

# A Review of the Toxicology and Epidemiology of Wollastonite

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Wollastonite is a naturally occurring calcium silicate ( $\text{CaSiO}_3$ ) that is produced in both powder and fibrous forms. It is a valuable industrial mineral used in plastics, ceramics, metallurgical applications, paint, and friction products. For some applications wollastonite serves as an asbestos replacement. To varying degrees, wollastonite grades contain respirable particles/fibers, some of which have lengths and diameters that might be biologically active if deposited and retained in the lung. In this review we provide background information on wollastonite properties, markets, production and use, regulatory classification, and occupational exposure limits. We also summarize the available studies on the toxicology and epidemiology of wollastonite. We conclude that there is inadequate evidence for the carcinogenicity of wollastonite in animals and, based on strong evidence that wollastonite is not biopersistent, believe that a well-designed animal inhalation bioassay would have a negative result. The epidemiological evidence for wollastonite is limited, but does not suggest that workers are at significant risk of an increased incidence of pulmonary fibrosis, lung cancer, or mesothelioma. Morbidity studies have demonstrated a nonspecific increase in bronchitis and reduced lung function. It is prudent, however, to continue product stewardship efforts by wollastonite producers to control workplace exposures and to monitor scientific developments.

## CHEMICAL AND PHYSICAL PROPERTIES, PRODUCTION, AND MARKETS

Wollastonite (CASRN 13983-17-0, EINECS No. 237-772-5) is a naturally occurring calcium silicate ( $\text{CaSiO}_3$ , molecular weight 116.2) with a theoretical composition of 48.3% CaO and 51.7%  $\text{SiO}_2$ . Table 1 provides data on the chemical composition of a sample of commercial wollastonite products. Synthetic wollastonite is also produced in relatively minor quantities.

Natural wollastonite is an acicular (needlelike) mineral that occurs in triclinic and monoclinic varieties. It is typically white or cream in color, but also may be light yellow, pink, gray, or very pale shades of green and brown (see, e.g., Virta, 2003). The

specific gravity of solids ranges from 2.87 to 3.09 (IARC, 1997; NYCO Minerals, 2004). Pure wollastonite melts at  $1540^\circ\text{C}$ , although the fluid temperature for commercially produced wollastonite may be as low as  $1380^\circ\text{C}$  (NYCO Minerals, 2004). Wollastonite has an average pH of 9.9 in a 10% hydrous slurry (Fattah, 1994). The coefficient of expansion is  $6.5 \times 10^{-6}$  mm/mm/ $^\circ\text{C}$ . To minimize gas evolution in certain applications, a low (<1%) loss on ignition is desirable (NYCO Minerals, 2004). The dry brightness and whiteness of wollastonite are important properties for certain filler and ceramic applications. The GE brightness (determined by measuring the reflectance of finely ground powder relative to a standard [magnesium oxide or barium sulfate] assigned a brightness of 100) for commercial wollastonite products ranges from 80 to 95 (NYCO Minerals, 2004).

Natural wollastonite may contain trace amounts of aluminum, iron, magnesium, manganese, potassium, and sodium (Virta, various years; IARC, 1997). It was named after the English chemist and mineralogist William Hyde Wollaston in 1822 (NYCO Minerals, 2004; IARC, 1997).

Selected synonyms and (current and past) trade names include Aedelforsite, Cab-O-Lite, Casiflux, FW, Gillebachite, HG, Hycon, Kemolit, Mengshan NFW, NYAD, NYCOR, NYGLOS, OTAFILL, RRIMGLOS, Ravaite, Schalstein, table spar, tabular

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TABLE 1  
Chemical composition of commercial wollastonite products

Component	NYAD G, U.S.	Partek, Finland	VANSIL, U.S.	Kemolit, India	China	
					HG Acicular	Mengshan NFW-XA
CaO	46.15%	45%	44.0%	47.0%	>45%	>46%
SiO <sub>2</sub>	51.60%	52%	50.0%	49.5%	>50%	>49%
Al <sub>2</sub> O <sub>3</sub>	0.34%	0.4%	1.8%	0.60%	<0.8%	<0.8%
MgO	0.38%	0.6%	1.5%	NR	<1.0%	<0.8%
Fe <sub>2</sub> O <sub>3</sub>	0.77%	0.2%	0.3%	0.43%	<0.3%	<0.25%
Na <sub>2</sub> O or K <sub>2</sub> O	0.05%	0.11%	0.2%	0.13%	NR	NR
TiO <sub>2</sub>	0.05%	<0.05%	NR	Trace	NR	NR
MnO	0.16%	<0.01%	<0.1%	0.29%	NR	NR

*Note.* Sources: Finland, IARC (1997); NYAD G, technical data sheet furnished by NYCO Minerals, Inc.; Kemolit, <http://www.pvnet.cz/www/minko/pokus/stavebchem/wollast/kemolit.htm>; VANSIL, from R. T. Vanderbilt web site; HG Acicular from Dalian Huanqiu Minerals Group web site, <http://chinawollastonite.com/e-cpjs-1.htm>; Mengshan NFW-XA from Xinyu South Wollastonite Industry Company web site, [http://wollastonite.en.alibaba.com/product/50021244/50108432/Wollastonite\\_Needle\\_Powder/Wollastonite\\_Needle\\_Powder.html](http://wollastonite.en.alibaba.com/product/50021244/50108432/Wollastonite_Needle_Powder/Wollastonite_Needle_Powder.html).

spar, ULTRAFIBER, VANSIL, Vilnit(e), Wolkron, and wollastonite (NIOSH, 1997; IARC, 1997; Mindat.org, 2004; various MSDSs).

