphous silica.* No information regarding susceptible populations for a-silica was identified.

#### 3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to silica. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to silica. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to silica can be consulted for medical advice.

Silicosis is an irreversible, progressive, fibrotic lung disease that can continue to progress even after removal from exposure. No established treatments to reverse pulmonary fibrosis or stop its progression have been identified. Supportive therapy may include supplemental oxygen, antibiotic treatment of infections, and vaccinations for influenza and pneumococcal pneumonia. Patients also should undergo periodic tuberculosis screening. Treatment with bronchodilators and corticosteroids may be useful if the patient has changes of COPD (Dart et al. 2002; Hoffman et al. 2014).

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

##### 3.11.1 Reducing Peak Absorption Following Exposure

No methods have been identified to reduce peak absorption following exposure to c-silica or a-silica.

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#### 3.11.2 Reducing Body Burden

No methods have been identified to reduce body burden of c-silica or a-silica.

#### 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No methods have been identified to interfere with the mechanisms for toxic action of c-silica or a-silica.

### 3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silica is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of c-silica and a-silica.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 3.12.1 Existing Information on Health Effects of Silica

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to silica are summarized in Figures 3-8 and 3-9. The purpose of this figure is to illustrate the existing information concerning the health effects of silica. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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**Figure 3-8. Existing Information on Health Effects of Acute Silicosis**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation*	●	●	●	●				●	●	
Oral			●		●					
Dermal										

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation*								●		
Oral	●	●								
Dermal										

**Animal**

● Existing Studies

\*For inhalation toxicity, the focus of this toxicological profile for crystalline silica is on health effects associated with occupational exposure (silicosis, lung cancer, COPD, renal toxicity, tuberculosis, and autoimmune disorders). Other effects in humans were not evaluated. Studies on effects of inhalation exposure of animals were not reviewed.

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**Figure 3-9. Existing Information on Health Effects of Amorphous Silica**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation			●							
Oral										
Dermal										

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●		●	●	●	●	●			●
Dermal										

**Animal**

● Existing Studies

### 3. HEALTH EFFECTS

***Crystalline Silica.*** The focus of this toxicological profile for c-silica is on health effects associated with inhalation exposure in occupational settings (silicosis, lung cancer, COPD, renal toxicity, tuberculosis, and autoimmune disorders). Information regarding effects of inhalation exposure to c-silica is derived from an extensive database of occupational exposure studies. Effects of occupational exposure to c-silica typically occur after prolonged (chronic) exposure (years). Intermediate-duration exposure typically is not associated with adverse health effects, although intermediate-duration occupational exposure to high levels of respirable c-silica may cause acute silicosis. Exposure to respirable c-silica in ambient air has not been associated with adverse health effects. Adverse health effects have not been associated with c-silica following oral or dermal exposure.

***Amorphous Silica.*** Few studies have evaluated the effects of exposure to a-silica in humans or animals, with most data obtained from animal studies. Pulmonary fibrosis has been reported in a-silica workers, although co-exposure to c-silica could not be ruled out. Animal studies show that inhalation of a-silica produces pulmonary inflammation and reversible fibrosis, but silicosis is not observed. Other than pulmonary effects, no other effects associated with inhaled a-silica have been established. Available data for oral exposure are inadequate to establish adverse effects of a-silica in humans or animals. Adverse health effects have not been associated with dermal exposure to a-silica.

#### **3.12.2 Identification of Data Needs**

For c-silica, the focus of data needs is on the primary health effects associated with inhalation exposure in occupational settings (silicosis, lung cancer, COPD, kidney effects, tuberculosis, and autoimmune disorders). Thus, data needs for other health effect end points were not evaluated for inhaled c-silica. Given the lack of data for oral c-silica and inhaled and oral a-silica, comprehensive evaluations of data needs for these exposures were conducted. The effects of c-silica and a-silica have not been investigated in humans or animals following dermal exposure. As the dermal route is not considered a major route of exposure for silica compounds, data needs for dermal exposure to c-silica and a-silica were not evaluated.

#### **Acute-Duration Exposure.**

***Crystalline Silica.*** Adverse effects of occupational (inhalation) exposure to c-silica occur after intermediate (>14 days to <1 year) or chronic exposure (years) and are not associated with exposure durations of  $\leq 14$  days.

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The oral database for acute exposure to c-silica is limited to a single study in rats exposed to 50 mg c-silica/kg/day in drinking water as sodium metasilicate for 8 days (Öner et al. 2005, 2006). Effects in tissues from exposed rats were altered responses of cardiac tissue to various contractile and dilatory stimuli, and altered ammonia,  $\gamma$ -GT, and glutathione levels in cultured renal slices. The toxicological significance of these findings is not known. No exposure-related changes were observed in glomerular filtration rate. No other end points were evaluated. Considering the limitations of the available data, well-designed acute oral toxicity studies of c-silica may provide evidence to identify critical effects and establish NOAEL and LOAEL values.

***Amorphous Silica.*** The database is lacking studies evaluating the effects of acute-duration inhalation exposure to a-silica in humans. However, data are adequate to identify the critical effect following acute exposure to a-silica in animals. Available data indicate that the primary target of acute toxicity is the respiratory system, with transient pulmonary lesions and markers of inflammation after exposure to concentrations as low as 5 mg/m<sup>3</sup> for 3–14 days (Arts et al. 2007; Reuzel et al. 1991; Warheit et al. 1991, 1995). At higher exposure levels ( $\geq 87$  mg/m<sup>3</sup>) for 2 weeks, hematological effects (increased erythrocytes, hemoglobin, and pack cell volume) and decreased body weight were observed (Reuzel et al. 1991). Additional acute inhalation studies evaluating dose- and duration-dependence would provide more information on other potential effects and may identify critical effects and establish NOAEL and LOAEL values.

With the exception of an oral LD<sub>50</sub> study in Sprague-Dawley rats (Lewinson et al. 1994), studies evaluating effects of acute oral exposure of humans or animals to a-silica were not identified. Considering the lack of the available data, well-designed acute oral toxicity studies of a-silica may provide evidence to identify critical effects and establish NOAEL and LOAEL values.

**Intermediate-Duration Exposure.**

***Crystalline Silica.*** Intermediate-duration inhalation exposure typically is not associated with adverse health effects in workers, although occupational exposure to high levels (not defined; also called ‘intense exposure’) of respirable c-silica, such as in sand blasting, may cause accelerated silicosis (Beckett 1997; Leung et al. 2012). Accelerated silicosis may occur after weeks of intense exposure, but typically occurs 5–10 years after the start of exposure. Results of available occupational studies do not provide information on dose- or duration-dependence of intermediate-duration exposure associated with the



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development of accelerated silicosis. Therefore, additional occupational exposure studies of workers with accelerated silicosis that provide exposure-response and duration-response data may define the NOAEL and LOAEL values for accelerated silicosis associated with intense exposure.

Studies evaluating the effects of intermediate-duration oral exposure of humans or animals to c-silica were not identified. Given the lack of information, well-designed intermediate-duration oral toxicity studies of c-silica would provide information about potential effects of exposure and possibly establish critical effects and NOAEL and LOAEL values.

***Amorphous Silica.*** The database is lacking studies evaluating the effects of intermediate-duration inhalation exposure to a-silica in humans. However, data are adequate to identify the critical effect following intermediate exposure to a-silica in animals. Available data indicate that the primary target of acute toxicity is the respiratory system, with evidence of transient pulmonary lesions and markers of inflammation after exposure to concentrations as low as 5 mg/m<sup>3</sup> for 4–13 weeks (Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Warheit et al. 1991, 1995). The only other systemic effect reported in intermediate-duration inhalation studies in animals included hematological effects (increased neutrophils, increased erythrocytes, hemoglobin, and pack cell volume) at 30 mg/m<sup>3</sup> for 13 weeks (Reuzel et al. 1991). Given the lack of information, well-designed intermediate-duration inhalation toxicity studies of a-silica would provide information about potential effects of exposure and possibly establish critical effects and NOAEL and LOAEL values.

A single study investigating the effects of intermediate-duration oral exposure of rats to a-silica was identified (Lewinson et al. 1994). Results showed histological effects on the liver (atrophy of the hepatic epithelium, condensation of the cytoplasm, loss of basophilic structure, and hyperchromatic and contracted nuclei) following an 8-week exposure to an escalating dosage regimen at doses up to 16,000 mg/kg/day. However, no histopathological effects were observed in other organ systems. Given the lack of information, well-designed intermediate-duration oral toxicity studies of a-silica would provide information about potential effects of exposure and possibly establish critical effects and NOAEL and LOAEL values.

#### **Chronic-Duration Exposure and Cancer.**

***Crystalline Silica.*** The available database for chronic-duration occupational exposure to c-silica is extensive and identifies silicosis, lung cancer, COPD, renal effects, tuberculosis, and autoimmune

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disorders as targets. For all health effects, comparison of exposure-response data across studies can be challenging due to potential differences in toxicological potency of c-silica polymorphs and exposures to co-contaminants. Additional occupational exposure studies providing quantitative information of c-silica polymorphs and co-contaminants may provide useful information to determine the basis of differences in study results from different occupational cohorts.

Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis (Checkoway et al. 1997; Chen et al. 2001, 2012; Churchyard et al. 2004; Hedlund et al. 2008; Hnizdo and Sluis-Cremer 1993; Hughes et al. 1998, 2001; Kreiss and Zhen 1996; Mannerje et al. 2002a, 2002b; McDonald et al. 2005; Muir et al. 1989a, 1989b; Mundt et al. 2011; Steenland and Brown 1995a; Vacek et al. 2011). However, the low end of the exposure-response curve is not well-defined, with silicosis and death due to silicosis observed for the lowest cumulative exposure ranges reported. For the lowest cumulative exposure range of 0–0.2 mg/m<sup>3</sup>-year, silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). For mortality due to silicosis, the lowest cumulative exposure range of 0.1–1.23 mg/m<sup>3</sup>-year was associated with an increased risk of mortality (hazard ratio: 1.89; 95% CI: 1.60, 2.24) (Chen et al. 2012). Additional occupational studies focused on lower c-silica exposures may provide information to identify no-effect levels or threshold levels for silicosis or mortality due to silicosis.

c-Silica is classified as a human lung carcinogen (IARC 2012; NIOSH 2002; NTP 2014). IARC (1997, 2012) acknowledged that some occupational exposure studies did not show an association between c-silica exposure and lung cancer, possibly due to the characteristics of c-silica in different occupational settings or other factors affecting its biological activity; in addition, other confounding factors and biases may have influenced study results (e.g., errors in estimating c-silica exposure levels, absence of or presence and severity of silicosis, adequate control of confounding from smoking, and unaccounted occupational co-exposures that may have contributed to lung cancer risk). (Brown 2009; Checkoway 2000; Checkoway and Franzblau 2000; Cox 2001; NIOSH 2002; Pelucchi et al. 2006; Smith et al. 1995; Soutar et al. 2000; Steenland and Ward 2014). Additional, well-controlled occupational exposure studies would provide important information regarding the exposure-response relationship for c-silica-induced lung cancer and the relationship between silicosis and lung cancer.

Occupational exposure to c-silica has been associated with increased risk of a wide-spectrum of renal pathologies, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, glomerulonephritis, and renal damage associated with autoimmune disorders (Calvert et al. 1997; Rapiti

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et al. 1999; Steenland 2005; Steenland et al. (2001b). However, exposure-response relationships for these effects are not well-defined. Additional occupational exposure studies providing quantitative exposure data may allow for identification of NOAEL and LOAEL values for renal toxicity.

The oral database for chronic-duration exposure to c-silica is limited to a few epidemiological studies evaluating potential noncancer effects of silica (form not reported, assumed to be c-silica) in drinking water, including renal disease and cognitive effects. Silicon dioxide levels in water were significantly positively correlated with developing Balkan nephropathy (BN; an endemic chronic kidney disease of the Balkan Peninsula); however, the study authors proposed that it is more likely that the silicon dioxide content in drinking water is correlated with the substance or substances causing the disease, rather than the underlying cause of BN (Radovanovic et al. 1991). Additionally, lower silica content has been reported in wells from BN-endemic villages, compared with control villages (reviewed by Voice et al. 2006). Therefore, additional studies evaluating renal disease and silica content in drinking water may not be warranted. Two French studies did not find an adverse association between silica levels in drinking water and cognitive decline in an elderly population (Gillette-Guyonnet et al. 2005; Jacqmin-Gadda et al. 1996). Given the lack of data on chronic-duration oral exposure in humans and animals, well-designed chronic-duration oral toxicity studies of c-silica would provide information about potential effects of exposure and possibly establish critical effects and NOAEL and LOAEL values.

***Amorphous Silica.*** The available epidemiological studies in humans occupationally exposed to a-silica are inadequate to determine whether or not a-silica causes lung disease in humans, as workers often had exposure to both amorphous and c-silica, as well as other inorganic dusts (Choudat et al. 1990; Gamsky et al. 1992; Jorna et al. 1994). However, it is important to note that silicosis has generally not been observed in epidemiological studies in workers with long-term exposure to a-silica with no known exposure to c-silica (reviewed by McLaughlin et al. 1997; Merget et al. 2002). A limited number of human studies have reported an increased risk of lung cancer or mesothelioma in industries with occupational exposure to a-silica; however, the usefulness of these studies is limited due to potential co-exposure to c-silica and lack of quantitative exposure data (Brooks et al. 1992; Checkoway et al. 1993; Le Blond et al. 2010; Rothschild and Mulvey 1982; Sinks et al. 1994; reviewed by McLaughlin et al. 1997; Merget et al. 2002). Available occupational exposure studies do not identify targets other than the respiratory system. Additional occupational exposure studies that have quantitative data on a-silica exposure and account for c-silica exposure would be helpful in defining the dose-response relationship between inhalation of a-silica and respiratory system toxicity. Additional studies also may identify other systemic targets for occupational exposure to a-silica. Available data from two chronic animal studies indicate that chronic

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inhalation exposure to a-silica can lead to pulmonary inflammation in rats, guinea pigs, and rabbits and early nodular fibrosis and reduced lung function in monkeys (Groth et al. 1981; Schepers 1981). However, a near-complete reversal of adverse effects was observed during a recovery period of 3–9 months. Other effects observed in chronic inhalation studies included altered hematological parameters in rabbits (increased erythrocytes, hemoglobin, and pack cell volume), but not monkeys, rats, or guinea pigs (Groth et al. 1981; Schepers 1981). No other systemic targets were identified in these chronic animal studies. Given the lack of data on chronic-duration oral exposure, well-designed chronic-duration inhalation toxicity studies of a-silica in animals would provide information about potential effects of exposure and possibly establish critical effects and NOAEL and LOAEL values.

The oral database for chronic-duration exposure to a-silica is limited to a single 24-month study in rats (Lewinson et al. 1994). In this study, the only administered dose level of 100 mg/kg/day was identified as a NOAEL for a lack of systemic effects. The reliability of this study is low due to small animal groups (20/sex), lack of concurrent control, and use of a single dose level that did not approach the MTD. Considering the limitations of the available data, well-designed chronic toxicity studies of a-silica may provide evidence to establish a LOAEL and critical effects for long-term oral exposure.

**Genotoxicity.**

**Crystalline Silica.** Results of numerous studies indicate that c-silica is a genotoxic agent in mammalian cells, with the ability to cause mutagenicity, clastogenicity, and DNA-damage. Chromosomal and DNA damage in peripheral lymphocytes and increased micronuclei formation in peripheral lymphocytes and nasal epithelial cells have been observed following occupational exposure to c-silica (Basaran et al. 2003; Demircigil et al. 2010; Sobti and Bhardwaj 1991); however, data are insufficient to determine the exposure-response relationship. Additional occupational exposure studies providing quantitative exposure data may allow for the determination of exposure-response relationships between inhaled c-silica and genotoxicity. *In vivo* studies in rodents exposed to c-silica by intratracheal instillation show DNA damage to lung epithelial cells (Knaapen et al. 2002; Seiler et al. 2001a, 2001b, 2001c). Results of *in vitro* studies also indicate that c-silica causes DNA damage, mutagenicity, and clastogenicity (Cakmak et al. 2004; Driscoll et al. 1997; Fanizza et al. 2007; Hart and Hesterberg 1998; Li et al. 2007; Msiska et al. 2010; Nagalakshmi et al. 1995; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000; Zhong et al. 1997b). Additional occupational exposure studies providing quantitative exposure data may allow for the determination of exposure-response relationships between inhaled c-silica and genotoxicity.

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***Amorphous Silica.*** Studies evaluating genotoxicity in humans following occupational exposure to a-silica were not identified. The few *in vivo* studies in animals were negative for mutations and induction of micronuclei (Johnston et al. 2000; Morita et al. 1997). However, results of *in vitro* studies show that a-silica can cause DNA and chromosomal damage, although conflicting results have been observed (Elias et al. 2006; Guidi et al. 2013; Liu et al. 1996a; Zhong et al. 1997b). Additional occupational exposure studies, *in vivo* animal studies, and *in vitro* studies would provide important information to clarify conflicting results and determine if a-silica is genotoxic under conditions of occupational exposure.

**Reproductive Toxicity.**

***Crystalline Silica.*** Results of an environmental study of pregnant women to c-silica in drinking water suggest that the risk of spontaneous abortion was increased in the highest exposure tertile (3.7–32.0 mg/L) (Aschengrau et al. 1989). The form of silica was not specified, although the study authors assumed that exposure was to c-silica. Due to limitations in study design (lack of data on water consumption, organic contaminants, and no controls for other environmental exposures), interpretation of study results is difficult. No studies evaluating reproductive effects in animals following oral exposure to c-silica were identified. Well-controlled reproductive studies in animals would provide information regarding the potential reproductive effects of oral c-silica.

***Amorphous Silica.*** No studies evaluating reproductive effects in humans following inhalation exposure to a-silica were identified. No histopathological changes to reproductive organs or effects on reproductive performance were observed in rats exposed to oral a-silica at a daily dose of 500 mg/kg/day for 6 months (Lewinson et al. 1994). Results of this study indicate that reproductive effects of oral a-silica are probably not of concern; therefore, additional developmental studies do not appear to be critical.

**Developmental Toxicity.**

***Crystalline Silica.*** No studies evaluating developmental effects in humans or animals following oral exposure to c-silica were identified. Well-controlled developmental studies in animals would provide information regarding the potential reproductive effects of oral c-silica.

***Amorphous Silica.*** No studies evaluating developmental effects in humans or animals following inhalation exposure to a-silica were identified. No developmental effects were observed in offspring of

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rats exposed to dietary  $\alpha$ -silica for 6 months, based on results of two matings (Lewinson et al. 1994). Results of this study indicate that developmental effects of  $\alpha$ -silica are probably not of concern; therefore, additional developmental studies do not appear to be critical.

**Immunotoxicity.**

**Crystalline Silica.** Numerous retrospective cohort and case-control studies have evaluated potential associations between c-silica exposure and a wide spectrum of autoimmune disorders, including systemic sclerosis (scleroderma), rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis (Bartunkova et al. 2006; Beaudreuil et al. 2005; Bovenzi et al. 1995, 2004; Brown et al. 1997; Burns et al. 1996; Calvert et al. 2003; Conrad et al. 1996; Cooper et al. 2010; Cowie 1987; Diot et al. 2002; Englert et al. 2000; Finckh et al. 2006; Gold et al. 2007; Gregorini et al. 1993; Hogan et al. 2001; Klockars et al. 1987; Lacey et al. 1997; Koskela et al. 1987b; Makol et al. 2011; Maitre et al. 2004; Marie et al. 2014; Nuyts et al. 1995; Rafnsson et al. 1998; Rihova et al. 2005; Rodnan et al. 1967; Rosenman and Zhu 1995; Rosenman et al. 1999; Silman and Jones 1992; Sluis-Cremer et al. 1985, 1986; Steenland and Brown 1995b; Steenland et al. 1992, 2001b; Stolt et al. 2005, 2010; Stratta et al. 2001b; Turner and Cherry 2000; Walsh 1999). However, exposure-response relationships for these effects are not well-defined. Additional occupational exposure studies providing quantitative exposure data may allow for identification of NOAEL and LOAEL values for autoimmune disorders.

**Amorphous Silica.** No studies evaluating immunological or lymphoreticular effects in humans following inhalation or oral exposure to  $\alpha$ -silica were identified. No immune system toxicity was observed in rats exposed by inhalation to  $\alpha$ -silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991) or in monkeys, rats, or guinea pigs following exposure to  $\alpha$ -silica at up to 9.9 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981). Similarly, no immune system effects were observed in rats exposed to oral  $\alpha$ -silica at doses of 500 mg/kg/day for 6 months or 100 mg/kg/day for 24 months (Lewinson et al. 1994). Given the limited data on  $\alpha$ -silica and the immunotoxicity associated with c-silica, additional well-controlled occupational and animal studies would provide information regarding the potential for  $\alpha$ -silica to produce autoimmune disorders.

**Neurotoxicity.**

**Crystalline Silica.** No associations were observed between oral exposure of humans to c-silica and cognitive impairment or increased risk of Alzheimer's disease (Gillette-Guyonnet et al. 2005; Jacqmin-

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Gadda et al. 1996). No studies evaluating neurological effects in animals following oral exposure to c-silica were identified. Given the low level of absorption following oral exposure to c-silica, additional studies on neurotoxicity of oral c-silica are not critical.

***Amorphous Silica.*** No changes in brain weight or central or peripheral nervous tissue histology were observed in rats exposed to inhaled a-silica at concentrations up to 30 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No signs of neurotoxicity were observed in rats exposed to oral a-silica 500 mg/kg/day for 6 months or 100 mg/kg/day for 24 months. Given the low level of absorption following oral to a-silica, additional studies on neurotoxicity of a-silica are not critical.

**Epidemiological and Human Dosimetry Studies.** Numerous occupational exposure studies have been conducted on the effects of inhalation exposure to c-silica. These are reviewed above (Chronic-Duration Exposure and Cancer). Of special value in any ongoing or future occupational exposure studies is reliable exposure data, including quantitative data on the level and duration of exposure for c-silica and a-silica polymorphs.

#### **Biomarkers of Exposure and Effect.**

***Exposure.*** Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that systemic distribution occurs in humans following inhalation exposure (Ibrahim et al. 2011). This suggests that urine may be an excretory pathway for c-silica absorbed from the respiratory tract. However, no studies examining the relationship between urinary silica and cumulative exposure were identified. Research examining the link between urinary silica and cumulative exposure may provide information that urinary silica serves as a biomarker for exposure.

***Effect.*** Silicosis is a unique effect of exposure to c-silica. However, other than the signs and symptoms associated with silicosis, no other markers of effect have been identified. Several studies have examined the association between biomarkers of oxidative stress and inflammation in blood and urine in small numbers of silica-exposed workers and in laboratory animals. Markers examined include lactate dehydrogenase, alkaline phosphatase, tumor necrosis factors, interleukins, Clara cell proteins, and numerous proinflammatory cytokines (Aggarwal 2014; Altindag et al. 2003; Braz et al. 2014; Deb et al. 2012; Jiang et al. 2015; Sauni et al. 2012; Sellamuthu et al. 2011; Slavov et al. 2010; Wang et al. 2007). Additional research on the association between biomarkers and silica-exposed workers would be important to determine if such biomarkers could be used for early detection of silica-induced toxicity.

## 3. HEALTH EFFECTS

**Absorption, Distribution, Metabolism, and Excretion.**

**Absorption.** Quantitative estimates regarding absorption and pulmonary retention of c-silica and a-silica polymorphs are not available. Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that absorption occurs in humans following inhalation exposure (Ibrahim et al. 2011). Several studies have evaluated the pulmonary deposition and retention of c-silica and a-silica in the lung of animals (Borm et al. 2002; Case et al. 1995; Davis 1986; Dobрева et al. 1975; Donaldson and Borm 1998; Dufresne et al. 1998; Kelly and Lee 1990; Loosereewanich et al. 1995; Reuzel et al. 1991; Schepers 1981). Additional studies to determine quantitative estimates of pulmonary retention and clearance of c-silica and a-silica following inhalation exposure may provide important information regarding the toxic pulmonary load of silica compounds. Results of a single study evaluating the absorption of oral c-silica in rats indicates that silica was not absorbed (Gonzalez et al. 1991). Given the lack of quantitative information on pulmonary and oral absorption of c-silica and a-silica, well-controlled studies in humans and animals would provide important information to more fully describe the absorption of silica compounds.

**Distribution.** Little information is available regarding extrapulmonary distribution of silica compounds. Occupational exposure studies indicate that inhaled c-silica distributes to the kidney, although quantitative information regarding distribution was not identified (Giles et al. 1978; Hauglustaine et al. 1980; Ibrahim et al. 2011; Saldanha et al. 1975). Studies in rats show distribution to blood, lymph nodes, thymus, kidney, liver, and spleen (Absher et al. 1992). No studies of distribution of silica compounds following oral exposure were identified. Given the lack of qualitative and quantitative information on distribution, well-controlled studies in humans and animals would provide important information to more fully describe the distribution of silica compounds.

**Metabolism.** Absorbed silica compounds are not metabolized. Additional studies on metabolism are not considered critical.

**Excretion.** Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that urine may be an excretory pathway for silica absorbed from the respiratory tract (Ibrahim et al. 2011). Ingested silica is excreted in the feces; however, there are no studies on urinary excretion of absorbed oral silica. Studies on urinary excretion of silica in workers and animals would provide information on relative contribution of excretory pathways and quantitative estimates on retention and excretion of silica.



### 3. HEALTH EFFECTS

**Comparative Toxicokinetics.** Very little is available on the post-absorptive kinetics of absorbed silica compounds. Silica is distributed to tissues outside of the respiratory tract. Additional studies on distribution and mechanisms of excretion would be useful to gain a better understanding of non-respiratory toxic effects.

**Methods for Reducing Toxic Effects.** Silicosis is an irreversible, progressive, fibrotic lung disease that can continue to progress even after removal from exposure. Other than supportive therapy, no established treatments to reverse pulmonary fibrosis or stop its progression have been identified.

**Children's Susceptibility.** Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No information regarding susceptibility of children to c-silica or a-silica has been identified. Silicosis is strictly an occupational disease that occurs from prolonged (years) exposure. As such, studies on children's susceptibility are not considered critical.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

#### 3.12.3 Ongoing Studies

Ongoing research identified in the National Institute of Health (NIH) RePORTER (2015) database is summarized in see Table 3-22).

## 3. HEALTH EFFECTS

**Table 3-22. Ongoing Studies on Silica Compounds**

Principal investigator	Study topic	Institution	Sponsor
Downey, GP	Mechanism-of-action study in mouse fibroblasts	National Jewish Health, Denver, Colorado	National Institute of Environmental Health Sciences
Fattman, CL	Use of stem cells as therapy for silicotic lung disease using mice as the animal model	University of Pittsburg at Pittsburg, Pittsburg, Pennsylvania	National Institute of Environmental Health Sciences
Holian, A	Mechanisms of c-silica-induced fibrosis examining the role of activated lung macrophages and natural killer (NK) lymphocytes	University of Montana, Missoula, Montana	National Institute of Environmental Health Sciences
Kelly, C	Mechanism of tissue-specific fibrosis in autoimmune-prone mice	Integrated Laboratory Systems, Inc., Research Triangle Park, North Carolina	National Institute of Environmental Health Sciences
Larue, AC	The potential of circulating fibroblast precursor as a biomarker of pulmonary fibrosis using a silica mouse model	Ralph H. Johnson VA Medical Center, Charleston, South Carolina	Veteran's Administration
Laskin, DL	Mechanism examining the role of caveolin-1 and TNF $\alpha$ in silica-induced toxicity	The State University of New Jersey at Rutgers, Rutgers, New Jersey	National Cancer Institute
Migliaccio, CT	Mechanism of multiple cell types and soluble factors in silicosis	University of Montana, Missoula, Montana	National Center for Research Resources
Ortiz, LA	Role of tumor necrosis factor receptor-1 phosphorylation on silica-induced lung injury	University of Pittsburg at Pittsburg, Pittsburg, Pennsylvania	National Institute of Environmental Health Sciences
Ortiz, LA	Mechanisms of bone marrow derived mesenchymal stem cells to employ microvesicles as a means to deliver peptides, miRNAs, and mitochondria to reprogram the innate immunity and ameliorate silicosis	University of Pittsburg at Pittsburg, Pittsburg, Pennsylvania	National Heart, Lung, and Blood Institute
Pollard, KM	Characterization of silica-induced immunological responses leading to autoimmunity in mice	Scripps Research Institute, La Jolla, California	National Institute of Environmental Health Sciences

Source: RePORTER 2015.

## 4. CHEMICAL AND PHYSICAL INFORMATION

### 4.1 CHEMICAL IDENTITY

The synonyms, trade names, chemical formulas, and identification numbers of silica and selected forms of silica are provided in Table 4-1.

### 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of silica and selected silica forms is provided in Table 4-2.

Silica occurs naturally in crystalline and amorphous (or non-crystalline) forms, herein referred to as c-silica and a-silica, respectively. Silica has one general Chemical Abstract Service registry number (CASRN 7631-86-9) and more specific CASRNs for individual silica forms and preparations. Both the crystalline and amorphous forms of silica are composed of a 1:2 net ratio of silicon atoms to oxygen atoms, corresponding to an empirical formula of  $\text{SiO}_2$  and the chemical name silicon dioxide (IARC 1997). All silica compounds are silicon dioxide. The internal chemical structure of most forms of silica consists of each silicon atom bonded to four oxygen atoms in a silicon and oxygen tetrahedral ( $\text{SiO}_4$ ) or pyramidal unit with four triangular sides. Crystalline forms of silica have regular, repeating three-dimensional patterns with internal oxygen atoms shared between two tetrahedral silicon atoms. Terminal oxygen atoms are negatively charged ions at environmentally relevant pH (OSHA 2013c). Amorphous forms of silica are composed of highly disordered, randomly linked silicon and oxygen tetrahedral units with no defined pattern. X-ray diffraction patterns distinguish crystalline polymorphs from each other and c-silica from a-silica (discussed in Section 7.2).

The surface properties of silica compounds, even the same polymorph, varies. Both c- and a- forms of silica have surfaces composed of siloxane (covalently bonded silicon and oxygen; Si-O-Si) and silanol groups (Si-OH) (Rimola et al. 2013; Zhuravlev 2000). Exposure to water will break silicon-oxygen bonds on the surface of silica to form silanols. In contrast, heating silica results in condensation of pairs of silanols to form siloxane bridges. In general, c-silica surfaces tend to have more order, although some c-silica is found with an outer layer of a-silica. a-Silica may contain a c-silica component from exposure to high temperatures and pressures (e.g., flux calcination). Grinding silica results in either heterolytic cleavage or homolytic cleavage of silicon-oxygen bonds at the surface interfaces producing  $\text{Si}^+$  and  $\text{SiO}^-$  surface charges or surface radicals, respectively (Fubini et al. 1995). The total concentration and

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Silica and Compounds<sup>a</sup>**

Characteristic	Information			
Chemical name	Silica	Quartz	Cristobalite	Tridymite
Chemical form <sup>b</sup>	Silica	Crystalline silica	Crystalline silica	Crystalline silica
Synonym(s)	Silicon dioxide; diatomaceous earth; diatomaceous silica; diatomite, precipitated amorphous silica; silica gel, silicon dioxide (amorphous); silica colloidal <sup>c,d</sup>	$\alpha$ -quartz; quartz; agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Silica, crystalline-cristobalite; $\alpha$ -cristobalite; $\beta$ -cristobalite	Silica, crystalline-tridymite; $\alpha$ -tridymite; $\beta$ 1-tridymite; $\beta$ 2-tridymite
Registered trade name(s)	No data	CSQZ; DQ 12; Min-U-Sil; Sil-Co-Sil; Snowit; Sykron F300; Sykron F600	No data	No data
Chemical formula	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>
Chemical structure	Not applicable	$\alpha$ -quartz: trigonal crystal	$\alpha$ -cristobalite: tetragonal crystal	$\alpha$ -tridymite: orthorhombic crystal
Identification numbers:				
CAS registry	7631-86-9	14808-60-7	14464-46-1	15468-32-3
NIOSH RTECS <sup>d,e</sup>	VV7310000	VV7330000	VV7325000	VV7335000
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data	No data
HSDB	7168 and 682	7168 <sup>c</sup>	7168 <sup>c</sup>	682 <sup>c</sup>
NCI	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Silica and Compounds<sup>a</sup>**

Characteristic	Information			
Chemical name	Kieselguhr	Kieselguhr, soda ash flux-calcined	Vitreous silica	Kieselguhr, calcined
Chemical form <sup>b</sup>	Amorphous silica	Amorphous silica	Amorphous silica	Amorphous silica
Synonym(s)	Diatomite; silica, Amorphous-diatomaceous earth uncalcined; diatomaceous earth, natural	Diatomaceous earth, flux-calcined	Fused silica	Calcined diatomite
Registered trade name(s)	Celatom, Celite, Clarcel; Decalite; Fina/Optima; Skamol	Celatom, Celite, Clarcel; Decalite; Fina/Optima; Skamol; Silica, Amorphous, diatomaceous earth (containing <1% c-silica); Flux-calcined diatomaceous earth	No data	No data
Chemical formula	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>
Chemical structure	Not applicable <sup>f</sup>	Not applicable <sup>f</sup>	Not applicable <sup>f</sup>	Not applicable <sup>f</sup>
Identification numbers:				
CAS registry	61790-53-2	68855-54-9	60676-86-0	91053-39-3 <sup>g</sup>
NIOSH RTECS <sup>d,e</sup>	HL8600000	No data	VV7328000	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data	No data
HSDB	682 <sup>c</sup>	682 <sup>c</sup>	682 <sup>c</sup>	No data
NCI	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Silica and Compounds<sup>a</sup>**

Characteristic	Information		
Chemical name	Fumed silica	Precipitated silica	Silica gel
Chemical form <sup>b</sup>	Amorphous silica	Amorphous silica	Amorphous silica
Synonym(s)	Pyrogenic silica	Silica, amorphous-precipitated silica	
Registered trade name(s)	Suprasil TAFQ	FK; Hi-Sil; Ketjensil; Neosyl; Nipsil; Sident; Sipernat; Spherosil; Tixosil; Ultrasil	Art Sorb; Britesorb; Diamantgel; Gasil; KC- Trockenperlen; Lucilite; Silcron; Silica-Perlen; Silica-Pulver; Sylobloc; Syloid; Sylopute; Trisyl
Chemical formula	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>
Chemical structure	Not applicable <sup>f</sup>	Not applicable <sup>f</sup>	Not applicable <sup>f</sup>
Identification numbers:			
CAS registry	112945-52-5	112926-00-8	63231-67-4
NIOSH RTECS <sup>d,e</sup>	VV7310000	VV8850000	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	682 <sup>c</sup>	682 <sup>c</sup>	682 <sup>c</sup>
NCI	No data	No data	No data

<sup>a</sup>All information obtained from IARC (1997) except where noted.

<sup>b</sup>a-Silica may contain c-silica; c-silica content varies based on methods of preparation and purification (IARC 1997).

<sup>c</sup>Associated chemical (HSDB 2009a, 2012).

<sup>d</sup>NIOSH 2015a, 2015b.

<sup>e</sup>PCS 2001, 2016a, 2016b, 2016c.

<sup>f</sup>Amorphous, randomly linked silicon and oxygen tetrahedral units with no defined pattern.

<sup>g</sup>Florke et al. 2008.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Silica and Compounds<sup>a</sup>**

Property	Information			
Chemical name	Quartz	Cristobalite	Tridymite	Kieselguhr
Chemical form <sup>b</sup>	Crystalline silica	Crystalline silica	Crystalline silica	Amorphous silica
Molecular weight	60.1	60.1	60.1	60.1
Color	Colorless, white, black, purple, or green solid	Colorless, white, or yellowish solid	Colorless or white solid	Colorless crystals or white powder
Physical state	Solid	Solid	Solid	Solid
Melting point (°C) <sup>c</sup>	573 (α-quartz converts to β-quartz); 870 (β-quartz converts to tridymite)	1,713	1,470 (tridymite converts to cristobalite)	1,710
Boiling point (°C)	2,230	2,230	2,230	2,230
Density (g/cm <sup>3</sup> ) at 20°C <sup>d</sup>	2.648 (α-quartz)	2.334	2.265	2.2 at 25°C
Odor	Odorless	Odorless	Odorless	No data
Odor threshold:				
Water	Not applicable	Not applicable	Not applicable	No data
Air	Not applicable	Not applicable	Not applicable	No data
Taste	Tasteless	Tasteless	Tasteless	No data
Taste threshold	Not applicable	Not applicable	Not applicable	No data
Solubility:				
Water at 20°C	Insoluble	Insoluble	Insoluble	Poorly to insoluble
Other solvents	Dissolves in hydrofluoric acid but insoluble in most other acids and organic solvents <sup>e</sup>	Dissolves in hydrofluoric acid	Dissolves in hydrofluoric acid	No data
Partition coefficients:				
Log K <sub>ow</sub>	No data	No data	No data	No data
Log K <sub>oc</sub>	No data	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	No data	No data	Negligible at 20°C
Henry's law constant at 25°C	No data	No data	No data	No data
Auto ignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors (ppm to mg/m <sup>3</sup> )	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Silica and Compounds<sup>a</sup>**

Property	Information		
Chemical name	Kieselguhr, soda ash flux-calcined	Vitreous silica	Kieselguhr, calcined
Chemical form <sup>b</sup>	Amorphous silica	Amorphous silica	Amorphous silica
Molecular weight	60.1	60.1	60.1
Color	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder
Physical state	Solid	Solid	Solid
Melting point (°C)	1,710	1,713 <sup>c</sup>	1,710
Boiling point (°C)	2,230	2,230	2,230
Density (g/cm <sup>3</sup> ) at 20°C	2.2 at 25°C	2.196 <sup>c</sup>	2.2 at 25°C
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water at 20°C	Poorly to insoluble	Poorly to insoluble	Poorly to insoluble
Other solvents	No data	Dissolves in hydrofluoric acid	No data
Partition coefficients:			
Log K <sub>ow</sub>	No data	No data	No data
Log K <sub>oc</sub>	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C
Henry's law constant at 25°C	No data	No data	No data
Auto ignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m <sup>3</sup> )	No data	No data	No data
Explosive limits	No data	No data	No data



## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Silica and Compounds<sup>a</sup>**

Property	Information		
Chemical name	Precipitated silica	Fumed silica	Silica gel
Chemical form <sup>b</sup>	Amorphous silica	Amorphous silica	Amorphous silica
Molecular weight	60.1	60.1	60.1
Color	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder
Physical state	Solid	Solid	Solid
Melting point (°C)	1,710	1,710	1,710
Boiling point (°C)	2,230	2,230	2,230
Density (g/cm <sup>3</sup> ) at 20°C	2.2 at 25°C	2.2 at 25°C	2.2 at 25°C
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water at 20°C	Poorly to insoluble 80–130 ppm <sup>e,f</sup>	Poorly to insoluble	Poorly to insoluble
Other solvents	No data	No data	No data
Partition coefficients:			
Log K <sub>ow</sub>	No data	No data	No data
Log K <sub>oc</sub>	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C
Henry's law constant at 25°C	No data	No data	No data
Auto ignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m <sup>3</sup> )	No data	No data	No data

<sup>a</sup>All information obtained from HSDB (2009, 2012) except where noted.