After mining and beneficiation, wollastonite can also be surface treated or modified with various materials (including stearates, zircoaluminate, titanates, and organosilanes, such as amino- and epoxy-silanes) for improved performance in certain higher value applications (Fattah, 1994). Silane treatment levels are typically 0.5–1% of mineral weight (Ciullo & Robinson, 2002b). Surface treatments improve the adhesion between the wollastonite and the polymers to which it is added (Fattah, 1994; Virta, 2003). Surface-treated grades are manufactured in blenders and subsequently dried at elevated temperatures to ensure complete reaction and drive off by-products (Ciullo & Robinson, 2002a). Surface-treated wollastonite is sold under such (current and past) trade names as FILLEX, NYCHEM, NYGLOS, TREMIN AST/EST/MST/TST/VST, VANCOTE, WOLLASTOCOAT, and WOLLASTOKUP.

Wollastonite is used in diverse applications—including asbestos replacement (see Fattah, 1994, for details). Domestic markets (with estimated 1999 share in parentheses) include plastics (37%), ceramics (28%), metallurgical applications (10%), paint (10%), friction products (9%), and miscellaneous others (6%) (Virta, 2003). Wollastonite applications are similar in most other countries, although there are country-specific applications. For example, in China wollastonite is used, inter alia, as a substitute for wood pulp in the manufacture of high-quality paper (Anonymous, 2003).

Natural wollastonite is found in various deposits throughout the world, including the United States (New York and

California), Australia, Canada, Chile, China, Finland, India, Mexico, Morocco, Namibia, North Korea, Pakistan, Serbia, South Africa, and Turkey (Virta, various years; Crooks, 1999). Ores from the major wollastonite deposits reportedly range from 18% to 97% wollastonite (IARC, 1997; Virta, 2001). Associated minerals include calcite (calcium carbonate), garnet (calcium iron silicate, calcium aluminum silicate), diopside (calcium magnesium silicate), prehnite (calcium aluminum silicate hydroxide), epidote (calcium aluminum iron silicate hydroxide), apatite (calcium [fluoro, chloro, hydroxyl] phosphate), sphene (calcium titanium silicate), idocrase (calcium magnesium iron aluminum silicate hydroxide), and quartz (Virta, 2003; Fattah, 1994; IARC, 1997; Ciullo & Robinson, 2002a). Mineral processing steps (e.g., physical sorting, flotation, filtration, air classification, drying, magnetic sorting, crushing, and grinding) depend on the associated minerals and desired physical form (grade) of the final product (NYCO Minerals, 2004). For example, garnet and diopside are removed using high-intensity magnetic separators (Ciullo & Robinson, 2002a; Virta, 2003; NYCO Minerals, 2004). Calcite, diopside, and feldspars can be removed by flotation. The method of milling (e.g., use of impact versus attrition mills), inter alia, determines the aspect ratio of the finished product (Ciullo & Robinson, 2002a). In broad terms, after mining and crushing (for initial size reduction), wollastonite is processed using *wet* (flotation) or *dry* (magnetic separation) methods. The details of processing and beneficiation methods are regarded as proprietary (NYCO Minerals, 2004).

Synthetic wollastonite is made, inter alia, by combining quicklime with quartz, calcium carbonate, and calcium hydrate. It is produced in Belgium, Brazil, China, and Germany (Fattah,

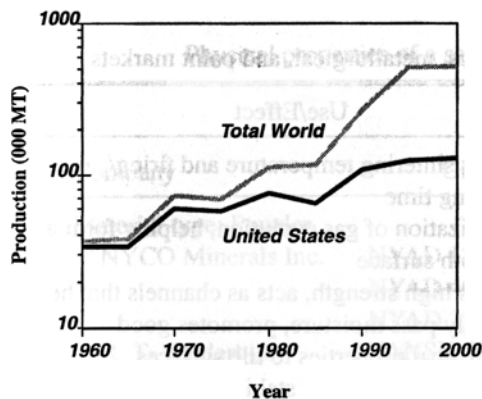


FIG. 1. Wollastonite production in the United States and the world, 1960–2000 (DiFrancesco & Virta, 2004).

1994). For additional information on synthetic wollastonite processes and markets, see Fattah (1994) and Ibañez and Sandoval (1998).

Natural wollastonite was originally mined in the United States in California as early as 1930 (ending in 1970) and later (post 1953) in New York (Virta, various years; NYCO Minerals, 2004)—from both surface and underground mines. Production of natural wollastonite began in Finland in the 1950s (Koskinen et al., 1997), in Mexico in the late 1960s, in India and Africa in the 1970s, and in China in the 1980s (NYCO Minerals, 2004).

Figure 1 shows both the U.S. and total world output of wollastonite from 1960 to 2000 (DiFrancesco & Virta, 2004). The United States accounted for a majority of world production until the mid-1980s. World production of wollastonite in 2000 was approximately 605,000 MT, of which the United States accounted for an estimated 130,000 MT in 2000 (Virta, various years). Although the domestic wollastonite production quantity is significant, it is relatively small in comparison to some other mineral fibers. For example, domestic glass wool production in 2001 was approximately 1,950,000 MT, and rock and slag wool production was 746,000 MT in the same year (IARC, 2002).

Only two companies in the United States, NYCO Minerals, Inc., and Gouverneur Talc Company (a subsidiary of R. T. Vanderbilt Co.), currently produce wollastonite. The only domestic wollastonite mines and beneficiation facilities are located in New York State.

Natural wollastonite is classified as a nonfuel industrial mineral, along with others including barite, clays, diatomite, feldspar, fluorspar, gypsum, kyanite, mica, olivine, perlite, phosphate rock, pumice, salt, talc, pyrophyllite, and vermiculite. According to data from the U.S. Geological Survey (USGS), the annual quantity of wollastonite mined in the United States is comparable to but slightly larger than those for kyanite, fluorspar, vermiculite, olivine, and talc, but less than annual production quantities for the other nonfuel industrial minerals.

Figure 2 shows the estimated world share of production for several countries in 2003; major world producers include (in de-

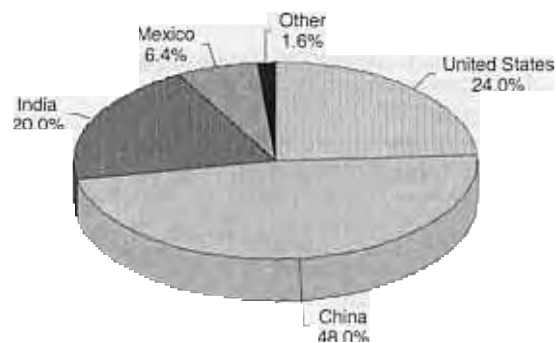


FIG. 2. Wollastonite production by country in 2003 (Virta, 2003).

scending order) China, the United States, India, and Mexico (Virta, 2003). Minor producers include Finland, Morocco, Namibia, North Korea, Pakistan, and Turkey.

Canada has wollastonite deposits in British Columbia (British Columbia Geological Survey, 1999), Nova Scotia (Luke, 1990), Ontario (Bowdidge, 1996; Grammatikopoulos Clark, 2001; Grammatikopoulos et al., 2003), and Quebec (Fattah, 1994). However, Canada has produced only minor amounts of wollastonite, most recently (1997–1998) by Orleans Resources at Lac St.-Jean, Quebec. (This operation has been dismantled [Virta, 2001; Anonymous, 2004].)

Table 2 shows some of the key properties of wollastonite for ceramic, plastics, metallurgical, and paint applications (Fattah, 1994). Virta (2001) also provides a useful discussion of key wollastonite properties and functions by market.

Wollastonite grades with relatively high aspect ratio (HAR or acicular grades) are used as an asbestos replacement in fire-resistant wallboard and cement products as well as friction products (Fattah, 1994; Virta, various years). Construction applications include wallboard, roofing tiles, slates, shaped insulation, and sidings. High-aspect-ratio wollastonite is also used in non-refractory high-temperature applications. Powdered (milled or low aspect ratio) wollastonite is another form used for certain applications (particularly ceramics and metallurgy).

Wollastonite breaks down during processing into fibers of varying aspect ratios. Wollastonite is produced in various particle sizes and fiber diameters and lengths. The acicularity (aspect ratio) reportedly varies from 3:1 to 5:1 for low-aspect-ratio or powder grades, to 10:1 to 20:1 for high-aspect-ratio (also termed *acicular*) grades (Fattah, 1994; IARC, 1997). In addition to particle size and aspect ratio, technical specifications for various grades of wollastonite may include types (if any) of surface treatment. Table 3 provides data on the average length, diameter, aspect ratio, and surface area for a sample of wollastonite powder and acicular grades currently sold in the United States. Note that the physical dimensions of the particles/fibers shown in Table 3 are for the *bulk* material, not for aerosols found in the workplace. Schneider et al. (1983) present models for estimation of the diameter–length distribution of aerosols given estimates of the distribution in bulk. When particles and fibers

TABLE 2  
Selected wollastonite properties and their uses for ceramic, plastics, metallurgical, and paint markets

Application	Property	Use/Effect
Ceramics	Fluxing action	Lowers sintering temperature and firing/cooling time
	Limited loss on ignition, no carbonate content	Minimization of gas evolution, helping form a smooth surface
	Acicularity	Imparts high strength, acts as channels that help rapidly pass moisture, promotes good acoustical properties to tile surfaces
	Low thermal expansion	Improves dimensional stability
	Coefficient/resistance to thermal shock	
	46–49% CaO content	Improves glaze strength and surface finish in alkaline glazes
Plastics	48–52% SiO <sub>2</sub> content	Replaces some feldspar, silica, and kaolin
	Acicularity	Reinforces plastic and imparts smooth finish
	Dimensional stability	Reduces shrinkage
	Low water absorption	Increases stain resistance
	Low plasticizer absorption, low viscosity at high loadings	Allows higher filler loading
	High brightness/whiteness	Reduces pigment loading
	Dielectric properties	Increases electrical insulation
Metallurgical	Hardness	Increases wear resistance
	Low-temperature fluxing	Imparts better surface finish in continuous-cast steel; inhibits sparking in welding
Paints	Acicular crystals	Act as flattening agents, improve toughness and durability of coating
	Low oil absorption	Reduced volume of binder required
	pH 9.9 (in 10% solution)	Helps neutralize acid shifts and prevents corrosion
	Chemically inert	Provides chemical stability
	High brightness/whiteness	Reduces pigment loading requirement

Note. From Fattah (1994).

are dispersed into the air during handling/processing, the thinner fibers and smaller particles tend to remain airborne.

Thus, the measured average or median diameter in an aerosol should be smaller than the average diameter in the bulk material. Because the lengths and diameters of wollastonite structures are correlated, the average length of structures in the aerosol is less than that of the bulk material. As can be seen from Table 3, these commercial materials vary greatly in terms of the lengths and diameters of the particles/fibers.

Because certain wollastonite grades are used as asbestos replacements and contain some respirable particles/fibers (including long, thin fibers with potentially greater biological activity), numerous studies have been made of the toxicology and epidemiology of wollastonite. This review summarizes the available health-related information for *natural* wollastonite. (Synthetic wollastonite [calcium silicate] has also been studied in rodents [Davis et al., 1983; Bolton et al., 1986] and has been found to be “harmless to rats at the doses tested.”) As adverse

effects on the lung are the chief health concerns associated with respirable fibers and dusts, this review focuses on such endpoints as fibrosis, lung cancer, and mesothelioma.