<sup>b</sup>a-Silica may contain c-silica; c-silica content varies based on methods of preparation and purification (IARC 1997).

<sup>c</sup>IARC 1997.

<sup>d</sup>Haynes et al. 2014.

<sup>e</sup>EPA 1996.

<sup>f</sup>The solubility of silica is influenced by several factors including temperature and pH; it is affected by the presence of trace metals and the rate of solubility is dependent on the particle size and presence of an external a-silica layer on the particle surface (IARC 1997).

## 4. CHEMICAL AND PHYSICAL INFORMATION

arrangement of silanol on the surface of c- and a-silica can vary greatly. Thus, for a single polymorph of c- or a-silica, surface chemistry of the compound may vary, depending upon production method and degree of hydration. As discussed in Sections 2.2 and 3.5.2, the biological activity of both c-silica and a-silica polymorphs is affected by surface chemistry of the silica particle (Donaldson and Borm 1998; Greenberg et al. 2007; Guthrie 1995; Mossman and Churg 1998; Mossman and Glenn 2013).

c-Silica is polymorphic, meaning that there are several distinctly different crystalline forms with the same chemical composition. c-Silica polymorphs have regular, repeating three-dimensional patterns with long-range order; however, discernable variations in tetrahedral orientation and crystal symmetry differentiate the polymorphs. c-Silica is often referred to as quartz. Quartz is the most common naturally occurring form of silica and is the second most common mineral in the world (USGS 1992). Other common forms of c-silica are tridymite and cristobalite, and less common forms of c-silica are keatite, coesite, stishovite, amethyst, and moganite (NIOSH 2002). Interconversion of the silica polymorphs occurs upon heating or cooling (see Section 6.3.2 for additional information).

The term ‘free silica’ refers to pure c-silica. Major impurities in c-silica polymorphs include aluminum, iron, titanium, lithium, sodium, potassium, and calcium ions (IARC 1997). The concentration of these impurities varies depending on the sample source, but is generally <1.0% in weight as oxide. Natural quartz may contain elemental impurities that are substitutions for silicon. Elemental impurities may also be present as internal or surface defects (Guthrie 1995). c-Silica substances containing other elements, such as sodium, potassium, calcium, magnesium, iron, and aluminum substituted into the crystalline matrix, are referred to as silicates (EPA 1996; USGS 1992).

a-Silica is composed of a random network of tetrahedral silica, and does not display long-range order. a-Silica forms are classified as natural or synthetic a-silica based on their origin. Synthetic a-silica forms are further classified by their preparation method; there are wet process silica forms, which include precipitated silica and silica gels, and thermal process silica forms, including pyrogenic (or fused) silica. Surface-modified silica is physically or chemically treated a-silica (IARC 1997).

Silica is a stable oxide of silicon. c-Silica does not readily react with most acids, but does react with hydrofluoric acid to produce silicon tetrafluoride gas (IARC 2012; OSHA 2013c). c-Silica also reacts with alkaline aqueous solutions and catechol (IARC 2012). a-Silica will react with mineral acids and alkaline solutions (OSHA 2013c).

## 4. CHEMICAL AND PHYSICAL INFORMATION

In general, silica is considered poorly water soluble and chemically unreactive in the environment (EPA 1991; IARC 1997). The water solubility of silica has some variation due to differences in trace metal impurities and hydration (OSHA 2013c). Solubility is lower for c-silica polymorphs than for a-silica, and anhydrous a-silica dissolves less rapidly than hydrated a-silica (IARC 1997). a-Silica dissolves in water to form monosilicic acid (Waddell 2006). External conditions such as higher temperatures and pH increase the water solubility of silica. The hydrophilicity of c-silica particles increases in humid conditions because an external layer of hydroxylated silica (silanol; SiOH) forms on the surface of the particles. Fresh surfaces of silica exposed by fracture are highly reactive and have a propensity to produce surface radicals; however, the surface is inactivated once hydrated (Costa et al. 1991; Fubini et al. 1995). Aged quartz has an external amorphous layer, referred to as a Beilby layer. The Beilby layer is more water soluble than the underlying c-silica (IARC 1997; OSHA 2013c).

Particle size has also been found to influence the rate of solubility. Silica particulate surface areas and sizes are distinguishable based on their source. Ground vitreous silica and c-silica particles have acute edges and heterogeneous particle sizes; surface areas range from 0.1 and 10 to 15 m<sup>2</sup>/g (IARC 1997). Diatomaceous earth and cristobalite particles from diatomaceous earth are found in a variety of shapes and surface areas. Calcinated diatomaceous earth particles have surface areas that range from 2 to 20 m<sup>2</sup>/g. Pyrogenic a-silica particles are nonporous, smooth, round aggregates with surface areas that range from 50 to 400 m<sup>2</sup>/g. Precipitated a-silica particles have sizes and porous structures that vary in surface area from 50 to approximately 1,000 m<sup>2</sup>/g, depending on the procedure used in their preparation. Nanoscale forms of silica were not included in this assessment.

## 4. CHEMICAL AND PHYSICAL INFORMATION

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## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process silica because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

Silica exists in the natural environment and is produced in crystalline and amorphous forms (OSHA 2013c). Sand and gravel, quartz crystals, and diatomite are the three predominant commercial silica product categories (IARC 2012). c-Silica is a common component of igneous rocks such as granite, rhyolite, quartz diorite, quartz monzonite, and andesite. Naturally occurring silica is mined from the earth's crust (USGS 1992). Typically, silica is mined using open pit or dredging methods with standard mining equipment (USGS 2014b). The major component of sand and gravel is quartz. The quartz content of crushed stone varies from region to region.

The U.S. Geological Survey (USGS 2015) reported sand and gravel in two mineral commodity summaries, industrial sand and gravel or commercial sand and gravel. An estimated 139 million metric tons of silica, in the form of industrial sand and gravel, were produced throughout the world in 2012 (USGS 2014b). The United States (50.7 million metric tons), Italy (16.4 million metric tons), Germany (7.5 million metric tons), Turkey (7 million metric tons), France (6.3 million metric tons), Australia (5.3 million metric tons), Spain (5 million metric tons), the United Kingdom (3.8 million metric tons), and Japan (3.2 million metric tons) were the highest producing countries in 2012. The USGS performed a voluntary survey in 2012 of U.S. industrial sand and gravel producers from 77 operations, which represented 75% of the U.S. total production (combined). The survey data indicated that the Midwest produced over half (56%) of the 50.7 million metric tons of industrial sand and gravel produced in the United States, followed by the South at 36%, the West at 5%, and the Northeast at 3% (USGS 2014b). Demand for hydraulic fracturing sand has resulted in increased industrial sand and gravel production capacity in the United States through ongoing permitting and opening of new mines (USGS 2015).

In 2012, the United States produced 812 million metric tons of construction sand and gravel (USGS 2014c). Construction sand and gravel were produced by 4,100 companies and government agencies in the United States (USGS 2015). Texas, California, Minnesota, Washington, Michigan, Colorado, Arizona, North Dakota, Wisconsin, and Ohio accounted for about 55% of total U.S. output.

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Quartz crystal for electronics is predominantly from cultured, not natural, crystal. Synthetic quartz crystals are grown in specific shapes and sizes in heavy-duty autoclaves at 1,500–20,000 pounds/inch<sup>2</sup> and 250–450°C (USGS 1992). No companies in the United States reported production of cultured quartz crystal in a 2012 USGS voluntary survey (USGS 2014b). Cultured quartz crystal is produced primarily in Asia.

Quartz has two forms,  $\alpha$ -quartz and  $\beta$ -quartz. The thermodynamically stable form of quartz under ambient conditions is  $\alpha$ -quartz;  $\beta$ -quartz forms at temperatures  $>573^{\circ}\text{C}$  (USGS 1992). Quartz has a range of physical forms with different sizes, shapes, surface area, roughness, and sorption capacity. Natural quartz is collected from ore through a beneficiation process where raw material is milled and ground into particles and separated into desired mineral and waste. Grinding of sand or gravel is sometimes required to achieve a desired silica material; these processes increase the levels of dust containing respirable c-silica (NTP 2014). Idiomorphic quartz, lump quartz, quartz pebbles, granular quartz, quartz sand, quartz powder, and quartz rock are quartz raw material forms (Florke et al. 2008). Silica flour is an extremely fine-grade silica sand product. Tripoli (CASRN 1317-95-9) is a form of microcrystalline quartz with an extremely small particle size (NIOSH 2011).

Cristobalite is a form of c-silica formed at temperatures  $>1,470^{\circ}\text{C}$  (OSHA 2013c). High-temperature calcined and high-temperature flux-calcined diatomaceous earth may contain cristobalite, formed during the calcination process of diatomaceous earth (Mossman and Glenn 2013). Cristobalite may be formed from quartz during the pouring of metal in foundries where quartz is used to make molds and cores (IARC 1997). Tridymite is a form of c-silica formed at temperatures  $>870^{\circ}\text{C}$  (OSHA 2013c). Both cristobalite and tridymite are found in volcanic rocks and glass (Mossman and Glenn 2013).

Flint, chalcedony, agate, chert, and novaculit are cryptocrystalline silica. Cryptocrystalline silica is silica with submicrometer crystals formed by geological crystallization or compaction of a-silica (IARC 1997; USGS 1992). Forms of c-silica are gemstones (USGS 2014a, 2015). The estimated values in 2012 of U.S. natural quartz gemstone production were \$383,000 and \$261,000 for macrocrystalline and cryptocrystalline quartz, respectively (quantity in mass not reported). The macrocrystalline quartz gemstones are amethyst, aventurine, blue quartz, citrine, hawk's eye, pasiolite, prase, quartz cat's eye, rock crystal, rose quartz, smoky quartz, and tiger's eye; the cryptocrystalline quartz gemstones are agate, carnelian, chalcedony, chrysoprase, fossilized wood, heliotrope, jasper, moss agate, onyx, and sard.

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Biogenic silica is a-silica from living matter, such as plants and diatoms, radiolarians, or silicoflagellates. Certain species of plants and animals, known as diatoms and radiolarians, respectively, extract dissolved silica from their aqueous environment to form structures and shells (USGS 1992). Diatoms and radiolarians are biological sources of silica. The remains of diatoms and radiolarians in sediment can harden into diatomite and radiolarite. Diatomite or Kieselguhr, which is also known as diatomaceous earth, is a loosely coherent, chalk-like sediment that contains up to 94% SiO<sub>2</sub> (IARC 1987). Kieselguhr is obtained through open pit mining (HSDB 2009). In 2014, an estimated 800,000 tons of diatomite was produced at 11 mining areas and 9 processing facilities in California, Nevada, Oregon, and Washington (USGS 2015). The estimated world mine reserves of diatomite is large (>360 million metric tons). In 2014, total (world) mine production was 2.36 million metric tons, with 800,000 metric tons in the United States, 430,000 metric tons in China, and 325,000 metric tons in Denmark. The largest diatomite deposits in the world are located in Lompoc, California (Florke et al. 2008). Diatomites are also mined in Georgia, Mississippi, Nevada, Oregon, and Washington.

In general, synthetic a-silica forms have very high purity. Diatomite (or Kieselguhr) is a sedimentary rock that typically contains 86–94% silica (0.1 to 4.0% c-silica). Aluminum oxide, iron (III) oxide, titanium dioxide, and calcium, magnesium, sodium, and potassium ions are common impurities in diatomite (IARC 1997). Flux-calcined diatomaceous earth is produced when diatomite is heated with flux and typically contains between 40 and 60% cristobalite (OSHA 2013c). The highest synthetic a-silica production capacity in 2004 was in Europe (36%), followed by North America (26%), China (25%; estimated), and Japan (13%) (Waddell 2006).

Pyrogenic (or fumed) silica is typically >99.8% silica (IARC 1997). It is prepared by vaporizing silica at 2,000°C or oxidizing organic or inorganic silicon compounds (Waddell 2006). Vitreous silica (or fused silica) is glassy silica formed by melting and rapidly cooling c-silica to avoid recrystallization (Florke et al. 2008; Smith 2006). Vitreous silica is also formed by vapor-phase hydrolysis of silicon tetrachloride in a methane oxygen flame. Transparent fused silica is formed from exposing 15 nm silica particles to 1,200°C and 13.8 MPa (2,000 psi) or by electric arc fusion of pure silica sand (Waddell 2006).

Precipitated silica is a finely divided synthetic a-silica produced by precipitation from a vapor or solution (EPA 1996). Some precipitated silica and silica gels are prepared with washing steps, which reduce metal oxide impurities to 100–1,000 ppm (IARC 1997). Silica gel is a synthetic amorphous form of hydrous silica containing an interconnected random array of spheroidal particles with 2–10-nm diameters and surface areas of approximately 300–1,000 m<sup>2</sup>/g SiO<sub>2</sub> (Florke et al. 2008). Silica gel is produced when

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

aqueous alkali metal silicate is neutralized under acidic conditions, initiating the polymerization of a-silica into small spheroids. Silica gel has three variations referred to as hydrogel, aerogel, and xerogel based on the production method used (Waddell 2006).

## 5.2 IMPORT/EXPORT

In 2012, 306,000 metric tons of industrial sand were imported into the United States and 4.36 million metric tons were exported. The largest quantities of industrial sand and gravel imported were from Canada (226,000 metric tons) and Mexico (64,000 metric tons) (USGS 2014b). The largest quantities of industrial sand and gravel exported were from the United States to Canada (2.33 million metric tons), Mexico (807,000 metric tons), and Japan (632,000 metric tons). In 2013, 160,000 metric tons of industrial sand were imported into the United States and 2.96 million metric tons were exported.

In 2013, 3 million metric tons of construction sand were imported into the United States (USGS 2015). The largest quantities of construction sand and gravel imported were from Canada (2.37 million metric tons), Mexico (210,000 metric tons), The Bahamas (150,000 metric tons), and other (270,000 metric tons). In 2014, 3,000 tons of diatomite were imported for use and 87,000 tons were exported (USGS 2015). Imports were from Mexico (1,080 metric tons), France (990 metric tons), China (300 metric tons), and others (630 metric tons).

## 5.3 USE

Sand and gravel are used for road building and concrete construction (OSHA 2013c). In the United States, an estimated 44% of construction sand and gravel is used for concrete aggregates; the remainder is used for road base and coverings and road stabilization (25%), asphaltic concrete aggregates and other bituminous mixtures (13%), construction fill (12%), concrete products (1%), plaster and gunite sands (1%), snow and ice control (1%), and filtration, golf courses, railroad ballast, roofing granules, and other miscellaneous uses (3% combined) (USGS 2015).

Heavy industry uses quartz sand to produce high-temperature or refractory silica brick, foundry molds, and cores for the production of metal castings (IARC 2012). The oil and gas industry uses a water-sand mixture to fracture rock. Silica sand is used as a proppant, to prop open fractures and promote hydrocarbon flow and extraction. Water and proppants make up 98–99.5% of typical fracturing fluids. Silica sand with a round spherical shape and commonly graded particle distribution is specifically selected for hydraulic fracturing fluid production. Resin-coated silica is also used as a proppant



## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

(Holloway and Rudd 2014). In the United States, an estimated 72% was used as hydraulic fracturing sand and well-packing and cementing sand; the remainder was used for glassmaking sand (13%), foundry sand (6%), whole-grain fillers and building products (3%), other whole-grain silica (2%), ground and unground sand for chemicals (2%), and other uses (2%) (USGS 2015). c-Silica is used as an asphalt filler and in bricks, mortar, plaster, caulk, roofing granules, wallboard, concrete, and dimension stone in building materials (IARC 2012). Quartz is used as filler in plastics, rubber, and paint or as an abrasive (e.g., blasting, scouring cleansers, sawing, and sanding). Quartz sand is used in municipal water filter beds and sewage treatment plants for filtering out impurities, sediment, and bacteria. Sand and gravel aggregates are used as abrasives on roads in winter (EC 2013).

c-Silica is used in products such as art clay, glazes, cleansers, cosmetics, pet litter, furniture foam, personal care products, talcum powder, and Jeweler's rouge (buffing agent) and as a gemstone (e.g., amethyst, citrine, and quartz) (IARC 2012; USGS 1992). Silica gemstones are used in jewelry, for collections, decorative art objects, and exhibits (USGS 2014a). Cristobalite sand, powder, and flour are used in the production of plastics, adhesives, wall paint, texture coatings, and road paint (Florke et al. 2008).

Quartz sand is used to manufacture glass and pure silicon for computer chips. Sand with >98% silica content is used for glass and ceramics. Finely ground c-silica is used to make ceramics (e.g., pottery, brick, and tile), porcelain, and fine china (IARC 2012; USGS 1992). Windows and specialized devices such as lasers use optical-grade quartz, while electronic-grade quartz is required for electronic circuits. Electronic-grade quartz crystal is used for accurate filters, frequency controls, and timers used in electronic circuits (USGS 2014b). Piezoelectric quartz crystals convert mechanical pressure into electricity and are used in advanced communication systems (IARC 2012; USGS 1992).

Silica stone, a type of c-silica, is produced to manufacture files, deburring-tumbling media, oilstones, and whetstones (USGS 2014b). Artificial, decorative stone products for bathroom and kitchen countertops are manufactured with up to 93% silica content (Kramer et al. 2012). Quartzite, tripoli, ganister, chert, and novaculite are commercially produced silica products (NTP 2014).

Tripoli is extremely fine-grained c-silica, used as a functional filler and extender in adhesives, plastics, rubber, and sealants, and in toothpaste, tooth polishing compounds, industrial soaps, metal- and jewelry-polishing compounds, and buffing and polishing compounds for lacquer finishing in the automobile industry (OSHA 2013c; USGS 2014b). Silica flour (CASRN 14808-60-7) is a fine grade of silica with

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

particles up to 100 µm in diameter used in toothpaste, scouring powders, metal polishes, paints, rubber, paper, plastics, wood fillers, cements, road surfacing materials, and foundry applications (NIOSH 1981; NTP 2009).

Diatomite is used for removing microbial contaminants (e.g., bacteria, protozoa, and viruses) in public water systems (USGS 2015). In 2014, diatomite was used predominantly in filter aids (58%), absorbents (14%), cement (14%), and fillers (13%), and for other specialized applications such as pharmaceutical and biomedical uses (1%). Diatomaceous earth silica and silica gel are used as insecticides and acaricides to control insects, mites, and ticks (EPA 1991). The particle size of diatomaceous earth influences the insecticidal efficacy (Vajias et al. 2009). These compounds act as pesticide carriers and abrasive desiccants, which remove oily, protective films causing insects to dry out and die. Diatomite is applied to stored grain, food stores, feed, and ornamental plants, as well as on pets and their living or sleeping areas.