#### OCCUPATIONALLY EXPOSED POPULATION

Occupational exposure to wollastonite could occur during its mining, processing, and use. The National Occupational Exposure Survey (NOES) conducted in the early 1980s estimated the total worker population in the United States potentially exposed to wollastonite as 70,383 workers (NOES, 1981–1983). (The standard error of this estimate is approximately 9000.) NOES did not measure actual exposure to any agent, but inferred this exposure based upon products used. Thus, for example, the NOES estimate for wollastonite totaled 21,873 workers in Standard Industrial Classification (SIC) Code 17 (special trade contractors), which includes such occupations as tile setters, plumbers, pipefitters and steamfitters, glaziers, roofers, sheet-metal duct

TABLE 3  
Physical properties of a sample of wollastonite grades currently in production

Company	Grade	Average length (microns)	Average diameter (microns)	Surface area (m <sup>2</sup> /gr)	Average aspect ratio
Material type: Powder					
NYCO Minerals Inc.	NYAD 1250	13.0	3.7	2.6	
	NYAD 400	15.0	3.7	1.6	
	NYAD 325	16.0	4.0	1.3	
R. T. Vanderbilt	VANSIL W10	24.5	6.7	1.6	
	VANSIL W20	12.5	3.4	2.4	
	VANSIL W40	11.3	2.6	2.7	
	VANSIL W50	9.6	2.5	4.2	
Material type: Acicular					
NYCO Minerals Inc.	NYAD G	60	6.2	0.5	15:1
	NYGLOS 12	23	3.1	0.8	15:1
	NYGLOS 8	21	3.5	1.2	19:1
	NYGLOS 5	18	3.7	2.0	13:1
	NYGLOS 4	14	2.7	2.2	8:1
	NYGLOS 4W	12	2.6	2.2	6:1
	NYGLOS 2	10	2.5	3.7	6:1
R.T. Vanderbilt	VANSIL WG	90	6.0	1.2	15:1
	VANSIL HR-1500	60	4.3	1.6	14:1

*Note.* Technical data provided by NYCO Minerals, Inc., and/or R. T. Vanderbilt technical data sheets. Reported densities are all close to 2.87 to 3.09 g/cm<sup>3</sup>. These data refer to bulk materials.

installers, and cementing and gluing machine operators—most of whom would have only incidental exposure or exposure to an encapsulated form of wollastonite. Thus, the NOES estimate should be regarded as an upper bound on the actual exposed population. The NOES estimate has not been updated. Over the period from 1982 to 2002, domestic wollastonite consumption grew from 70,000 MT to 119,000 MT (DiFrancesco & Virta, 2004), equivalent to a compound average annual rate of increase of 2.7%/yr. However, worker productivity has also increased. For example, U.S. Department of Labor Bureau of Labor Statistics data indicate that the index of output per hour in manufacturing increased from 88.4 (1992 = 100) in 1987 to 146.5 in 2002, equivalent to a 3.4%/yr compound average annual rate of growth. Thus, it is likely that the potentially exposed population is lower now than in the 1980s.

Based on published annual reports and Internet postings, we estimate that the present number of persons engaged in the mining, beneficiation, and production of wollastonite in the United States—those likely to have the highest exposure—is at most 220.

#### OCCUPATIONAL EXPOSURE LIMITS

In the United States and several other countries, occupational exposure limits (OELs) for wollastonite are identical to those for inert or nuisance dusts referred to as “particulates not otherwise regulated” (PNOR). The applicable Occupational

Safety and Health Administration (OSHA) permissible exposure limit (PEL) for calcium silicate (OSHA Table Z-1) is an 8-h time weighted average (TWA): 15 mg/m<sup>3</sup> (total dust) and 5 mg/m<sup>3</sup> (respirable dust). The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (REL) applicable to wollastonite are 10 mg/m<sup>3</sup> (total dust) and 5 mg/m<sup>3</sup> (respirable dust) (NIOSH, 2004). The American Conference of Governmental Industrial Hygienists (ACGIH) has established threshold limit values (TLV) of 10 mg/m<sup>3</sup> (total dust) and 3 mg/m<sup>3</sup> (respirable dust) TWA for particulates not otherwise classified (PNOC) (ACGIH, 2003). ACGIH has also established a TLV for calcium silicate (synthetic; containing no asbestos and <1% crystalline silica) of 10 mg/m<sup>3</sup>.

In some countries, OELs for wollastonite are expressed in fiber concentration, rather than gravimetric, units. For example, in the Province of Quebec, Canada, the OEL for wollastonite is 1 fiber (WHO) per cubic centimeter (f/cm<sup>3</sup>) (Morel-à-l’Huisser, 1995). In Denmark, the OEL for wollastonite is 1 f/cm<sup>3</sup> and in Sweden it is 0.5 f/cm<sup>3</sup> (natural fiber) (European Commission, 2000).

#### REGULATORY STATUS AND TOXICOLOGY REVIEWS

In a review of potential health effects of various fibers, a U.S. Environmental Protection Agency (EPA) scientist (Vu, 1994) wrote that the available animal studies “seem to indicate a low hazard potential for wollastonite,” but noted that wollastonite

might present a health hazard and that "additional epidemiological investigations and chronic inhalation animal studies are needed to fully assess the health effects."

The U.S. EPA provides no listing for wollastonite on the Integrated Risk Information System (IRIS).

The National Toxicology Program (NTP) does not list wollastonite as either known or reasonably anticipated to be a carcinogen.

California has not placed wollastonite on the Proposition 65 list of materials known to the State of California to cause cancer.

Wollastonite is not included in the European Community priority list (under Council Regulation [EEC] 793/93 on the evaluation and control of the risks of existing substances) and is not classified in the Annex I of Directive 67/548/EEC.

The Medical Research Council of the University of Leicester considered wollastonite along with other possible substitutes for chrysotile asbestos (MRC, 2000) and noted that use of wollastonite as a substitute for chrysotile asbestos could potentially reduce fiber exposures, but added that the major benefit of substitution would accrue from the reduced biopersistence (discussed later), leading to lower continuing lung burdens for comparable exposures.