α-Silica is used at levels up to 2% by weight in food products (IARC 1997). α-Silica is used as an anti-caking agent and as an excipient in pharmaceuticals. α-Silica is used in cosmetics such as makeup preparations, hair dyes and colors, hair bleaches, hair straighteners, permanent waves, hair preparations, personal cleanliness products, skin care preparations, bubble baths, bath oils, tablets, and salts, body and hand preparations (excluding shaving preparations), moisturizing preparations, underarm deodorants, paste masks, perfumes, foot powders and sprays, cleansing products, and suntan gels, creams, and liquids (HSDB 2009).

Silica gel is used as a desiccant and adsorbent for water and other species, thickener in dentifrice, matting agent in coatings, chromatographic media, and catalyst support. Silica fume, α-silica formed as a byproduct of silicon metal or ferrosilicon alloy production, is used in cement, concrete, and mortars to improve strength and durability (Florke et al. 2008).

Transparent and nontransparent vitreous glass is used in tubing, rods, crucibles, dishes, boats, chromatographic substrate, precious-metal thermocouples protection, high temperature pyrometry prisms, lenses, cells, windows, other optical components, lasers, mercury vapor lamps, transducers, semiconductor technology, space shuttle windows, and optical fibers (Smith 2006).

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

**5.4 DISPOSAL**

In the United States, approximately 34% of glass containers are recycled (USGS 2015). Foundry sand and cullet or glass pieces are also recycled, but to a lesser extent. Asphalt road surface layers, cement concrete surface layers, and concrete structures are recycled; however, it is considered to be a small percentage of aggregate (or total) amount used. Approximately 13.7 kkg of Portland cement concrete was recycled in 2012 (USGS 2014c).

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## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

Silica is ubiquitous and is widespread in the environment. It is of particular concern in areas adjacent to crystalline silica mining, processing, and transporting facilities (Richards and Brozell 2015; Richards et al. 2009).

Silicate minerals and quartz comprise approximately 80 and 12% by volume of the earth's crust, respectively (IARC 1997). Generally, silica deposits are quartz (or derived from quartz), formed by metamorphism, sedimentation, or igneous activity. Silica-containing deposits are found in every land mass and strata from every period of geological time (IARC 1987). Sea sand is almost pure silica (HSDB 2012). Silica is also present in air, water, and food. Silica enters environmental media naturally through the weathering of rocks and minerals. Anthropogenic releases of silica are primarily in the form of air emissions. Silica undergoes atmospheric transport as a fractional component of particulate emissions (EPA 1996).

The primary route of exposure for the general population is thought to be via inhalation of c-silica during the use of commercial products containing quartz (IARC 2012). Silica is an air contaminant and significant amounts of a-silica and c-silica may be found in fly ash from power stations and various manufacturing facilities (IARC 1997). Silica-containing dust is produced during rock cutting, drilling, crushing, grinding, mining, abrasion, pottery making, and diatomaceous earth processing (HSDB 2012). a-Silica fibers have been identified as smoke constituents in air samples collected near burning sugarcane fields and near rice farming operations (IARC 1997).

The major features of the biogeochemical cycle of silica include dissolution of terrestrial or lithogenic silica in marine sediments, Aeolian dust settling on the ocean water surface, weathering of continental rocks, and silica settling out of water into sediment from biogenic sources (Tréguer and De La Rocha 2013). Bioavailable silicic acid,  $\text{Si(OH)}_4$ , reaches concentrations up to 2 mM when dissolving in water from minerals in near-neutral pH conditions (Lickiss 2006). Some organisms in water, including diatoms and radiolarian, build up exoskeletons of hydrated silica from silicic acid. Rice, millet, sugarcane, and wheat plants accumulate a-silica; dried sugarcane leaf has silica concentrations ranging between 0.45 and 1.8 weight % (LeBlond 2010; Rabovsky 1995).

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Background gravimetric airborne dust concentrations of remote continental air are  $0.04 \text{ mg/m}^3$ , of which  $\geq 10\%$  is c-silica (Moore 1999). In urban areas across the United States, the measured mean 24-hour average ambient c-silica concentration ranged from  $0.0009$  to  $0.008 \text{ mg/m}^3$  for particles in the size range of  $2.5\text{--}15 \text{ }\mu\text{m}$  (Davis et al. 1984). Average ambient levels of silica in metropolitan areas of the United States generally have ranged between  $0.001$  and  $0.003 \text{ mg/m}^3$  with  $<15 \text{ }\mu\text{m}$  aerodynamic diameter (EPA 1996). Typical silica concentrations in waters are  $13 \text{ ppm}$  for lakes,  $3\text{--}15 \text{ ppm}$  for major rivers,  $1\text{--}10 \text{ ppm}$  for seawater,  $2\text{--}60 \text{ ppm}$  for wells, and  $50\text{--}300 \text{ ppm}$  for wells in volcanic and oil fields (Ning 2002).

Since silica is ubiquitous in the environment, the general population will be exposed to silica by inhalation of ambient air and ingestion of food and water. a-Silica compounds are used as pesticides that are applied to crops and are used near food handling and preparation areas (EPA 1991). Silica is used in food packaging; therefore, food is expected to be a source of exposure to silica for most people (FDA 2015a, 2015b). The use of other consumer items such as cosmetics, cleansers, and toothpaste that also contain silica will result in exposure to silica.

Occupational exposures to silica occur during the mining and processing of metals, nonmetals, and coal, and in many other industries because silica is extremely common, is widely used in materials and products, and is naturally occurring. Occupations in mines and mills (metal, nonmetal, and coal), gas and oil drilling with hydraulic fracturing, granite quarrying and processing, crushed-stone and related industries, foundries, the ceramics industry, manufacture and installation of kitchen countertops, construction, and sandblasting operations are most frequently found to have respirable quartz levels  $>0.1 \text{ mg/m}^3$  (NTP 2014). In agriculture operations, such as plowing, harvesting, using machinery, burning agricultural waste, and processing agricultural products, silica exposure from the soil may occur (NIOSH 2002). Individuals living in the vicinity of industrial emission sources, quarries, or sand and gravel operations may be exposed to elevated levels of respirable c-silica. Local meteorological conditions, such as wind and rain, especially in deserts and areas near recent volcanic eruptions and mine dumps, are expected to influence the location and spread of silica-containing dust (IARC 1987).

## 6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011,

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1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes  $\geq 25,000$  pounds of any TRI chemical or otherwise uses  $>10,000$  pounds of a TRI chemical in a calendar year (EPA 2005).

**6.2.1 Air**

There is no information on releases of silica to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Silica may be released to air by natural and human processes. c-Silica is emitted into the ambient environment as a component of particulate emissions (EPA 1996). Process-stream air emissions of c-silica occur during activities, such as brick making, and fugitive emissions of c-silica occur ancillary to activities. For example, soil particles containing c-silica enter the atmosphere when vehicles travel on unpaved roads as fugitive emissions. Ambient dust containing silica by fugitive emissions include agricultural tilling, burning (forest and non-forest fires), construction, mining, quarrying, hydraulic fracturing, paved and unpaved roads, and wind erosion sources. Soil geology factors are an important source of variability in c-silica emissions by fugitive releases in construction.

There are multiple possible sources of ambient silica. Industrial quarrying and mining are inherently dusty and are expected to contribute to ambient c-silica emissions (EPA 1996). c-Silica may be released during metallurgic manufacturing, although this is dependent on the c-silica use and application of particulate pollution control efforts. Power plant emissions contain c-silica from spent ash and combustion (EPA 1996). Sanding roads for deicing activities in winter may be a potential exposure route for silica as particulate emissions (EPA 1996).

Cristobalite dust may become released into the air by volcanic eruptions (OSHA 2013c). Forest fire and crop burning may emit silica. The original a-silica in vegetation can be released in an amorphous form when combustion occurs at lower temperature, but may release cristobalite and quartz when burned at

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higher temperatures (EPA 1996). Wind erosion emissions of silica, where particulate aerosols are generated from air currents moving over soil, may spread c-silica particles in soils, and vary based on soil parameters, climatic factors, geographic features, vegetation type, and farming practices (EPA 1974).

In urban areas across the United States, the measured mean 24-hour average ambient c-silica concentration ranged from 0.0009 to 0.008 mg/m<sup>3</sup> for particles in the size range of 2.5–5 µm, as presented in Table 6-1 (EPA 1996). The mass median aerodynamic diameters (MMADs) of most c-silica particles released into the environment were >2.5 µm. Average ambient levels of silica with <15 µm aerodynamic diameter in metropolitan areas of the United States generally have ranged between 0.001 and 0.003 mg/m<sup>3</sup> in most circumstances and are not expected to exceed an annual average of 0.008 mg/m<sup>3</sup> (EPA 1996).

Green et al. (1990) evaluated agricultural particulate emissions and background emissions using regional historical data in Alberta, Canada. Variability was associated with the farm and the crops raised. Background total suspended particulate levels ranged from 0.040 to 0.080 mg/m<sup>3</sup>, with 0.85–17.5% c-silica.

PM<sub>10</sub> concentrations obtained 22–745 m downwind from a sand and gravel facility in California ranged from approximately 0.026 to 1.026 mg/m<sup>3</sup> (Shiraki and Holmen 2002). The airborne quartz mass concentrations from the three downwind sites ranged from 0.0262 to 0.0972 mg/m<sup>3</sup>. Samples obtained at one site 1,495 m upwind had mass concentrations of quartz ranging from 0.0041 to 0.0163 mg/m<sup>3</sup>.

In another study, the measured ambient concentrations of PM<sub>4</sub> c-silica ranged from below the detectable limit (0.0003 mg/m<sup>3</sup>) to 0.0028 mg/m<sup>3</sup> in samples collected upwind and downwind of quarry and processing equipment at Carroll Canyon and Vernalis plants in California (Richards et al. 2009). The 8-hour working shift PM<sub>10</sub> c-silica concentrations ranged from 0.001 to 0.0109 mg/m<sup>3</sup>. The study was sponsored by the National Stone, Sand, & Gravel Association and samples were collected downwind of four crushing plants processing high-quartz-content rock (Richards et al. 2009).

Recent air monitoring reports conducted by the Minnesota Air Pollution Authority evaluated c-silica in PM<sub>10</sub> and PM<sub>4</sub> particles in ambient air near industrial sand mining, processing, and transport sites (MPCA 2015a, 2015b). For PM<sub>10</sub> particles, almost all measurements were below the detectable limits (0.001 mg/m<sup>3</sup>), with all values <0.002 mg/m<sup>3</sup> (MPCA 2015a).



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**Table 6-1. Average Quartz Concentrations in Ambient Air for Sites in 22 U.S. Cities—Dichotomous Samples**

Site <sup>b</sup>	N <sup>c</sup>	Coarse quartz ( $\mu\text{g}/\text{m}^{-3}$ )		Fine quartz ( $\mu\text{g}/\text{m}^{-3}$ )		TDM <sup>a</sup> ( $\mu\text{g}/\text{m}^{-3}$ )		Quartz percentage of TDM <sup>a</sup>	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Coarse	Fine
Akron, OH	7	4.2	1.4	<0.1	0.1	71.2	16.1	5.9	<0.1
Boston, MA	1	8.0	—	0	—	140.8	—	5.7	0
Braidwood, IL	1	4.4	—	0	—	57.2	—	7.7	0
Buffalo, NY	14	2.3	1.4	0.1	0.3	83.6	26.6	2.8	0.1
Cincinnati, OH	2	2.6	1.5	0	—	63.2	1.0	4.1	0
Dallas, TX	4	2.6	1.0	0.3	0.3	62.7	22.9	4.2	0.5
El Paso, TX	10	2.2	1.1	0.1	0.1	76.5	43.2	2.9	0.1
Five Points, CA	3	6.6	3.2	1.0	1.2	124.8	84.1	5.3	0.8
Hartford, CT	2	3.0	2.1	0	—	54.8	6.2	5.5	0
Honolulu, HI	1	1.2	—	1.2	—	47.1	—	2.6	2.6
Inglennook, AL <sup>d</sup>	8	5.2	1.7	0.3	0.2	72.6	14.0	7.2	0.4
Kansas City, KS	8	4.7	2.6	0.4	0.4	69.2	28.3	6.8	0.6
Kansas City, MO	3	4.2	3.0	0.1	0.1	58.6	21.6	7.2	0.2
Minneapolis, MN	6	3.7	2.3	0.1	0.1	46.5	7.9	8.0	0.2
Portland, OR	7	1.4	0.6	<0.1	0.1	133.9	122.2	1.0	<0.1
Research Triangle Park, NC	3	0.9	0.5	0.4	0.1	37.0	3.5	2.4	0.1
Riverside, CA	4	3.0	1.1	0	—	106.6	42.2	2.8	0
St. Louis, MO	5	4.4	2.6	0.1	0.1	57.0	11.5	7.7	0.2
San Jose, CA	6	1.9	0.9	<0.1	0.1	67.0	27.3	2.8	<0.2
Seattle, WA	1	1.0	—	0.1	—	36.1	—	2.8	0.3
Tarrant, AL <sup>d</sup>	6	4.3	2.3	1.9	1.0	101.9	57.7	4.2	1.9
Winnemucca, NV	5	5.9	4.3	0.8	0.7	65.7	47.4	9.0	1.2

<sup>a</sup>Total dichotomous mass.<sup>b</sup>Post office state abbreviations used.<sup>c</sup>Number of filters analyzed.<sup>d</sup>North Birmingham.

Source: EPA 1996

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For PM<sub>4</sub> particles, almost all measurements were below the detectable limits (0.0012 mg/m<sup>3</sup>), with all concentrations <0.007 mg/m<sup>3</sup> (MPCA 2015b). Air monitoring in downtown Winona, Minnesota showed that the c-silica concentration was <0.0005 mg/m<sup>3</sup> in all samples (MPCA 2015c).

**6.2.2 Water**

There is no information on releases of silica to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

c-Silica is virtually insoluble in water at standard atmospheric temperatures and pressures; however, it has a strong affinity for water and may form hydrogen-bonds with water (Moore 1999). On the surface of c-silica, Si(O)<sub>4</sub> tetrahedron may contain (OH)<sub>2</sub> groups instead of oxygen. Within the c-silica crystal structures, (OH)<sub>4</sub> may replace Si(O)<sub>4</sub> groups. The term ‘dissolved silica’ (dSi) corresponds to silicic acid, which is formed from inorganic silicon dissolving from lithogenic sources, such as silicate minerals, as part of the weathering process. c-Silica is virtually insoluble in water; however, dissolved silica flows from rivers and groundwater into the ocean where it may settle into marine sediments or be taken up by organisms as part of the biogeochemical silica cycle (Tréguer and De La Rocha 2013). The transformation and degradation of silica in water is further discussed in Section 6.3.2.2.

Quartz sand is used in municipal water filter beds and sewage treatment plants for filtering out impurities, sediment, and bacteria.

**6.2.3 Soil**

There is no information on releases of silica to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Silica is a component of sediments, soils, and rock-forming minerals in magmatic and metamorphic rocks (Florke et al. 2008). Quartz is present in trace to major amounts in sedimentary (e.g., sandstones and conglomerates) and metamorphic rock types (IARC 2012). Silicon dioxide and silica gel are released to soil as registered pesticides for use on food and nonfood crops (EPA 1991).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.3 ENVIRONMENTAL FATE****6.3.1 Transport and Partitioning**

Quartz, cristobalite, and tridymite are found in rocks and soil and can be released to the environment through natural processes, such as weathering or volcanic eruptions, and from anthropogenic sources, such as foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth (IARC 2012). At least a trace amount of c-silica, in the form of quartz, is present in all soils (USGS 1992). Quartz is the major component of sand and dust particulate matter in air.

Silica particles may be transported by wind or water currents as part of the biogeochemical silica cycle. Dissolved silica is transported by river and groundwater sources into the ocean. Ocean water also contains silica from dissolution of terrestrial lithogenic silica in marine sediments, Aeolian dust settling on the ocean water surface, and weathering of continental rocks (Tréguer and De La Rocha 2013). Silica deposits may settle out of water into sediment from biogenic sources. c-Silica may undergo atmospheric transport as a fractional component of particulate emissions (EPA 1996).

**6.3.2 Transformation and Degradation**

Natural or synthetic changes in temperature and pressure may cause the crystalline structure of silica to change (IARC 2002). At elevated temperatures, the silica tetrahedron linkages break and reform into new crystalline structures (OSHA 2013c). Quartz, the most common form of c-silica, converts to cristobalite at 1,470°C, and cristobalite loses its crystalline structure and becomes amorphous fused silica at 1,723°C. The temperature-dependent transitions reverse at extremely slow rates. Different forms of silica co-exist after the heated silica crystal cools. At lower temperatures, the silica-oxygen bonds in the silica tetrahedron rotate or stretch, causing alpha and beta transitions that are readily and rapidly reversed upon cooling. Cristobalite and tridymite are formed when quartz or a-silica is subjected to extremely high temperatures (Leung et al. 2012; Mossman and Glenn 2013). Biogenic silicas are converted into cristobalite at approximately 800°C (IARC 1997). Cristobalite is produced (40–60% cristobalite in finished product) when diatomaceous earth (diatomite) is heated with flux (OSHA 2013c).

Natural activities may cause silica polymorph transformations. For example, lightning strikes or meteorite impacts can change alpha quartz into keatite or coesite (IARC 2002). Cristobalite may be produced by combustion metamorphism of naturally occurring substances (e.g., bituminous rocks, coal,

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or oil) (Clark and Peacor 1992). Anthropogenic activities may also cause transformation of silica from one polymorph into another (IARC 2012). Quartz in furnace bricks may convert to cristobalite when subjected to prolonged high temperatures. Burning of agricultural wastes, such as rice hulls, or forest fires may also cause  $\alpha$ -silica to convert to cristobalite.

**6.3.2.1 Air**

Little information is available on the atmospheric reaction of silica. The silica forms found in air as dusts are stable and not subject to photochemical reactions.

**6.3.2.2 Water**

Silicon dissolves from minerals in water forming bioavailable silicic acid ( $\text{Si}(\text{OH})_4$ ) reaching concentrations  $<2$  mM at near neutral pH (Lickiss 2006). Silicic acid polymerization rate is dependent on temperature, ionic strength of the solution, pH, and silica saturation. Polymerization is fast in neutral and slightly alkaline solutions, and slow at pH values of 2–3 (Icopini 2005; Ning 2002). For example, silica polymerization rates were evaluated at 25°C in a series of controlled experiments. The reported fourth-order rate constants for the 0.01 molal ionic strength experiment with an initial concentration of 20.8 mmolal were  $1.17 \times 10^{-9}$  millimolal<sup>-3</sup>·second<sup>-1</sup> at pH 3 and  $3.53 \times 10^{-10}$  millimolal<sup>-3</sup>·second<sup>-1</sup> at pH 11 (Icopini 2005). Soluble silica half-lives were reported to be approximately 355 minutes at pH 6.5, 55 minutes at pH 8, and 95 minutes at pH 8.75 (Zuhl and Amjad 2013).