Another assessment of the health effects of alternatives to chrysotile asbestos conducted for the Australian National Occupational Health and Safety Commission (NOHSC) (Douglas, 2001) concluded (based in part on IARC, 1997) that there was "sufficient evidence for the non-toxicity and non-carcinogenicity of wollastonite fibres in experimental animals" and that there was "inadequate evidence for the toxicity and carcinogenicity of wollastonite fibres in humans" [emphasis added.]

In arguably the most definitive assessments to date, the International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of natural wollastonite on two separate occasions (IARC, 1987, 1997; Wilbourn et al., 1997). In 1987, IARC concluded that there was *limited evidence* for the carcinogenicity of wollastonite to experimental animals and *inadequate evidence* for the carcinogenicity of wollastonite to humans. Upon reevaluation (IARC, 1997) in the light of additional studies, IARC placed natural wollastonite into Group 3 (*cannot be classified as to its carcinogenicity to humans*) based on the finding that there was *inadequate evidence* in both humans and animals for the carcinogenicity of wollastonite.

Since the 1997 IARC review, additional studies (discussed here) have been published. The new results certainly add to the knowledge base, but do not alter the conclusions of the most recent IARC Working Group.

## EPIDEMIOLOGICAL EVIDENCE

Results of well-designed and statistically powerful epidemiological (e.g., cohort, case-control, and correlation [or ecological]) studies are typically accorded substantial weight in occupational health assessments and carcinogen classification. Historical exposure levels may be greater than those at present, but are very much beneath those typically used in animal

studies. Thus, little or no extrapolation is necessary. Moreover, no animal-to-human conversion factors arising from possible dosimetry or potency differences are required to make risk estimates applicable to humans.

The available epidemiological evidence on natural wollastonite (discussed next) includes morbidity studies on two cohorts, one in Finland and the other in the United States, and a mortality study of Finnish workers.

Workers in a Finnish limestone-wollastonite mill and mine were included in *morbidity* studies (Huuskonen et al., 1982, 1983a, 1983b; Huuskonen & Tossavainen, 1996; Koskinen et al., 1997). The most recent reports on this morbidity study (Huuskonen & Tossavainen, 1996; Koskinen et al., 1997) were not considered in the IARC (1997) classification. Forty-nine workers (mean exposure 25 yr; range 4–42 yr) were included in the cohort studied (Koskinen et al., 1997); work histories and symptoms of chronic bronchitis were recorded, radiographs were classified using International Labor Office (ILO) conventions, and spirometry, and diffusion capacity were measured. Four workers were studied using high-resolution computed tomography (HRCT) and bronchoalveolar lavage (BAL). Lung tissue specimens were available for two workers. The mean concentrations of total dust in the open-pit mine and mill measured in 1981 varied among operations and ranged from 0.3 to 67 mg/m<sup>3</sup> and that of fibers from 5.1 to 33 f/cm<sup>3</sup> (Huuskonen et al., 1983a). Note that some of the historical mean exposures exceed current OELs for wollastonite and/or nuisance dusts.) In addition to calcite, the average respirable fraction contained 15% wollastonite and 3% quartz. Later dust measurements (Koskinen et al., 1997) indicated fiber concentrations ranging from 0.04 to 3.4 f/cm<sup>3</sup> for wollastonite mining and milling and from 0.09 to 1.2 f/cm<sup>3</sup> for calcite mining. Tremolite (asbestiform) fibers were also observed in some airborne dust samples in calcite mining and milling (0.1 f/cm<sup>3</sup> in secondary crushing).

Two workers (4%) had small irregular opacities (ILO 1/0)—suggestive of diffuse interstitial fibrosis—and one worker ILO 0/1. However, HRCT (generally considered to be more sensitive) indicated no parenchymal fibrosis in the two workers with the ILO 1/0 classification.

Nine workers (18%) were found to have pleural plaques, of which five had "possible" or "probable" asbestos exposure (four based on work history and one on finding asbestos fibers in BAL). The remaining four workers lacked any indication of asbestos exposure and the authors concluded, "Therefore an association between wollastonite exposure and pleural plaques was possible . . . . However, such an association would be difficult to explain biologically" (Koskinen et al., 1997, p. 46). Multivariate logistic regressions indicated no association of plaques with the duration of wollastonite or asbestos exposure. Wollastonite fibers were not found in any of the four workers for which BAL data were available nor in the available lung tissue samples. (This reflects the relatively low biopersistence of wollastonite, discussed later). The authors found no correlation between the lung function variables and the duration of exposure

to wollastonite mine and mill work. The authors (Koskinen et al., 1997) concluded, "Our observations did not produce any evidence indicating that long-term exposure to wollastonite causes parenchymal fibrosis of the lungs. If wollastonite is fibrogenic, such a property cannot be strong. The exposed cohort showed pleural plaques. As the risk of contracting plaques was not related to the duration of wollastonite exposure, the cause of the plaques remains unclear. Moreover, our findings indicate that, under the exposure conditions of the Finnish mine and mill in our study, wollastonite fibers are poorly retained in human lungs. This finding may also explain the absence of fibrosis in our material" (pp. 46–47). Hillerdal (2001) noted that in industrialized countries in the cities 2 to 4% of all males above age 40 yr are usually carriers of plaques. According to Hillerdal (2001), "Plaques are in themselves harmless. They may be regarded as an objective sign of previous asbestos inhalation" (p. 3).