**6.3.2.3 Sediment and Soil**

Quartz is extremely resistant to physical and chemical breakdown by the weathering process (USGS 1992). The weathering rate of a square meter of catchment area from different geographic areas using field measurements is  $10^{-2}$ – $10^{-1}$  moles·m<sup>-2</sup>·year<sup>-1</sup> (Ning 2002).

**6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

Reliable evaluation of the potential for human exposure to silica depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of silica in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on silica levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to

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the amount that is bioavailable. The analytical methods available for monitoring silica in a variety of environmental media are detailed in Chapter 7.

#### 6.4.1 Air

Widespread occurrence and use of silica-containing materials result in silica-containing airborne dusts being present in the environment (Moore 1999). Silica particles suspended in the air create non-explosive dusts (OSHA 2013c). Silica from unconsolidated material on the earth's surface in the form of soils, deserts and beaches, volcanic ash, and extraterrestrial dust are natural sources of silica in air (Moore 1999). Remote continental air contains a background gravimetric airborne dust concentration of  $0.04 \text{ mg/m}^3$ , of which  $\geq 10\%$  is c-silica. Desert dust consists of fine particles ( $<10 \text{ }\mu\text{m}$ ) of quartz (IARC 1997).

Samples collected from an urban area in Rome, Italy between September 2004 and October 2005 were analyzed to determine the concentration of silica particles in the inhalable particulate fraction (De Berardis et al. 2007). The total  $\text{PM}_{10}$  particulate in the samples contained  $1.6 \pm 0.6$ – $10.4 \pm 1.4\%$  silica or  $0.00025$ – $0.00287 \text{ mg c-silica/m}^3$  air. The silica particles in the samples had a mean diameter range of  $0.3$ – $10.5 \text{ }\mu\text{m}$ , and  $>87\%$  had a diameter of  $<2.5 \text{ }\mu\text{m}$ . The authors hypothesized that Southern winds from the Sahara Desert carry silica particles into Mediterranean Europe. Corresponding data on the intensity and direction of the wind, humidity, and rain on and near sampling days demonstrated a strong relationship between the concentration of c-silica in the samples and meteorological-climate conditions. The weight percent of c-silica in particles was higher between April and June than the winter months.

The concentration of quartz was reported to be  $\leq 0.034 \text{ mg/m}^3$  in air samples from Tokyo in 1965. The concentration of cristobalite and potential sources of airborne silica were not reported (NTP 2009). Dust samples collected from two communes in a sandy area of Gansu Province, China during the windy season ranged from  $8.35$  to  $22 \text{ mg/m}^3$ . The dust consisted of fine particles ( $<5 \text{ }\mu\text{m}$ ) with a free silica content of  $15$ – $26\%$  (IARC 1997).

Volcanic ash collected at  $34$ – $36 \text{ km}$  altitude from El Chichón (Mexico) were composed of  $35\%$  cristobalite and keatite. Volcanic ash collected from Mount St. Helens in Washington State contained  $3$ – $7\%$  c-silica (IARC 1997).

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Air monitoring was performed using PM<sub>10</sub> high volume samplers at two locations near an industrial slate pencil site and at one control site 5 km away (Bhagia 2009). The quartz concentrations were 0.04107±0.02125–0.05722±0.02205 mg/m<sup>3</sup> near the slate industrial site and 0.00351±0.00145 mg/m<sup>3</sup> at the control site. In another study, PM<sub>10</sub>, PM<sub>4</sub>, and PM<sub>2.5</sub> ambient air samples were obtained for indoor air in two villages neighboring stone crushing sites in India (Mukhopadhyay et al. 2011). The silica content in the samples was between 7 and 24%. The average ambient PM<sub>10</sub> values in the two neighboring communities were 0.77 and 0.46 mg/m<sup>3</sup>. The indoor air average PM<sub>4</sub> values were 0.5 and 0.65 mg/m<sup>3</sup>, respectively, and the PM<sub>2.5</sub> values were 0.13 and 0.28 mg/m<sup>3</sup>, respectively. The workers' average exposure to respirable particulates (PM<sub>4</sub>) in three stone crushing units ranged from 4.51 to 8.15 mg/m<sup>3</sup> (Mukhopadhyay et al. 2011).

In California, 1 of 11 samples obtained upwind of rice farming operations and half of the downwind samples contained a-silica at a concentration of 0.02 fibers/mL; the overall mean concentration of all downwind samples was 0.004 fibers/mL. Silica fibers (fiber length in the respirable dust fraction: >5 µm, with 90% of fibers <5 µm in length; range of fiber width: 0.2–75 µm), measured by polycarbonate membrane filter, were detected in 4 of 14 samples in neighboring towns on days when there was rice burning at a mean concentration of <0.004 fibers/mL (Lawson et al. 1995). a-Silica fibers were identified in three of seven smoke samples collected near burning sugarcane fields in Hawaii (IARC 1997).

#### 6.4.2 Water

Silicon dissolves from minerals in water, forming bioavailable silicic acid, Si(OH)<sub>4</sub>, reaching concentrations up to 2 mM at near neutral pH (Lickiss 2006). Organisms, such as diatoms and radiolarian, build up exoskeletons of hydrated silica from silicic acid in water. Plants use silicic acid to make silica materials for strengthened stems and leaves or protective spikes. Typical concentrations of silica in natural waters are 13 ppm for lakes, 3–15 ppm for major rivers, 1–10 ppm for seawater, 2–60 ppm for wells, and 50–300 ppm for wells in volcanic and oil fields (Ning 2002). The concentration of silica is low at the surface, increases with increasing depth, and is nearly exclusively in the monosilicic acid form.

Median seasonal concentrations of silica were reported for 12 sites in the Hudson River Basin in New York State (Wall et al. 1998). The samples taken between December and March had silica concentrations ranging from 2.8 to 10.0 mg/L. The samples collected between April and November had silica concentrations ranging from 0.72 to 9.1 mg/L. George et al. (2000) measured the total silica content in

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springs and wells in Southern Nevada. Total silica concentrations were detected for the low molecular weight silica that were not colloidal. The authors suggested that decreases in the silica concentration was due to biological causes, such as phytoplankton uptake, based on silica concentrations correlating to the nitrate concentration trend.

### 6.4.3 Sediment and Soil

Silica is ubiquitous in the environment; over 95% of the earth's crust is made of silica-containing minerals and c-silica (Uhrlandt 2006). c-Silica has been found in samples from every geologic era and from every location around the globe (USGS 1992). Alpha quartz is most common in nature, accounting for almost 12% by volume of the earth's crust (OSHA 2013c). At least a trace amount of c-silica, in the form of quartz, is present in all soils. Quartz is found as crystals, aggregates, or discrete particles (IARC 1997). The silica polymorphs, cristobalite and tridymite, are found in rocks, soil, and volcanic rocks. Volcanic rocks in California and Colorado are a major source of cristobalite and tridymite in the United States (NIOSH 1986). The c-silica polymorphs keatite, coesite, stishovite, and moganite are rarely found in nature (IARC 2012).

Quartz is an important component of many igneous and sedimentary rocks (IARC 1997). The sedimentary rocks sandstones, greywackes, and shales contain 82, 37, and 20% quartz by weight, respectively. Some of the igneous rocks that contain quartz are rhyolites, alkali granites, alkali rhyolites, and granites in 33.2, 32.2, 31.1, and 29.2% quartz by weight, respectively. Typically, silica sand deposits have a silica content of 95%, although impurities may reach up to 25% (NTP 2014).

Soils from North Carolina were analyzed for quartz content (Stopford and Stopford 1995). Sandy-loam soils with particles in the 4.25  $\mu\text{m}$  fraction had an average quartz content of 15.2%, clay soils had 2.2%, and sandy soils had 31.6%. Quartz was detected in dust samples collected from indoor and outdoor locations in Oman (Abdul-Wahab et al. 2005). Samples obtained inside and outside a residential house in Al-Suwayq (Oman) contained quartz and quartz, dolomite, and gypsum. Calcite, quartz, dolomite, and goethite were detected in the samples obtained in the residential house near the cement plant.

Settled dust collected from five family farms located in Lublin, Jastków, Konopnica, and Niemce, Poland contained 0.7–65.2% silica (Moloczniak 2002). Average free silica content in bituminous coal was 174,000 ppm (standard deviation 94,000) from Xuan Wei, China and 18,000 ppm (standard deviation

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17,000) from the United States (Large et al. 2009). Grainsize analysis of coal from Xuan Wei, China indicates that 35–55% of the total quartz had a particle size <10 µm.

a-Silica mean concentrations were 5.2, 4.7, and 3.9 mg Si/g in cultivated soil, meadow, and forest, respectively, from the Seine River watershed. Suspended matter from the winter and summer had a-silica average concentrations of 5.7±0.9 and 18.4 mg Si/g (Sferratore et al. 2006).

Ash from the Eyjafjallajökull Volcano eruption in 2010 and from the eruption of Grímsvötn, Iceland in 2011 was studied and compared to ash from Soufrière Hills Volcano, Montserrat that has been studied since eruptive activity began in 1995 (Horwell et al. 2013). Ash from Eyjafjallajökull had a c-silica abundance of 1.4–3.2 weight % and ash from Grímsvötn did not have detectable c-silica content. Ash samples from Soufrière Hills contained 5.2–15.2 weight % cristobalite and 1.2–1.6 weight % quartz (Horwell et al. 2010). c-Silica is formed in volcanic environments by lava dome eruptions with viscous, silicic magma extruded from the volcano at approximately 800°C, forming a dome of rock in the crater (Horwell et al. 2012).

#### 6.4.4 Other Environmental Media

a-Silica accumulates in rice, millet, sugarcane, and wheat plants (Rabovsky 1995). Liu et al. (1996a) measured free silica content of rice husk ash to be 91.4% (25.5% cristobalite and 3.6% tridymite) when the rice husk was burned at 1,100°C; however, the silica content was dependent on the temperature of burning. When the rice husk was burned at 350°C, the ash contained 23% free silica, of which 1.1% was quartz, 3.4% was cristobalite, and 0.5% was tridymite. Tridymite is rarely reported in the workplace or found in nature (Smith 1998).

Le Blond et al. (2010) reported raw air dried sugarcane leaf silica concentrations ranging between 0.45 and 1.8 weight %. Sugarcane trash ash burned at temperatures up to 1,056°C had silica concentrations ranging from 10.38 to 24.77 weight %. Bagasse, the fibrous remains left after sucrose extraction, is often burned as an energy source. The bagasse ash contained between 39.2 and 40.0 weight % silica content. No c-silica was found in the ash burned at temperatures <800°C; however, cristobalite and quartz formed when the sugarcane burned at higher temperatures.

High-purity, mesoporous a-silica was found in a study of the freshwater sponge, *Cauxi*. The study evaluated the skeleton and spicules of a sample made of glassy silica with a length of 305±18 and a width



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of  $15.6 \pm 1.5 \mu\text{m}$  (Jensen et al. 2009). An axial filament that is known to contain the silica catalyst protein, silicatein  $\alpha$ , was also evaluated.

**6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE**

Silica is ubiquitous in the environment. Over 95% of the earth's crust is made of silica-containing minerals and c-silica (Uhrlandt 2006). Silica exposure is expected in both occupational and general settings from the natural environment and consumer use of products containing silica (NTP 2014; USGS 1992). As silica is part of the natural environment and widely distributed in soils and rocks, exposure to silica is unavoidable. It is important to consider the form and availability of silica when discussing silica exposure because silica has multiple forms, particle sizes, surface areas, and surface chemistry (OSHA 2013c). Inhalation is expected to be the primary route of exposure to c-silica for the general population from the use of commercial products containing quartz (IARC 2012). Occupational exposure is further discussed in Section 6.7, Populations with Potentially High Exposures.

Silica is an established air contaminant. Local meteorological conditions can give rise to silica-containing dust, most notably in areas around recent volcanic eruptions, mine dumps, and deserts (IARC 1987). People who live near quarries, sand or gravel operations, or hydraulic fracturing operations may be exposed to respirable c-silica. Consumer exposure to respirable c-silica is possible from the use of abrasives, sand paper, detergent, grouts, and concrete (IARC 1997). Diatomaceous earth is used as a filler in reconstituted tobacco sheets and may be converted to cristobalite at high temperatures when passing through the burning tip of tobacco products (IARC 1987).

Dermal and oral exposure to quartz may occur through the use of consumer and commercial products, including cleansers, skin care products and soaps, art clays and glazes, pet litter, talcum powder, caulk, pharmaceuticals, putty, paint, and mortar (NTP 2009). A homeopathic remedy called silicea, prepared from flint, quartz, sandstone, and other rocks, is another potential source of dermal silica exposure. Exposure to a-silica may occur through dietary intake based on the widespread use of a-silica in the food, cosmetics, and pharmaceutical industries as anticaking agents or carriers. Although quantitative data are not available, diatomite fragments are present in drinking water worldwide, and ingestion of potable water containing quartz particles is a potential source of exposure for the general population (IARC 2012).

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**6.6 EXPOSURES OF CHILDREN**

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

As with adults, exposures of children to silica from breathing air, drinking water, and eating food is expected. As silica is part of the natural environment and found widely in soils, rocks, water, and foods, exposure to silica is unavoidable. Children are likely to ingest dirt from their unwashed hands or when playing with soils, and may be exposed to silica in this manner. Children living in proximity to mines, quarry sites, or industries that release silica particulates to the environment may be exposed to higher levels of silica than are found in the natural environment via inhalation of silica from dust that is entrained in air. Silica is a major component of sand and dirt and may be in many forms; some of these forms may be embedded in minerals.

Dermal and oral exposure may occur through the use of consumer and commercial products that contain silica, including cleansers, skin care products and soaps, art clays and glazes, talcum powder, and pharmaceuticals (NTP 2009). Both silicon dioxide and diatomaceous earth may be found in food and are listed on the Everything Added to Food in the United States (EAFUS) report of items added directly to food that the FDA has either approved as food additives or listed or affirmed as Generally Recognized As Safe (GRAS) (FDA 2013). However, average daily intakes and exposure information for children were not available.

In one study, respirable c-silica measurements ranged from <0.008 to 0.074 mg/m<sup>3</sup> in 11 high school ceramics classrooms located in Salt Lake County, Utah, with up to 88% quartz found in one sample

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(Fechser et al. 2014). The respirable c-silica measurements ranged from 0.005 to 0.039 mg/m<sup>3</sup> in the kiln. Inside control samples all had respirable c-silica concentrations <0.012 mg/m<sup>3</sup> with 55% quartz and outside control samples had respirable c-silica concentrations of 0.012 mg/m<sup>3</sup> with ≤65% quartz.

**6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES**

Respirable c-silica is extremely common, is widely used in materials and products, and is naturally occurring; therefore, occupational exposures occur in a variety of industries and occupations (NIOSH 2002). Metal, nonmetal, and coal mines and mills, granite quarrying and processing sites, hydraulic fracturing operations, crushed-stone industries, foundries, ceramics, construction, and sandblasting operations are most frequently found to have respirable quartz levels >0.1 mg/m<sup>3</sup> (NTP 2014). Main industries where c-silica exposure is likely are those that require job activities involving the movement of earth, disturbing products containing silica, and handling or use of sand and other silica-containing products (IARC 1997, 2012). Workers in other industries also have reported exposure to silica, including shipbuilding and repair, rubber and plastics, paint, soap and cosmetics, roofing asphalt and felt, agricultural chemicals, jewelry, arts, crafts, sculpture, counter manufacture and installation, dental material, boiler scaling, and automobile repair (NIOSH 2002).

A total of 81,221 workers had the potential to be exposed to quartz at 4,077 facilities in 59 industries in 1972–1974 based on data from a National Occupational Hazard Survey conducted from 1972 to 1974 (NIOSH 1976). The survey for 1981–1983 reported that 944,731 workers (112,888 women) were potentially exposed to quartz and 31,369 workers (2,228 were women) were potentially exposed to cristobalite (NIOSH 1990). NIOSH estimated that approximately 1.7 million workers had the potential to be exposed to respirable c-silica based on data from 1986, of which 722,708 workers were in mining industries and 522,748 workers were in non-mining industries (NIOSH 2002).

Yassin et al. (2005) estimated that 119,381 workers in the United States are potentially exposed to high levels of c-silica based on data from 7,209 personal sample measurements collected from 1988 to 2003 stored in the OSHA Integrated Management Information System (IMIS) database. Geometric mean airborne silica exposure levels among workers were 0.070 mg/m<sup>3</sup> from 1988 to 1991, 0.068 mg/m<sup>3</sup> from 1992 to 1995, 0.080 mg/m<sup>3</sup> from 1996 to 1999, and 0.073 mg/m<sup>3</sup> from 2000 to 2003. Freeman and Grossman (1995) evaluated data for measured respirable quartz in 1,655 inspections from 255 industries collected by OSHA. The most severe 8-hour TWA exposures were in the fabricated structural metal and painting and paper hanging industries.

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Radnoff et al. (2014) evaluated the occupational exposure of workers in Alberta, Canada to respirable quartz. Workers in the oil and gas industry had the highest maximum exposure of 8.6 mg/m<sup>3</sup>; however, workers in the sand and mineral processing industry had the highest geometric mean exposure to quartz at 0.09 mg/m<sup>3</sup>. Bricklayer and concrete job activities (coring, cutting, or finishing) had a geometric mean exposure concentration of 0.105 mg/m<sup>3</sup> respirable quartz exposure, which was the highest among the occupations in the study. In Italy, geometric mean occupational exposure respirable c-silica concentrations ranged from 0.007 mg/m<sup>3</sup> for workers in the manufacture of basic metals to 0.045 mg/m<sup>3</sup> for construction workers (Scarselli et al. 2014).

Agricultural workers in the United States may be exposed to dust containing a significant percentage of respirable c-silica (Linch et al. 1998). In agriculture operations, plowing, harvesting, using machinery, burning agricultural waste, and processing agricultural products are possible routes of silica exposure from the soil (NIOSH 2002). Farmers may be exposed to biogenic a-silica during harvesting and may be exposed to a-silica and cristobalite during crop burning or incineration (Rabovsky 1995). Agricultural workers from 10 farms in Yolo and Solano counties in California wore personal sampling equipment to measure exposure to inhalable and respirable dust levels (Nieuwenhuijsen et al. 1999). The geometric mean concentration of respirable dust ranged from 0.05 to 2.83 mg/m<sup>3</sup> (the dust contained 18.6% c-silica). Inhalable dust concentrations ranged from 0.30 to 45.14 mg/m<sup>3</sup> and contained 7.4% c-silica overall. Respirable silica concentrations were measured for farm workers in eastern North Carolina (Archer et al. 2002). The mean silica concentrations ranged from below the level of detection (0.005 mg/m<sup>3</sup> quartz) to 3.91±2.31 mg/m<sup>3</sup> for sweet potato planting in Wayne County.

Respirable quartz concentrations were measured at three South African farms with either sandy, sandy loam, or clay soil (Swanepoel 2011). The geometric mean respirable quartz concentrations were 0.0317, 0.0316, and 0.031 mg/m<sup>3</sup> for the sandy soil, sandy loam soil, and clay soil farms, respectively. The level of silica in air collected from five family farms located in Lublin, Jastków, Konopnica, and Niemce, Poland contained 1.1–22% silica (Moloczniak 2002).

Industrial hygiene practices such as engineering controls, tailored work practices, respirators, and worker training can be used to minimize potential silica health hazards. In the construction industry, wet cutting using water to control airborne dust levels and vacuum dust collection are used to reduce silica dust exposure (OSHA 2009). Construction workers may become exposed to silica from sand, concrete, rock, soil, mortar, plaster, and shingles (NIOSH 2002). In ‘new’ construction, concentrations of respirable c-silica range from 0.013 to 1 mg/m<sup>3</sup> (Radnoff et al. 2014). In the United States, a study evaluated silica

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exposure at 36 construction sites (Rappaport et al. 2003). The highest exposures, with a median silica concentration of 1.28 mg/m<sup>3</sup>, were from painters, followed by laborers at 0.350 mg/m<sup>3</sup>, bricklayers at 0.320 mg/m<sup>3</sup>, and operating engineers at 0.075 mg/m<sup>3</sup>. Quartz dust geometric mean concentrations ranged from 0.01 mg/m<sup>3</sup> (geometric standard deviation of 2.6) to 0.61 mg/m<sup>3</sup> (geometric standard deviation of 5.4) for the tuck point grinder job in a personal silica exposure monitoring data study of the construction industry (Flanagan et al. 2006).

Abrasive blasting is considered to be one of the more hazardous operations involving silica, and it is important for workers performing this task to use proper respiratory protection (Madl et al. 2008). A study was performed to evaluate 11,845 measurements obtained for exposure to respirable c-silica in the construction industry (Beaudry et al. 2013). The majority of the measurements (92%) were obtained with personal measurement devices from 1974 to 2009. The highest geometric mean concentration of c-silica that workers were exposed to was 1.59 mg/m<sup>3</sup> for the abrasive blasting task. In New Jersey, occupational exposure monitoring was performed for a footbridge repainting project using a substitute abrasive with no to low abrasive content in 2002 (Meeker et al. 2005). The workers' exposures to respirable silica were still high, most likely because a high level of silica contaminant, ranging from 0.52 to 25.66 mg/m<sup>3</sup>, was found in the surface paint. Personal samples for exposure to quartz were collected on heavy and highway construction workers (Woskie et al. 2002). The geometric mean concentration for respirable quartz ranged from 0.007 to 0.026 mg/m<sup>3</sup> for the job tasks of operating engineers and laborers, respectively. Personal breathing zone air samples were collected to analyze home construction roof workers' exposure to c-silica (Hall et al. 2013). The 8-hour respirable dust concentration ranged from 0.2 to 3.6 mg/m<sup>3</sup>. The respirable silica 8-hour exposures ranged from 0.04 to 0.44 mg/m<sup>3</sup>. The geometric mean concentrations of respirable silica were 0.12, 0.14, 0.16, and 0.14 mg/m<sup>3</sup> for four companies.

Granite and marble countertop workers had 8-hour TWA exposures as high as 3.07 mg/m<sup>3</sup> (14% quartz) in a 1999 OSHA inspection and 7.4 mg/m<sup>3</sup> (0.7% quartz) based on personal monitoring data (Fairfax and Oberbeck 2008). Akbar-Khanzadeh et al. (2007) measured the concentration of c-silica dust and respirable particulate matter encountered during indoor concrete grinding, wet grinding, and ventilated grinding and uncontrolled conventional grinding. The mean TWA c-silica dust concentrations with no general ventilation were 86.0 mg/m<sup>3</sup> for uncontrolled grinding, 1.40 mg/m<sup>3</sup> for wet grinding, and 0.161 mg/m<sup>3</sup> for local exhaust ventilation grinding; when general ventilation was used, the dust concentrations were 25.4 mg/m<sup>3</sup> for uncontrolled grinding, 0.521 mg/m<sup>3</sup> for wet grinding, and 0.148 mg/m<sup>3</sup> for local exhaust ventilation grinding. c-Silica dust mean concentrations during surface concrete grinding with a 100–125 mm grinding cup were 0.17 and 0.11 mg/m<sup>3</sup> with a HEPA-cyclone and

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HEPA tank, 0.54 and 0.12 mg/m<sup>3</sup> with a shop vacuum, 0.96 and 0.27 mg/m<sup>3</sup> with wet grinding, and 23.6 and 5.78 mg/m<sup>3</sup> with and without general ventilation, respectively (Akbar-Khanzadeh 2010). When a 180-mm cup was used, the silica dust concentrations were 0.54 and 0.20 mg/m<sup>3</sup> with a HEPA-cyclone and HEPA tank, 1.90 and 0.14 mg/m<sup>3</sup> with a shop vacuum, 8.83 and 2.08 mg/m<sup>3</sup> with wet grinding, and 55.3 and 15.1 mg/m<sup>3</sup> with and without general ventilation, respectively.

The mean exposure to respirable dust and quartz was reported for the Dutch construction industry (van Deurssen et al. 2014). The overall mean concentrations were 0.88 mg/m<sup>3</sup> for respirable dust and 0.10 mg/m<sup>3</sup> for quartz. The concentrations ranged from 0.02 to 33.76 mg/m<sup>3</sup> for respirable dust and from 0.01 to 1.36 mg/m<sup>3</sup> for quartz.

Workers in the nonmetal mining operations (i.e., sandstone, clay, shale, and miscellaneous nonmetallic mineral mills) had higher exposure to silica dust than those in metal mining operations. Baggers, general laborers, and personnel involved in the crushing, grinding, and sizing operations had the highest exposure within the mills (IARC 1987). In samples obtained from metal and nonmetal mines from 2005 to 2010, the respirable dust geometric mean concentrations were highest in underground nonmetal and limestone mining samples at 0.88 and 0.73 mg/m<sup>3</sup>, with quartz present in 0.029 and 0.024 mg/m<sup>3</sup>, respectively (Watts et al. 2012). The highest geometric mean quartz concentration was found in underground sand and gravel mines at 0.068 mg/m<sup>3</sup>.

In a cohort mortality study of North American industrial sand workers, the overall geometric mean exposure to respirable c-silica was calculated to be 0.042 mg/m<sup>3</sup> based on 14,249 measurements taken between 1974 and 1998 (Rando et al. 2001). Granite shed workers in Elberton, Georgia were exposed to respirable c-silica at a mean exposure concentration of 0.052 mg/m<sup>3</sup> (Wickman and Middendorf 2002). Exposure surveys were conducted in a granite quarry with side-by-side arrays of four closed-face cassettes, four cyclones, four personal environmental monitors, and a real-time particle counter (Sirianni et al. 2008). c-Silica concentrations ranged from 0.41 mg/m<sup>3</sup> from a personal exposure monitor to 12.38 mg/m<sup>3</sup> for a closed-face cassette. Differences were reported related to the size and silica content of airborne particles depending on the tools being used and the granite activity level at the time of sampling.

In a c-silica occupational exposure study performed in the United States, a geometric mean of 0.065 mg/m<sup>3</sup> was reported for all occupations in the stonework masonry based on data collected between 1988 and 2003 (Yassin et al. 2005). A study evaluating the occupational exposure for workers at 18 silica sand plants from 1974 to 1996 from 4,269 respirable dust samples, reported a geometric mean quartz

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concentration of 25.9 mg/m<sup>3</sup> (geometric standard deviation of 10.9), and samples ranged from <1 to 11,700 mg/m<sup>3</sup> (Sanderson 2000).

An average concentration of 0.22 mg/m<sup>3</sup> was reported for 148 carvers at a stone-carving company in Thailand (Yingratanasuk et al. 2002). Pestle makers and mortar makers had exposure to c-silica at concentrations of 0.05 and 0.88 mg/m<sup>3</sup>, respectively. Personal sampling by workers in a small-scale mining operation reported 15.5 mg/m<sup>3</sup> respirable dust, 2.4 mg/m<sup>3</sup> respirable c-silica, 1.5 mg/m<sup>3</sup> respirable combustible dust, and 28.4 mg/m<sup>3</sup> ‘total’ dust during activities such as drilling, blasting, and shoveling (Bratveit et al. 2003). Respirable dust and respirable c-silica were 4.3 and 1.1 mg/m<sup>3</sup>, respectively, during shoveling and loading of sacks. An overall geometric mean of 0.09 mg/m<sup>3</sup> of respirable c-silica was reported from samples collected at seven U.K. quarries between 1978 and 2000 (Brown and Rushton 2005).

Occupational exposure of coal miners to respirable coal mine dust in the United States was evaluated using data collected from 1995 to 2008 (Joy 2012). Quartz content in airborne dust was variable, and >5% quartz content was found in 20,193 samples (21.6%) below the 0.100 mg/m<sup>3</sup> respirable dust standard. Average respirable quartz concentrations exposure for miners at surface coal mines in the United States ranged from 0.08 mg/m<sup>3</sup> in 1986 to 0.15 mg/m<sup>3</sup> in 1982 based on data from the Mine Safety and Health Administration (MSHA) inspectors (Piacitelli et al. 1990).

Average exposure was calculated using MSHA compliance data from 16,578 measurements at 4,726 mines obtained from 1998 to 2002 (Weeks and Rose 2006). Continuous miner operators were exposed to a mean concentration range of 0.0061–0.2717 mg/m<sup>3</sup>. Workers in underground mines had the highest geometric mean concentration of 0.050 mg/m<sup>3</sup>. Workers in strip and open pit mines and mills or preparation plants had slightly lower mean concentrations of 0.047 and 0.045 mg/m<sup>3</sup>, respectively.

The overall geometric mean concentration of respirable c-silica was 0.027 mg/m<sup>3</sup> for underground coal mining in the United Republic of Tanzania (Mamuya et al. 2006). Employees for the development team, mine team, transport team, and maintenance team reported geometric mean concentrations of 0.073, 0.013, 0.006, and 0.016 mg/m<sup>3</sup>, respectively. A study evaluating respirable samples for silica exposure from two copper mines in Mufulira and Nkana, Zambia reported concentrations of 0.143±0.2 and 0.060±0.06 mg/m<sup>3</sup> of respirable quartz, respectively (Hayumbu 2008). The mean respirable quartz concentration reported in Ontario gold mines ranged from 0.02 mg/m<sup>3</sup> for the task operations designated

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as other to 0.17 mg/m<sup>3</sup> for the conveying and transporting operations (Verma et al. 2014). The highest (or maximum) concentration reported was 0.85 mg/m<sup>3</sup> for the Conveying and Transporting task.

Personal respirable dust exposures were collected at crushed stone facilities in the United States (Kullman et al. 1995). Workers with limestone were exposed to dust with an 11% mean  $\alpha$ -quartz content or a geometric mean concentration of 0.04 mg/m<sup>3</sup> (standard deviation 1.88). Workers with granite were exposed to dust with 37% mean  $\alpha$ -quartz content or a geometric mean concentration of 0.06 mg/m<sup>3</sup> (standard deviation 1.94). Workers with Traprock were exposed to dust with 15% mean  $\alpha$ -quartz content or a geometric mean concentration of 0.04 mg/m<sup>3</sup> (standard deviation 1.62). Silica flour is made by drying and milling mined quartz into fine particles, many of which are respirable (MMWR 1989). The MSHA measured respirable quartz exposures at 28 plants using personal breathing-zone air samplers and found free silica levels above the MSHA permissible exposure limit (PEL) of 0.1 mg/m<sup>3</sup> in 52% of the samples.

Exposure levels to airborne respirable dust with quartz powder sizes of 1.52–3.04 or 3.04–6.08  $\mu$ m in quartz manufacturing units in India were studied (Fulekar 1999). The mean respirable dust exposure level was 2.93 mg/m<sup>3</sup> and exposures ranged from 0.11 to 11.2 mg/m<sup>3</sup> with a high silica content, ranging from 86 to 98%. The TWA exposure of stone crushing laborers in India for PM<sub>2.5</sub> c-silica was 2.29 mg/m<sup>3</sup> (Semple et al. 2008). Occupational exposure to silica was evaluated at slate pencil manufacturing units in India (Fulekar and Khan 1995). Total and respirable dust was present at concentrations up to 380.50 and 31.44 mg/m<sup>3</sup>, respectively, based on data from the study performed in 1977. Total and respirable dust was present at concentrations as low as 4.04 and 0.61 mg/m<sup>3</sup>, respectively, in a study performed in 1991. The free silica content was 35–40, 42–47, and 35–47% in three studies performed in 1977, 1982, and 1991 respectively.

Quartz exposure levels were measured in the Alta, Northern Norway slate industry (Bang and Suhr 1998). The slate factory had respirable quartz average concentrations of 0.12 mg/m<sup>3</sup> inside and 0.13 mg/m<sup>3</sup> outside. c-Silica exposure was measured in the Norwegian silicon carbide industry using 720 fiber samples, 720 respirable dust samples, and 1,400 total dust samples (Foreland et al. 2008). Respirable cristobalite geometric mean levels ranged from below the limit of detection to 0.038 mg/m<sup>3</sup> (geometric standard deviation of 2.0). Respirable quartz geometric mean levels ranged from below the limit of detection to 0.020 mg/m<sup>3</sup> (geometric standard deviation of 2.1). Personal airborne geometric mean concentrations of quartz and cristobalite were 0.013 mg/m<sup>3</sup> (geometric standard deviation of 4.58) and 0.010 mg/m<sup>3</sup> (geometric standard deviation of 2.10) for workers performing the carboselector job (Dion et



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al. 2005). The workers with the job title, Attendant in Acheson furnace maintenance, had a geometric mean quartz exposure of  $0.079 \text{ mg/m}^3$  (geometric standard deviation of 1.49).

During the hydraulic fracturing process, large quantities of silica sand, with up to 99% silica, are used for pumping into wells at high pressure (Chalupka 2012). Data from 111 personal breathing zone samples at 11 sites in five states were evaluated by NIOSH to determine worker exposures to respirable c-silica during hydraulic fracturing (Esswein et al. 2013). The median percentage of quartz in 111 personal breathing zone samples was 53%. Total geometric mean concentrations of respirable quartz were  $0.122 \text{ mg/m}^3$  for all samples and the geometric standard deviation was 1.152. Workers with the job titles, T-belt Operator and Sand Mover Operator, had the highest geometric mean concentrations of respirable c-silica of  $0.327$  and  $0.259 \text{ mg/m}^3$ , respectively, compared to other job titles.

Operations in the ceramic, brick, and clay industries result in c-silica emissions through kiln drying of clay and brick objects, crystalline sand processing, glass manufacturing, calcining of diatomaceous earth, and pottery manufacturing (EPA 1996). Birk et al. (2010) evaluated respirable c-silica measurements obtained from 1955 to 2006 for worker exposure in the ceramics industry. Typically, the highest exposure occurred in the historic samples obtained in 1955–1959 for all job task activities. The highest exposure geometric mean concentration of respirable c-silica in the 2000–2006 data set was from the preparation task at  $0.03 \text{ mg/m}^3$ . A heavy clay industry exposure study was performed with 18 factories from England and Scotland and 1,400 personal dust samples (Love et al. 1999). Mean quartz concentrations ranged from  $0.04$  to  $0.62 \text{ mg/m}^3$  for non-process workers and kiln demolition workers, respectively. Respirable  $\alpha$ -quartz concentrations were measured for workers in the refractory material manufacturing industries (Chen et al. 2007). A minimum variance unbiased estimate of the arithmetic mean respirable  $\alpha$ -quartz content ranged from  $0.0298 \text{ mg/m}^3$  in the crushing area to  $0.0681 \text{ mg/m}^3$  in the mixing area.

OSHA sampling on the melt deck and sprue line of a ductile and malleable iron foundry detected c-silica at  $0.21 \text{ mg/m}^3$  based on the TWA; however, employees engaged in the furnace cleaning and scrapping were exposed to  $7.92$  and  $0.54 \text{ mg/m}^3$ , respectively (Strelec 2010). Personal monitors were used to collect 158 measurements of respirable quartz from jobs conducted from 1993 to 1998 (Maxim et al. 1999). Most of the respirable c-silica concentrations, 91.14%, were less than the limit of detection; the remainder ranged from  $0.010$  to  $0.100 \text{ mg/m}^3$ . Occupational silica exposures were evaluated for workers at a grey and ductile iron foundry that manufactures heavy industrial castings, such as transmission

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housings for large trucks (Lee 2009). The 8-hour TWA c-silica concentrations ranged from 0.988 mg/m<sup>3</sup> for a molder to 4.38 mg/m<sup>3</sup> for a grinder based on the results obtained from personal sampling devices.

Andersson et al. (2012) performed an exposure assessment of quartz in Swedish iron foundries using both historical and current data. The job title with the highest mean quartz exposure was the furnace and ladle repair, with a total concentration of 0.42 mg/m<sup>3</sup>, and the lowest was the core maker, with a total concentration of 0.024 mg/m<sup>3</sup>. The arithmetic mean minimum variance unbiased estimate of respirable quartz exposure profiles for workers during a municipal waste incinerator relining ranged from 0.040 to 0.578 mg/m<sup>3</sup> (Shih et al. 2008). In Khaf, Iran, occupational exposure to respirable quartz was evaluated for workers at an iron ore mine (Naghizadeh et al. 2011). The maximum mean concentration of total quartz was at the crusher machine station at 26 mg/m<sup>3</sup> with a standard deviation of 7, and the minimum concentration was 0.012 mg/m<sup>3</sup> with a standard deviation of 0.002.

At a flat outdoor firing range in 2004, quartz levels were found to exceed 0.030 mg/m<sup>3</sup> (Mancuso et al. 2008); the likely source of the quartz was the sand on the floor of the range. In 2006, after the sand was changed, barrier curtains were added, and lava rock was added to the floor for silica exposure control, the quartz levels were below 0.018 mg/m<sup>3</sup>. At a tunnel type outdoor firing range, personal sampling devices found quartz silica levels ranging from 0.15 to 0.21 mg/m<sup>3</sup>. After Hurricane Sandy in 2012, clean-up workers were monitored for silica exposure (Freund et al. 2014). One measurement of 0.015 mg/m<sup>3</sup> taken at Rockaway, New York in the vicinity of sand was above the detection limit.

Occupational exposure to a-silica may occur in the use or manufacture of a-silica and a-silica-containing products, such as synthetic resins, plastics, lacquers, vinyl coatings, varnishes, pharmaceuticals, cosmetics, adhesives, paints, and foods (IARC 1997). Workers in other industries, such as glass, ceramics, cement, refractory brick, paper, paint, and rubber, may be exposed to various forms of a-silica when used as fillers, filters, or other purposes (NIOSH 2002).

Diatomaceous earth mining, processing, and production reported respirable dust levels ranging from 0.1 to 28.2 mg/m<sup>3</sup> with a c-silica content ranging from <1 to 75% (IARC 1997). Diatomaceous earth workers have the potential for inhalation exposure to high levels of respirable cristobalite and quartz that may be present as impurities or from heating silica (IARC 1997; Rabovsky 1995). In industries where silica products are heated, such as refractory brick and diatomaceous earth plants and ceramic and pottery manufacturing plants, occupational exposure to cristobalite may occur (IARC 1997).

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At a diatomaceous earth mining and milling facility in California, respirable c-silica average cumulative exposure was 0.29 mg/m<sup>3</sup> per years of employment. The c-silica content of the diatomaceous earth dusts varied from 1 to 25% from 1942 to 1994 (Park et al. 2002). Final cumulative exposures to total respirable dust and respirable c-silica dust were 7.31 mg/m<sup>3</sup>·years (average; 168.84 maximum) and 2.16 mg/m<sup>3</sup>·years (average; 62.52 maximum), respectively (Checkoway et al. 1997).