Workers at the Finnish limestone–wollastonite quarry were also subjects of a *mortality* study (Huuskonen et al., 1983b; Huuskonen & Tossavainen, 1996). The study covered the period 1923–1980 and included 238 workers (192 men and 46 women) who had been on the factory's payroll for at least 1 yr. Expected deaths were calculated from national age- and sex-specific death rates for 1952–1972. By the end of 1980, 79 deaths had occurred in the cohort versus 96 expected. Deaths were due to malignant neoplasms (all sites combined) for 10 men (standardized mortality ratio [SMR] = 0.64, 95% confidence interval [CI] 0.31–1.18) and two women (SMR 0.67, 95% CI 0.08–2.41). Deaths from cancer of the lung and bronchus included four men (SMR = 0.8, 95% CI 0.22–2.05) and no women (0.2 expected). (SMRs and CIs were calculated by the IARC working group [IARC, 1997] and are not reported in Huuskonen et al. [1983b].) There was a death due to a rare malignant mesenchymal tumor in a 73-yr-old nonsmoking woman, which a panel noted on reexamination showed features similar to a diffuse mesothelioma. The cohort was relatively small, a limitation of the study. Nonetheless, the study should be considered negative and the upper ends of the confidence intervals on the SMRs are not greatly different from 1.0. Moreover, the authors (Huuskonen et al., 1983b) note that estimated workplace concentrations were based only on "the present level of exposure, and they probably underestimate the exposure level in earlier years" (p. 171).

*Morbidity* studies were also conducted on a cohort of workers at a wollastonite mine in New York State (Shasby et al., 1979; Hanke & Sepulveda, 1983; Hanke et al., 1984). The first study (Shasby et al., 1979) included a cohort of 104 men, accounting for 72% of all men with at least 1 yr of exposure since 1952 when production began. The prevalence of symptoms of chronic bronchitis (23%) was higher in this cohort than in workers in nondusty environments but was not related to years of exposure. There was some evidence for increased obstructive lung disease, but the data were confounded by different age groups. No evidence was found for restrictive lung disease using chest radiography and spirometry.

Exposure data for the New York cohort were limited. Total dust concentrations ( $n = 97$ ) ranged from 0.9 to 10 mg/m<sup>3</sup>, de-

pending on job classification. Fiber concentrations ( $n = 15$ ) determined by phase-contrast optical microscopy (PCOM) ranged from 0.27 to 47.7 f/cm<sup>3</sup>, also depending on job classification (Hanke & Sepulveda, 1983). The total dust concentrations were beneath present U.S. regulatory limits for PNOR. However, many of the reported fiber concentrations exceed current OELs for those countries that have specific limits based on fiber concentrations. This facility has installed additional engineering controls to limit exposures since these measurements were taken.

In the 1982 morbidity study (Hanke et al., 1984) of the same cohort, pneumoconiosis was measured in 3% of the workers. This condition was present in these same workers in 1976 but showed no progression. Among workers examined in 1982, 52 workers included in a high dust (>30 dust-years) exposed subgroup had a statistically significantly lower ratio of FEV<sub>1</sub> (forced expiratory volume in 1 s) to FVC (forced vital capacity) and a statistically significantly lower peak flow rate than 86 age-matched control workers from a nearby electronics plant. This effect was independent of age, height, and smoking habits.

A review of the available morbidity data (Merchant, 1990) indicated that occupational exposure to wollastonite results in a "non-specific increase in bronchitis, reduced lung function and limited evidence of pneumoconiosis" (p. 291). Another reviewer (Lockey, 1996) concluded, based on this and other evidence reviewed below, that among the "various type [sic] of nonasbestos minerals, wollastonite has a low level of toxicity but very well may cause pleural and interstitial changes at exposure levels that are unusually high" (p. 340).

#### ANIMAL STUDIES: CANCER

Animal studies are typically accorded less weight in cancer assessments than human studies because (in order to minimize required sample sizes) experiments are conducted at high dose levels—which need to be extrapolated to lower concentrations found in the occupational environment. It is also necessary to make assumptions about the comparative dosimetry and potency of materials tested in animals and humans. Nonetheless, animal experiments can eliminate some of the difficulties of epidemiological studies (e.g., coexposure to other potentially toxic agents)—if properly designed.

The earliest studies of the effects of *intrapleural administration* of wollastonite and several other fibers on rats were reported by Stanton and colleagues (Stanton & Wrench, 1972; Stanton et al., 1981). In these studies, groups of 30–50 female Osborne-Mendel rats, 12–20 wk of age, received 40 mg/animal wollastonite dispersed in hardened gelatin directly on the left pleural surface by open thoracotomy. Four separate grades (composition and purity unspecified) of wollastonite (differing in length–diameter distribution) from the same (unidentified) Canadian mine were used. The rats were followed for 2 yr and the survivors were sacrificed. The reported incidences of pleural sarcomas were (a) wollastonite grade 1, 5/20; (b) wollastonite grade 2, 2/25; (c) wollastonite grade 3, 3/21; and (d) wollastonite grade 4, 0/24. In comparison, the incidence

for groups of animals treated with UICC crocidolite asbestos was 14/29 and those for two samples of tremolite were 22/28 and 21/28, respectively. Though undoubtedly important, these early studies suffered from several limitations. Perhaps most important, the wollastonite was not well characterized—a significant flaw, particularly when testing a naturally occurring substance. As noted in the International Uniform Chemical Information Database (IUCRID) entry for wollastonite (European Commission, 2000), “The wollastonite was neither physically nor chemically characterized; Canadian wollastonite is unknown to everyone in the mineral industry” (p. 15). In fact, there were no wollastonite mines operating in Canada at the time. There were operating Canadian mines containing wollastonite deposits; however, these produced other minerals, including asbestos. One notable occurrence of wollastonite is the Jeffrey mine in Asbestos, Quebec (<http://www.und.edu/instruct/mineral/geol1318/webpage/mau/>), which was a tremolite-containing chrysotile mine. Contamination of the wollastonite samples with asbestos (particularly amphibole forms) would be especially problematic. Second, the administration technique was potentially flawed because the hardened gelatin might increase the biopersistence of the implanted wollastonite. Moreover, inhalation is generally considered a preferable technique because this is the actual exposure pathway. In initially reviewing the animal data, IARC (1987) concluded that there was limited evidence of carcinogenicity in animals based on Stanton’s results. However, IARC (1997) later concluded that there was inadequate evidence of carcinogenicity in animals.

Pott et al. (1987, 1989) studied the effects of *intraperitoneal injection* of wollastonite and approximately 50 other dusts in rats. A group of 54 female Wistar rats, 8 wk of age, received 5 weekly intraperitoneal injections of 20 mg/animal wollastonite (from India) in saline. The number of wollastonite fibers in this sample (length  $\geq 5$   $\mu\text{m}$ , diameter  $\leq 3$   $\mu\text{m}$ , and aspect ratio  $\geq 5:1$ ) was  $430 \times 10^6$ ; median length and diameter were 8.1  $\mu\text{m}$  and 1.1  $\mu\text{m}$ , respectively. (There is a discrepancy in the reported median length of wollastonite fibers, which is given as 5.2  $\mu\text{m}$  in Pott et al. [1987] and 8.1  $\mu\text{m}$  in Pott et al. [1989].) Surviving animals were sacrificed after 130 wk. No tumors (0/54) were found in post-mortem examinations of the wollastonite-exposed group compared to 30/36 among a UICC Canadian chrysotile exposed group. Pott et al. (1989) concluded, “A rather large number of wollastonite fibres of Indian origin did not induce tumors. The durability of these fibres in water was low. However, Stanton et al. (1981) found some tumors after intrapleural administration of wollastonite from a Canadian mine. The differences in the results underline the experience gained with other mineral fibres. . . that the mineralogical name or trade name of a fibrous material generally does not give a sufficient indication of its carcinogenic potency” (pp. 177–178).

Muhle et al. (1991) and Rittinghausen et al. (1991) also studied the effects of *intraperitoneal injection* of wollastonite and crocidolite asbestos in rats. Results were consistent with those obtained by Pott and colleagues. A group of 50 female Wistar

rats, aged 11–12 wk, was treated with 2 intraperitoneal injections of a suspension of 30 mg wollastonite (obtained from Eternit with median fiber length 5.6  $\mu\text{m}$  and diameter 0.71  $\mu\text{m}$ ) in saline. The animals were sacrificed when moribund or when they reached 130 wk after the start of the treatment. No abdominal tumors were observed among animals treated with wollastonite. In a positive control group treated with 3 mg crocidolite, abdominal tumors were observed in 32/50 rats. No tumors (0/50) were detected in a saline (negative) control group. Muhle et al. (1991) concluded, “These data support the hypothesis that *long, thin, and durable fibres* are capable of inducing tumours” (emphasis added; p. 186).

McConnell et al. (1991) reported the results of an *inhalation study* of F344 rats exposed to 10 mg/m<sup>3</sup> (360 total fibers/ml) commercial wollastonite (NYAD-G from NYCO Minerals) conducted on behalf of the National Institute of Environmental Health Sciences. Length–diameter distributions were measured for both bulk material and the exposure aerosol using SEM. Groups of 78 male F344 rats were exposed to wollastonite (10 mg/m<sup>3</sup> 360 total fibers/ml or 55 fibers/ml with length  $\geq 5$   $\mu\text{m}$ , diameter  $\leq 1$   $\mu\text{m}$ , and aspect ratio  $\geq 3:1$ ) for 6 h/day, 5 days/wk, for either 12 or 24 mo; 2 control groups, an untreated chamber control, and a positive control exposed to chrysotile asbestos for 12 mo also at a concentration of 10 mg/m<sup>3</sup> (approximately 1000 total fibers/ml, 2.8 times greater than that for wollastonite) were included. (Current theory suggests that the concentration of long ( $\geq 20$   $\mu\text{m}$ ) fibers is a more relevant measure of potential biological effect. Based on the data given in Table 2 of McConnell et al. (1991), the concentrations of long wollastonite fibers and associated 95% confidence limits are 9.2 f/ml (95% CI 2.4, 28.3 f/ml). The manuscript does not present data on the length–diameter distribution of the chrysotile aerosol, so that corresponding long chrysotile fiber concentrations cannot be estimated. Histopathological examination of the lungs of rats held for a lifetime showed that wollastonite did not cause an increased tumor rate compared to controls. Additionally, the incidence of interstitial fibrosis among wollastonite-exposed animals was 0/57 after 12 mo and 1/60 after 24 mo, compared to 50/52 in the chrysotile-exposed group. The incidence of bronchoalveolar adenoma or carcinoma (total) was 1/56 in the chamber control group, and 0/57 and 1/60 in the groups exposed to wollastonite for 12 mo and 24 mo, respectively, compared to 20/52 in the chrysotile-exposed group. McConnell et al. (1991) ascribed the lack of response to wollastonite to its low biopersistence, noting, “This conclusion is important in explaining the lack of a carcinogenic response by wollastonite even though it would have been predicted to have carcinogenic activity based on the Stanton hypothesis” (p. 335). The 1997 IARC review group noted that the concentration of wollastonite fibers with length  $\geq 5$   $\mu\text{m}$  used in this study was relatively low, suggesting that the experiment lacked statistical power.

Adachi et al. (2001) reported on the results of *intraperitoneal administration* to 5-wk-old female F344 rats of 10 different fiber samples, including natural wollastonite (from China). All fibers

were administered at 10 mg/animal; based on the tumor incidence at this dose, doses for a second experiment were selected at either 5 mg/animal or 20 mg/animal. The Chinese wollastonite test fibers had geometric mean length and diameter of 10.5  $\mu\text{m}$  and 1.0  $\mu\text{m}$ , respectively (Kohyama et al., 1997). Animals were sacrificed at various times up to 2 yr and the cumulative incidence of mesothelioma was recorded. The article notes that mesotheliomas were found with silicon carbide, potassium titanate whisker, UICC chrysotile, and refractory ceramic fibers; data are presented on the cumulative incidence of mesotheliomas as a function of time for these fibers. Apparently no mesotheliomas were found in groups of rats exposed to glass wool, rock wool, or wollastonite, although the article is not explicit on this point.