In an occupational exposure study, 1,375 inhalable synthetic a-silica dust concentration measurements were performed from five German synthetic a-silica plants producing pyrogenic and precipitated forms of silica (Morfeld et al. 2014). Mean aerodynamic diameters of the a-silica were 200 µm. Exposures were grouped into categories of low (<1 mg/m<sup>3</sup>), medium (1–4 mg/m<sup>3</sup>), high (4–10 mg/m<sup>3</sup>), and peak (>10 mg/m<sup>3</sup>).

a-Silica fume is a byproduct of the ferrosilicon industrial process (IARC 1997). Total dust containing synthetic-precipitated a-silica was measured at three chemical plants at concentrations of 0–10.5 mg/m<sup>3</sup>. Total dust and respirable dust from personal samples obtained from synthetic pyrogenic fumed manufacturing plants was found at median concentrations of 0.61–6.5 and 0.2–2.1 mg/m<sup>3</sup>, respectively. One ferrosilicon industry exposure study reported 22.3% silica content (amorphous and crystalline) in total dust found at concentrations of 7.3 mg/m<sup>3</sup>. In another ferrosilicon industry exposure study, maintenance workers had respirable dust containing a-silica exposures ranging from 0.27 to 2.24 mg/m<sup>3</sup>.

## 6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silica is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silica.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

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**6.8.1 Identification of Data Needs**

**Physical and Chemical Properties.** The physical and chemical properties of the forms of silica are sufficiently well defined to allow an assessment of the environmental fate of these compounds (CRC 2014; HSDB 2009, 2012; IARC 1997). No additional data are needed at this time.

**Production, Import/Export, Use, Release, and Disposal.** According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2013, became available in October of 2014. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because many forms of silica occur naturally (IARC 1997) and are widely used in industry, in the manufacture of household products, and in processing, packaging, and preserving food (IARC 2012), the potential for human exposure to silica through ingestion of food and water and inhalation of airborne particulates is substantial. Recent data on production, import/export, and use are available (USGS 2015). Information on disposal of silica is limited. In the United States, about 34% of silica glass containers were recycled in 2014 (USGS 2015). Additional information on disposal would be useful in assessing the potential for the release of and exposure to silica.

**Environmental Fate.** Silica is a solid that partitions to air as dust, water, soil, and plant material. Silica in the environment can undergo various weathering dissolutions or precipitations. Partitioning to various media is determined by the physical and chemical properties of the form of silica and the characteristics of the environmental matrix affecting its solubility (IARC 1997; Ning 2002). Silica is transported through the atmosphere primarily as a constituent of soil and other particulate matter (EPA 1996). Transformations are not expected to occur during transport of silica through the atmosphere. Information on the environmental fate of silica is sufficient to permit a general understanding of transport and transformation in all environmental media. No additional information is needed at this time.

**Bioavailability from Environmental Media.** Very limited information is available regarding absorption following oral or dermal exposure; however, these pathways of exposure are not expected to be significant. No additional information is needed at this time.

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**Food Chain Bioaccumulation.** Diatoms are photosynthetic protists that take up dissolved silica from the water and precipitate opaline silica to form their cell wall (IARC 1997). a-Silica levels in diatoms ranges from <1% to approximately 50% by weight. Radiolarians and sponges also extract silica dissolved in water to form their shells. a-Silica has been found to accumulate in rice, millet, sugarcane, and wheat plants (Rabovsky 1995). No additional information is needed at this time.

**Exposure Levels in Environmental Media.** Reliable monitoring data for the levels of silica in contaminated media at hazardous waste sites are needed so that the information obtained on levels of silica in the environment can be used in combination with the known body burden of silica to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Silica is ubiquitous in the environment. c-Silica has been found in samples from every geologic era and from every location around the globe (USGS 1992). Typical concentrations of silica in natural waters is 13 ppm for lakes, 3–15 ppm for major rivers, 1–10 ppm for seawater, 2–60 ppm for wells, and 50–300 ppm for wells in volcanic and oil fields (Ning 2002). Average ambient levels of silica with <15  $\mu\text{m}$  aerodynamic diameter in metropolitan areas of the United States generally have ranged between 0.001 and 0.003  $\text{mg}/\text{m}^3$  in most circumstances and are not expected to exceed 0.008  $\text{mg}/\text{m}^3$  annual average (EPA 1996). More recent studies on the ambient levels of silica are needed.

**Exposure Levels in Humans.** Data on nonoccupational exposures to all forms of silica are extremely limited. Limited analytical methods reported the analysis of silica in biological materials. All forms of silica are considered to be poorly soluble particles. Inhaled silica particles, not cleared by mucociliary escalators or coughing, are embedded and remain in the lung (Cox 2011). Additional information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** Limited analytical methods reported the analysis of silica in biological materials. More recent studies on the ambient levels of silica are needed. Data were not available on the intake of silica in food eaten by children and from their diet. Current information on whether children are different in their weight-adjusted intake of silica via oral, inhalation, and dermal exposures was not located. A study to determine this information would be useful.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

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**Exposure Registries.** The information amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance; however, no exposure registries for silica were located. Silica is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. Silica will be considered in the future when chemical selection is made for sub-registries to be established.

### 6.8.2 Ongoing Studies

The NIH RePORTER (2015) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-2.

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**Table 6-2. Ongoing Studies on Silica**

Investigator	Affiliation	Research description	Sponsor
Chugh, Yoginder P	Southern Illinois University Carbondale	The USBM and NIOSH have done extensive research on coal and quartz dusts with an emphasis on eastern U.S. coal mines. The goals of this research are to develop physical and chemical characteristics of different particle size coal and quartz dusts from different unit operations. The sampling data from the Interior Coal Basin mines from MSHA and company dust data will also be utilized to identify occupations and locations most exposed. Surface and wettability characteristics for different size fractions of coal and silica dusts generated during mining, haulage, and roof support operations will be evaluated.	NIOSH
Miller, Frederick	NIEHS	Evaluation of exposures to items including silica to assess relationships and the development of systemic autoimmune diseases.	NIEHS

MSHA = Mine Safety and Health Administration; NIEHS = National Institute of Environmental Health Sciences;  
 NIH = National Institutes of Health; NIOSH = National Institute for Occupational Safety and Health;  
 USBM = U.S. Bureau of Mines

Source: NIH RePORTER 2015

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## 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring silica, its metabolites, and other biomarkers of exposure and effect to silica. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

### 7.1 BIOLOGICAL MATERIALS

Limited analytical methods reported the analysis of c-silica or a-silica in biological materials. All forms of silica are considered to be poorly soluble particles. Inhaled silica particles, not cleared by mucociliary escalators or coughing, are embedded and remain in the lung (Cox 2011).

OSHA method PV2121 characterizes the term ‘respirable dust’ as dust particle sizes with a median diameter of 3.5  $\mu\text{m}$ ; however, NIOSH Method 0600 lists a diameter size of 4  $\mu\text{m}$  (NIOSH 1998; OSHA 2015). The European standard PN-EN 481:1998 and international standard PN-ISO 7708:2001 describe the term ‘respirable dust’ as a cumulated log-normal distribution, with the median diameter of 4.25  $\mu\text{m}$  and geometric standard deviation of 1.5 (Maciejewska 2008).

NIOSH (2003b) Analytical Method 7601 is a standardized method used to determine the concentration of c-silica by x-ray diffraction (XRD) with filter redeposition in respirable or total dust, settled dust, and biological samples, although studies describing the use of this method with biological samples were not identified.

### 7.2 ENVIRONMENTAL SAMPLES

Table 7-1 lists the methods used for determining silica in environmental samples. Silica is a common material in the environment with many distinct forms. Determination of the form of silica present and concentration of each form of silica in a sample may be achieved through several different analytical

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**Table 7-1. Analytical Methods for Determining Silica in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (dust)	Collection with 10-mm nylon cyclone and 5- $\mu$ m PVC membrane	Method 7500; XRD	0.005 mg SiO <sub>2</sub> per sample 0.08	$\pm$ 18% (accuracy)	NIOSH 2003a
Air (dust)	Collection with PVC membrane filter	P-2; XRD	20 $\mu$ g quartz	$\pm$ 20% (accuracy)	MHSA 2013b
Air (dust)	Collection with 25 mm, 5- $\mu$ m PVC membrane filter or Ag filter (XRD), according to MDHS 14/3	MDHS 101; FT-IR or XRD	FT-IR: 20 $\mu$ g XRD: 10 $\mu$ g RSD 0.087	$\pm$ 20% (accuracy 0.5–2.0 limit value)	MHSA 2005
Air (dust)	Collection with 10-mm nylon cyclone and 37 mm, 5- $\mu$ m PVC membrane	Method 7602; IR	0.005 mg SiO <sub>2</sub> per sample RSD <0.15	Not reported	NIOSH 2003d
Air (dust)	Collection with 10-mm nylon cyclone and 0.8- $\mu$ m MCE or 5- $\mu$ m PVC membrane	Method 7501; XRD	5 $\mu$ g quartz	Not reported	NIOSH 2003c
Air (dust)	37 mm, 5- $\mu$ m PVC membrane	ID-142; XRD	20 $\mu$ g quartz RSD 0.11	$\pm$ 26% (error)	OSHA 1996
Air (dust)	Collection with 10-mm nylon cyclone and 37 mm, 5- $\mu$ m PVC membrane	Method 7603; IR, FT-IR	10 $\mu$ g quartz RSD 0.098	$\pm$ 25.6 to 43.4% (accuracy)	NIOSH 2003e
Air (dust)	Collection with membrane filter	P-7; IR	20 $\mu$ g quartz	$\pm$ 13% (accuracy)	MHSA 2013
Air (dust)	Collection with 37 mm, 5- $\mu$ m PVC membrane	MDHS 37; IR	Varies with particle size	Not reported	NIOSH 2002
Air (dust)	Collection with 37 mm, 5- $\mu$ m PVC membrane	MDHS 38; IR	Varies with particle size	Not reported	NIOSH 2002
Air (dust)	Collection with membrane filter	IR	5–27 $\mu$ g quartz 6–16 $\mu$ g cristobalite	Not reported	Foster and Walker 1984
Air (dust)	Collection with 10-mm nylon cyclone and 0.8- $\mu$ m MCE or 5- $\mu$ m PVC membrane	Method 7601; VIS	10 $\mu$ g SiO <sub>2</sub> per sample RSD 0.09	Not reported	NIOSH 2003b
Air (dust) and soil	48% HBF <sub>4</sub> at 70°C, filter, dissolve in 1:1 KHCO <sub>3</sub> and KCl, boiling water, add 0.1 mL 10% ammonium molybdate, adjust pH to 2.1	Spectrophotometer	8 $\mu$ g quartz	99.8%	Stopford 1994
Air (dust)	Collection with 37 mm, 5- $\mu$ m PVC membrane	LIBS	0.16 $\mu$ g/cm <sup>2</sup>	10% (relative errors)	Stipe et al. 2012

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**Table 7-1. Analytical Methods for Determining Silica in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (dissolved silica)	Filter sample with 0.45- $\mu$ m membrane filter; add molybdate ion in acidic solution to filtrate; the color complex is measured	Spectro-photometer/ EPA 370.1	2 mg silica/L	Not reported	NPDES 1978
Water (dissolved silica)	Add molybdate ion in ascorbic acid solution to filtrate; the color complex is measured	Spectro-photometer/ USGS NWQL I-2700-85	0.1 mg silica/L	Not reported	USGS 1989
Water (dissolved silica)	Filtered, acid preserved sample is mixed with 1% v/v HNO <sub>3</sub>	ICP-AES/ EPA 200.7	26 $\mu$ g/L (estimated)	96–104% (in tap water)	EPA 1994b
Water (dissolved silica)	Samples are solubilized or digested prior to analysis	ICP-AES/ EPA 6010c	0.017 mg/L (estimated)	Not reported	EPA 2000
Water (dissolved silica)	Sample undergoes a direct-reading, no preparation	ICP-AES/ USGS NWQL I-1472-87	0.01 mg/L (estimated)	Not reported	USGS 1987
Water (dissolved silica)	Acidify sample with HNO <sub>3</sub> to pH <2	AVICP-AES/EPA 200.5	0.01 mg silica/L	Not reported	EPA 2003
Water (dissolved silica)	Acidify sample with HNO <sub>3</sub> to pH <2	ICP-OES/ USGS NWQL I-4471-97	Not reported	Not reported	USGS 1998
Soil	LiCO <sub>3</sub> /H <sub>3</sub> BO <sub>3</sub> flux and stabilization with fluoride	AAS	Not reported	99.7%	Barredo and Diez 1980
Soil	Sample weighed	Thermal analysis	<1%	Not reported	Sheffield 1994

AAS = atomic absorption spectroscopy; AVICP-AES = axially viewed inductively coupled plasma-atomic emission spectrometry; EPA = Environmental Protection Agency; FT-IR = Fourier transform infrared spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-OES = inductively coupled plasma-optical emission spectrometry; IR = infrared spectrometry; MCE = mixed cellulose ester; MSHA = Mine Safety and Health Administration; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NWQL = National Water Quality Laboratory; OSHA = Occupational Safety and Health Administration; PVC = polyvinyl chloride; RSD = relative standard deviation; USGS = U.S. Geological Survey; VIS = visible absorption spectrophotometry; XRD = x-ray diffraction

## 7. ANALYTICAL METHODS

techniques. The use of XRD and infrared spectroscopy (IR) allows for the separate determination of quartz, cristobalite, and tridymite (Maciejewska 2008). The total content of all crystalline forms of silica is obtained with visible absorption spectrophotometry. Optical microscopy, electron microscopy, thermal analysis, selective dissolution, and density separation may also be used to analyze silica. Several analytical methods have been reported by regulatory agencies including NIOSH, OSHA, USGS, and MSHA.

Mineral interferences may be reduced prior to analysis with sample preparation techniques; for example, a phosphoric acid digestion is used if there is a presence of  $\alpha$ -silica (Talvitie 1951).  $\alpha$ -Silica and some smaller  $\alpha$ -silica particles dissolve in phosphoric acid (Eller 1999).  $\alpha$ -Silica particles  $<3 \mu\text{m}$  dissolve in hot phosphoric acid; therefore, the amount of free silica may be underestimated when using this method (Yabuta and Ohta 2003). Hydrochloric acid is used to remove calcite, magnetite, and hematite. Air samples collected with filters are ashed or dissolved in tetrahydrofuran (NIOSH 2003f). The ashed sample is suspended in a solvent and deposited onto an analytical filter. Another preparation method used to obtain the free silica in respirable dust samples uses pyrophosphoric acid and a closed vessel dissolution technique with microwave heating (Shinohara 1993).

Particle-size distribution of silica samples is measured by laser scattering or air-jet screening (Florke et al. 2008). Cyclone air samples, filter cassette, and filter media are used to retain the respirable dust fraction without non-respirable particles. Criteria for collecting particles of the appropriate size with cyclone air samplers are established by the International Organization for Standardization (ISO), the European Committee for Standardization (CEN), and ACGIH (NIOSH 2003f). The XRD, IR, and colorimetric analytical methods are subject to different particle size effects, and each cyclone exhibits its own unique particle collection characteristics (NIOSH 2003f).

XRD patterns are able to distinguish  $\alpha$ -silica polymorphs from each other and from other  $\alpha$ -silica forms. XRD patterns are produced specific to the  $\alpha$ -silica crystalline structure (IARC 1997). The polymorph  $\alpha$ -quartz has a primary diffraction line at  $26.66^\circ 2\theta$  ( $3.343 \text{ \AA}$ ). NIOSH (2003a) Analytical Method 7500 is a standardized method used to determine the concentration of  $\alpha$ -silica by XRD with filter redeposition in dust. NIOSH (2003c) Analytical Method 7501 is a standardized method used specifically for  $\alpha$ -silica in crystalline (e.g., quartz) matrices with XRD analysis. The Department of Labor's MSHA has method MDHS 101 (replaces MDHS 51/2), an XRD method for the determination of quartz in dust.

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c-Silica polymorphs have distinct infrared absorption patterns.  $\alpha$ -Quartz has a doublet at 798–790 and 779–780  $\text{cm}^{-1}$ , with secondary peaks at 694, 512, 460, 397, and 370  $\text{cm}^{-1}$  (NIOSH 2003f). Cristobalite peaks are found at 798, 623, 490, 385, 297, and 274  $\text{cm}^{-1}$  and tridymite peaks are found at 793, 617, and 476  $\text{cm}^{-1}$ . NIOSH (2003d) Analytical Method 7602 is a standardized method used to determine the concentration of c-silica by IR analysis in air dust samples. NIOSH (2003e) Analytical Method 7603 is a standardized method used to determine the concentration of c-silica in coal dust by Fourier transform infrared spectroscopy (FT-IR) or IR analysis. The Department of Labor's MSHA also has an IR method for the determination of quartz in respirable coal mine dust (MSHA 2013). MDHS 37 and MDHS 38 are other standardized methods used to determine the silica content of a sample by IR (NIOSH 2003f).

The combination of XRD and IR has been used to quantify the a-silica and c-silica content of samples to obtain the c-silica and total silica content, respectively (Bye et al. 1980). A direct differential scanning IR method has been described to determine the c-silica content in respirable atmospheric dust samples (Foster and Walker 1984). A difference spectrum method may be used to correct for interfering spectra when determining the c-silica content of dust samples with IR (Ojima 2003). Kaolinite is a commonly found mineral in coal mine dust that interferes with IR analysis of quartz, and corrections with a standard reference material have been suggested (Lee et al. 2013; NIOSH 2003f). Field-portable IR spectrometers are used to provide more timely estimates of silica exposure (Miller et al. 2012). A direct-on-filter method using partial least squares regression to the infrared transmission spectra of samples deposited on porous polymeric filters was developed to allow for the use of field-portable infrared spectrometers (Weakley et al. 2014).

NIOSH (2003b) Analytical Method 7601 is a standardized method used to determine the concentration of c-silica by visible absorption spectrophotometry (VIS) in respirable or total dust, settled dust, and biological samples. Colorimetric methods require preparation steps and color development methods (citric acid and tartaric acid); absorbance is measured at 785 nm (Stopford 1994). Colorimetric methods for c-silica are less precise than XRD or IR (NIOSH 2003f).

Laser-induced breakdown spectroscopy quantifies quartz in coal dust samples collected on filter media with extremely low ( $0.16 \mu\text{g}/\text{cm}^2$ ) limit of detection levels for silica (Stipe et al. 2012).

Dissolved silica concentrations are used to determine the silicon content of water (USGS 1998). Molybdate ion in acidic solution, when added to a water sample containing dissolved silica, forms a greenish-yellow color complex proportional to the dissolved silica and is measured spectrophoto-

## 7. ANALYTICAL METHODS

metrically. Dissolved silica in drinking, surface, and saline waters and domestic and industrial wastes is measured using EPA Method 370.1 or USGS NWQL I-2700-85 with a spectrophotometer (NPDES 1978; USGS 1989). Silica in solution is also measurable using inductively coupled plasma-atomic emission spectrometry (ICP-AES) according to EPA Method 200.7 or 6010.C or USGS NWQL I-1472-87 (EPA 1994b, 2000; USGS 1987), axially viewed inductively coupled plasma-atomic emission spectrometry (AVICP-AES) by EPA Method 200.5 (EPA 2003) and inductively coupled plasma/optical emission spectrometry by USGS NWQL I-4471-97 (USGS 1998). Samples prepared by EPA Method 200.2 are acidified, mixed, and held at a pH <2 (EPA 1994a).

The silica content of rock samples may be obtained by decomposing the sample in  $\text{LiCO}_3/\text{H}_3\text{BO}_3$  flux followed by stabilization in fluoride (Barredo and Diez 1980). An atomic absorption spectrophotometer (AAS) and EEL lamp are used to detect the major elements of the rock samples. Thermal analysis of c-silica, to measure the energy associated with phase changes based on changes in temperatures of samples, has also been developed (Sheffield 1994). An analytical procedure detects the a-silica content of a sample by converting to cristobalite with heating (Lange et al. 1981).

Scanning electron microscopy (SEM) identifies minerals by energy dispersive techniques and sometimes by morphology, but does not enable differentiation between the polymorphs of c-silica, a-silica, glasses, and opal (Miles 1999). The transmission electron microscope (TEM), when combined with energy dispersive X-ray spectroscopy and electron diffraction, is used to distinguish grains of c-silica.

Differentiation of the forms of a-silica involves investigation into the chemical composition, physical properties, and characteristics of the particles (Waddell 2006). The amount of silica, percentage of associated water, total solids content of nonoxidizable materials, presence of stabilizers and carbon content, level of soluble salts, metal impurities, and silanol group density are important chemical composition information. The pH, density and tamped density, viscosity, turbidity, refractive index, and light-scattering properties are important physical characteristics. Specific surface area, average particle size and size distribution, sieve residue, porosity (including average pore diameter and pore volume), degree of aggregation, and oil absorption information is used to characterize the silica particles. Although analytical techniques exist to distinguish between a-silica polymorphs, most are too sophisticated for routine measurements (IARC 1997). Therefore, environmental exposures are typically reported for a-silica, rather than for specific polymorphs.

## 7. ANALYTICAL METHODS

Particle-size measurement is important in silica-gel characterization. Granular gel standardized sieve screening uses method ASTM D 4513. Static light scattering and conductivity methods are preferred for particle size analysis of particles roughly 1–1,000 nm. Dynamic light scattering, electron microscopy, and small-angle X-ray scattering are used for particle sizes of roughly 10–1,000 nm (Florke et al. 2008).

Porosity of silica gels is described by pore diameter as microporous (<2 nm), mesoporous (approximately 2–50 nm), or macroporous (>50 nm) (Florke et al. 2008). Thermogravimetric analysis, vibrational spectroscopy, and nuclear magnetic resonance are used to study hydroxyl concentration, hydrogen bond interaction between hydroxyl groups, and distribution of silica-oxygen species on the surface of silica gel (Florke et al. 2008).

Density separation uses heavy liquids to separate particles and is based on differences in density of the forms of silica and silicates (Miles 1999), although it is usually impossible to fully liberate c-silica from other phases. This technique works best with (mono-mineral) mineral grains  $\geq 0.1$  mm.

### 7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silica is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silica.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

## 7. ANALYTICAL METHODS

**7.3.1 Identification of Data Needs****Methods for Determining Biomarkers of Exposure and Effect.**

*Exposure.* As discussed in Section 3.12.2, no biomarkers of exposure have been identified for silica. c-Silica has been detected in the urine of ceramic factory workers (Ibrahim et al. 2011) and development of sensitive analytical methods may be useful in the assessment of whether urinary silica could be used as a biomarker of exposure.

*Effect.* Sensitive biomarkers of effect have not been identified.

**Methods for Determining Parent Compounds and Degradation Products in Environmental**

**Media.** Silica is ubiquitous in the environment and does not degrade. It is found in air, water, soil, sediments, and food. Analytical methods exist for the analysis of silica in all of these environmental media, and these methods have the sensitivity to measure background levels and detect elevated concentrations due to anthropogenic sources (NIOSH 2002). Additional research to reduce chemical and matrix interferences is needed to improve the speed and accuracy of the analyses.

**7.3.2 Ongoing Studies**

No ongoing studies regarding analytical methods for measuring silica in biological materials or environmental media were located.



## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

The international and national regulations, advisories, and guidelines regarding silica in air, water, and other media are summarized in Table 8-1.

Silica polymorphs may have separate regulations, advisories, and guidelines. For example, general industry PELs for cristobalite and tridymite are lower than general industry PEL for quartz (OSHA 2013a).

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to Silica**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2015
	Silica, amorphous	Group 3 <sup>a</sup>	
	Silica dust, crystalline, in the form of quartz or cristobalite	Group 1 <sup>b</sup>	
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2015
	Silica, crystalline— $\alpha$ -quartz (1317-95-9; 14808-60-7) and cristobalite (14464-46-1)	0.025 mg/m <sup>3</sup> <sup>c</sup>	
	Silica, amorphous—diatomaceous earth (61790-53-2)	Withdrawn <sup>d</sup>	
	Silica, amorphous—fume (69012-64-2)	Withdrawn <sup>e</sup>	
	Silica, amorphous—fused (60676-86-0)	Withdrawn <sup>e</sup>	
	Silica, amorphous—precipitated silica and silica gel (112926-00-8)	Withdrawn <sup>e</sup>	
AIHA	ERPGs	No data	AIHA 2014

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to Silica**

Agency	Description	Information	Reference
NATIONAL ( <i>cont.</i> )			
DOE	PACs		DOE 2012a
	PAC-1 <sup>f</sup>		
	Silica amorphous hydrated	6 mg/m <sup>3</sup>	
	Silica, crystalline-quartz (silicon dioxide)	0.025 mg/m <sup>3</sup>	
	Cristobalite	0.075 mg/m <sup>3</sup>	
	Silica, amorphous fumed	6 mg/m <sup>3</sup>	
	Silica gel, amorphous synthetic	6 mg/m <sup>3</sup>	
	Diatomaceous earth (silica-amorphous diatomaceous earth, uncalcined)	18 mg/m <sup>3</sup>	
	Diatomaceous earth (flux calcinated; filter agent, celite; amorphous silica)	0.9 mg/m <sup>3</sup>	
	PAC-2 <sup>f</sup>		
	Silica amorphous hydrated	6 mg/m <sup>3</sup>	
	Silica, crystalline-quartz (silicon dioxide)	0.025 mg/m <sup>3</sup>	
	Cristobalite	0.41 mg/m <sup>3</sup>	
	Silica, amorphous fumed	6 mg/m <sup>3</sup>	
	Silica gel, amorphous synthetic	6 mg/m <sup>3</sup>	
	Diatomaceous earth (silica-amorphous diatomaceous earth, uncalcined)	200 mg/m <sup>3</sup>	
	Diatomaceous earth (flux calcinated; filter agent, celite; Amorphous silica)	9.9 mg/m <sup>3</sup>	
	PAC-3 <sup>f</sup>		
	Silica amorphous hydrated	85 mg/m <sup>3</sup>	
	Silica, crystalline-quartz (silicon dioxide)	0.025 mg/m <sup>3</sup>	
	Cristobalite	41 mg/m <sup>3</sup>	
	Silica, amorphous fumed	630 mg/m <sup>3</sup>	
	Silica gel, amorphous synthetic	6 mg/m <sup>3</sup>	
	Diatomaceous earth (silica-amorphous diatomaceous earth, uncalcined)	1200 mg/m <sup>3</sup>	
	Diatomaceous earth (flux calcinated; filter agent, celite; amorphous silica)	59 mg/m <sup>3</sup>	
EPA	AEGLs	No data	EPA 2015a
	Hazardous air pollutant	No data	EPA 2013a

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to Silica**

Agency	Description	Information	Reference
NATIONAL ( <i>cont.</i> )			
NIOSH	REL (10-hour TWA)		NIOSH 2015a, 2015b
	Silica, amorphous	6 mg/m <sup>3</sup>	
	Silica, crystalline (as respirable dust)	0.05 mg/m <sup>3</sup>	
	IDLH		
	Silica, amorphous	3000 mg/m <sup>3</sup>	
	Silica, crystalline (as respirable dust - cristobalite, tridymite)	25 mg/m <sup>3</sup>	
OSHA	Silica, crystalline (as respirable dust - quartz, tripoli)	50 mg/m <sup>3</sup>	
	PEL (8-hour TWA) <sup>g</sup>	0.05 mg/m <sup>3</sup>	OSHA 2016...
	Silica, respirable crystalline for general industry and maritime		
	PEL (8-hour TWA) <sup>h</sup>	0.025 mg/m <sup>3</sup>	OSHA 2016
	Silica, respirable crystalline for construction industry		
	PEL (8-hour TWA)	<u>80 mg/m<sup>3</sup></u> /%SiO <sub>2</sub>	OSHA 2013a 29 CFR 1910.1000, Table Z-3
	Silica, amorphous, including natural diatomaceous earth		
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013b 40 CFR 116.4
	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water standards	No data	EPA 2009
	National recommended water quality criteria: human health for the consumption of	No data	EPA 2015b
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013c 40 CFR 117.3
c. Food			
FDA	EAFUS		FDA 2013
	Silicon dioxide	Yes <sup>j</sup>	
	Diatomaceous earth	Yes <sup>i,k</sup>	

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to Silica**

Agency	Description	Information	Reference
NATIONAL ( <i>cont.</i> )			
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2015
	Silica, crystalline— $\alpha$ -quartz (1317-95-9; 14808-60-7) and cristobalite (14464-46-1)	A2 <sup>l</sup>	
	Silica, amorphous—diatomaceous earth (61790-53-2)	Withdrawn <sup>d</sup>	
	Silica, amorphous—fume (69012-64-2)	Withdrawn <sup>e</sup>	
	Silica, amorphous—fused (60676-86-0)	Withdrawn <sup>e</sup>	
NIOSH	Silica, amorphous—precipitated silica and silica gel (112926-00-8)	Withdrawn <sup>e</sup>	
	REL and IDLH		NIOSH 2015b
EPA	Silica, crystalline (as respirable dust)	Ca <sup>m</sup>	
	Carcinogenicity classification	No data	IRIS 2015
	Superfund, emergency planning, and community right-to-know	No data	EPA 2014a 40 CFR 302.4
	TSCA chemical lists and reporting periods	No data	EPA 2014b 40 CFR 712.30
NATIONAL ( <i>cont.</i> )			
DHHS	Carcinogenicity classification		NTP 2014
	Silica, crystalline (respirable size; no CAS No.)	Known to be a human carcinogen	

<sup>a</sup>Group 3: not classifiable as to its carcinogenicity to humans.

<sup>b</sup>Group 1: carcinogenic to humans.

<sup>c</sup>Respirable fraction.

<sup>d</sup>Withdrawn due to insufficient data on single-substance exposure; most are co-exposures with crystalline silica.

<sup>e</sup>Withdrawn due to insufficient data.

<sup>f</sup>Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2012b).

<sup>g</sup>Compliance schedule for general industry and maritime is June 23, 2018 (2 years after the effective rule date).

<sup>h</sup>Compliance schedule for construction industry is June 23, 2017 (1 year after the effective rule date).

<sup>i</sup>Both concentration and percent quartz for the application of this limit are to be determined from the fraction passing a size selector.

<sup>j</sup>The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

<sup>k</sup>Although listed as added to food, there is no current reported use of the substance.

<sup>l</sup>A2: suspected human carcinogen

<sup>m</sup>Ca = potential occupational carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to Silica**

Agency	Description	Information	Reference
<p>System; MCL = maximum contaminant level; NAS = The National Academies of Sciences; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; WHO = World Health Organization</p>			

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## 10. GLOSSARY

**Absorption**—The taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure**—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption**—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ( $K_{oc}$ )**—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio ( $K_d$ )**—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD)**—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a  $BMD_{10}$  would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

**Benchmark Dose Model**—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

**Bioconcentration Factor (BCF)**—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers**—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

**Cancer Effect Level (CEL)**—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen**—A chemical capable of inducing cancer.

**Case-Control Study**— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

**Case Report**—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series**—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

## 10. GLOSSARY

**Ceiling Value**—A concentration that must not be exceeded.

**Chronic Exposure**—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Cohort Study**—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

**Cross-sectional Study**—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

**Data Needs**—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

**Developmental Toxicity**—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship**—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

**Embryotoxicity and Fetotoxicity**—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

**Environmental Protection Agency (EPA) Health Advisory**—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Epidemiology**—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Genotoxicity**—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life**—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

**Immediately Dangerous to Life or Health (IDLH)**—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunologic Toxicity**—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

## 10. GLOSSARY

**Immunological Effects**—Functional changes in the immune response.

**Incidence**—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure**—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

**In Vitro**—Isolated from the living organism and artificially maintained, as in a test tube.

**In Vivo**—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)**—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects**—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations**—Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)**—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)**—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity**—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

**Mortality**—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

## 10. GLOSSARY

**Mutagen**—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy**—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity**—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

**No-Observed-Adverse-Effect Level (NOAEL)**—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ( $K_{ow}$ )**—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)**—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**Organophosphate or Organophosphorus Compound**—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)**—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide**—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics**—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

**Pharmacokinetic Model**—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model**—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

## 10. GLOSSARY

**Physiologically Based Pharmacokinetic (PBPK) Model**—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence**—The number of cases of a disease or condition in a population at one point in time.

**Prospective Study**—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

**q<sub>1</sub>\***—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q<sub>1</sub>\* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m<sup>3</sup> for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m<sup>3</sup> or ppm.

**Reference Dose (RfD)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)**—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity**—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study**—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

## 10. GLOSSARY

**Risk**—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

**Risk Factor**—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio**—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

**Short-Term Exposure Limit (STEL)**—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**Standardized Mortality Ratio (SMR)**—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity**—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen**—A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)**—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)**—An average exposure within a given time period.

**Toxic Dose<sub>(50)</sub> (TD<sub>50</sub>)**—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicokinetic**—The absorption, distribution, and elimination of toxic compounds in the living organism.

**Uncertainty Factor (UF)**—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

**Xenobiotic**—Any substance that is foreign to the biological system.



## APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

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are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

MRLs were not derived for c-silica or a-silica, as discussed in Section 2.3.

## APPENDIX B. USER'S GUIDE

### Chapter 1

#### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

### Chapter 2

#### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

#### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

## **Chapter 3**

### **Health Effects**

#### **Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

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**LEGEND****See Sample LSE Table 3-1 (page B-6)**

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Sample Figure 3-1 (page B-7)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

**SAMPLE**

**1** → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>2</b> → INTERMEDIATE EXPOSURE							
<b>3</b> →	Systemic	↓	↓	↓	↓	↓	↓
<b>4</b> →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<b>4</b> → CHRONIC EXPOSURE							
	Cancer					<b>11</b> ↓	
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs) Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors) NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

**12** → <sup>a</sup> The number corresponds to entries in Figure 3-1.  
<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

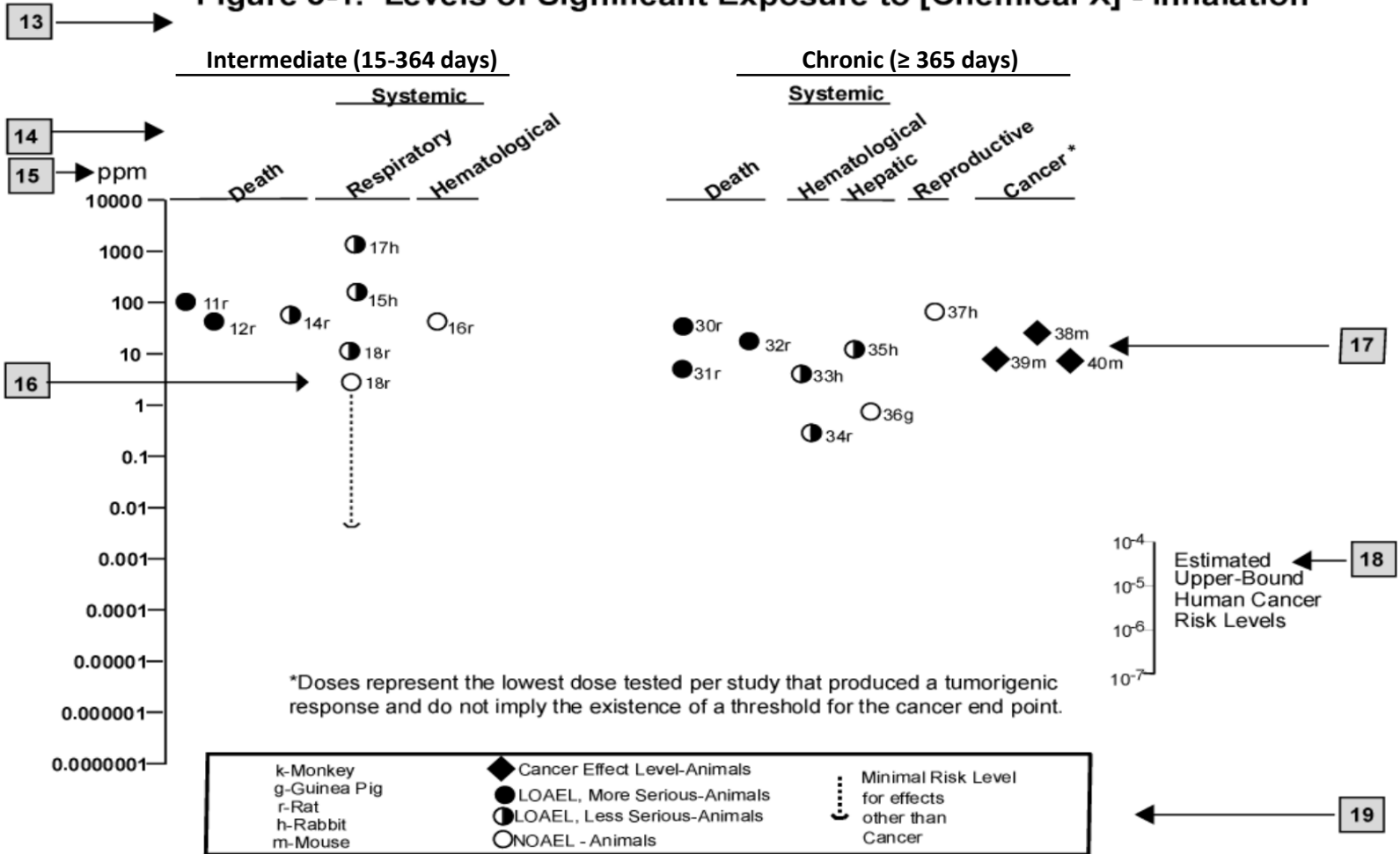
\*\*\*DRAFT FOR PUBLIC COMMENT\*\*\*

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# SAMPLE

### Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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## APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD <sub>x</sub>	dose that produces a X% change in response rate of an adverse effect
BMDL <sub>x</sub>	95% lower confidence limit on the BMD <sub>x</sub>
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>50</sub>	lethal concentration, 50% kill
LC <sub>Lo</sub>	lethal concentration, low
LD <sub>50</sub>	lethal dose, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT <sub>50</sub>	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

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MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSH TIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

## APPENDIX C

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

## APPENDIX C

WHO World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q <sub>i</sub> *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