Among the wollastonite studies just described, only the Stanton et al. (1981) results were positive. As already noted, however, there were significant limitations with respect to wollastonite characterization/representativeness and also the use of the gelatin. The other studies were all negative, though not without limitations. As noted, IARC (1997) concluded that there was *inadequate evidence* regarding the carcinogenicity of wollastonite in experimental animals. The 2001 Australian NOHSC review weighed the evidence slightly differently and concluded that there was *sufficient evidence for the non-toxicity and non-carcinogenicity of wollastonite fibres in experimental animals*.

#### OTHER ANIMAL STUDIES

Warheit et al. (1991) conducted a short-term (6 h/day for 3 or 5 days), high-dose (50 or 100 mg/m<sup>3</sup>, equivalent to 123–835 fibers/ml) *inhalation* study of CrI:CDBR rats exposed to wollastonite (NYAD-G from NYCO Minerals). Wollastonite fiber diameters ranged from 0.2 to 3  $\mu\text{m}$ . Rats were also exposed to 40 mg/m<sup>3</sup> crocidolite with a mean diameter of 0.15  $\mu\text{m}$ . The animals were evaluated at various periods ranging from 24 h to 30 days following exposure. The evaluations included analyzing the enzyme and protein levels in BAL fluids and the *in vitro* phagocytic capacities of alveolar macrophages recovered from exposed rats. Wollastonite exposure produced transient pulmonary inflammatory responses and increases in BAL fluid parameters only if the mass median aerodynamic diameter (MMAD) was 2.6  $\mu\text{m}$  and the exposure concentration exceeded 500 fibers/ml. The severity and duration of the response to wollastonite was less than that observed with crocidolite. This finding paralleled that of an earlier study by Warheit et al. (1984) on wollastonite (4–9  $\mu\text{m}$  long) on rat macrophages (percentage of activated macrophages and the ability of these macrophages to phagocytize carbonyl iron particles). Effects were noted with wollastonite exposure, but the authors concluded, “The results suggest that wollastonite fibers present a reduced inhalation hazard when compared to asbestos fibers” (p. 155).

The *inhalation* study of McConnell et al. (1991) summarized earlier also examined alveolar macrophage response and other parameters. This study found that wollastonite exposure produced a reversible alveolar macrophage response without

evidence of induction of fibrosis or neoplasms. In contrast, exposure to chrysotile produced significant fibrosis, hyperplasia, and bronchoalveolar carcinomas.

Cambelová and Juck (1994) performed an *intratracheal instillation* study of male Wistar rats exposed to various materials, including wollastonite (samples from China and NYCO Minerals), quartz, crocidolite (geometric mean length 3.9  $\mu\text{m}$ ), glass fiber (geometric mean length 45.1  $\mu\text{m}$ ), and two synthetic organic fibers (polyacrylonitrile with geometric mean length of 227.4  $\mu\text{m}$  and polypropylene with geometric mean length of 253.8  $\mu\text{m}$ ). The same gravimetric dose (25 mg in 1 ml saline) was used for each instillation. Three months after exposure the animals were sacrificed and lungs evaluated for hydroxyproline content—an indicator of fibrosis. Exposure to the wollastonite sample from China (geometric mean fiber length, diameter, and aspect ratio 11.6  $\mu\text{m}$ , 1.3  $\mu\text{m}$ , and 9.2:1, respectively) resulted in increased lung wet weights ( $p < .05$ ), lipid content ( $p < .001$ ), and hydroxyproline levels ( $p < .01$ ) compared with controls. However, the NYAD wollastonite (geometric mean fiber length, diameter, and aspect ratio 9.2  $\mu\text{m}$ , 1.2  $\mu\text{m}$ , and 7.9:1, respectively) produced only a small but significant ( $p < .05$ ) increase in hydroxyproline levels. The authors concluded, “For wollastonite, there was a significant increase in [measured effects] in comparison with the controls. The fibrogenicity was considerably less than that of crocidolite and quartz” (p. 343). IARC (1997) and McConnell (1995) questioned the experimental protocol employed and noted that a single bolus of 25 mg might induce a nonspecific response. McConnell (1995) noted, “In summary I am convinced that what the authors actually produced in their studies was a fibrogranulomatous bronchiolitis (probably occlusive) that would not have occurred if the fibres were given by inhalation, and therefore these results have no relevance for determining the potential health effects of wollastonite in humans.” (p. 621).

Hurbánková et al. (1995) noted that instillation (into the lung) of wollastonite long and short fibers did not influence significantly the cellular parameters studied, but amosite did, particularly the longer fibers. Several studies (see, e.g., Hamilton et al., 1996) have used wollastonite as a negative control in studying cytotoxicity. The comparisons with various types of asbestos are motivated by the findings that various types of asbestos are known carcinogens and because (as noted earlier) wollastonite is used as an asbestos substitute in certain applications.

Tátrai et al. (2004) conducted an *intratracheal instillation* (IT) study of male Sprague-Dawley rats exposed to Chinese wollastonite (44% fibers >20  $\mu\text{m}$  in length and 41% <1  $\mu\text{m}$  diameter) and UICC crocidolite. The animals were exposed to wollastonite and UICC crocidolite by a single intratracheal instillation (1 mg/animal) and sacrificed at 1, 3, or 6 mo postexposure. After 1 mo the wollastonite-exposed animals developed multifocal, mild chronic inflammation in the interstitium—corresponding to Wagner’s classification 3–4 (mild cellular change or minimal fibrosis). This inflammation did not progress among those animals examined after 3 and 6 mo. In contrast, after 1 mo the

crocidolite-exposed animals developed a very intense multifocal inflammation, which became more intense (Wagner grade 6–8, indicative of moderate to severe fibrosis) at 3 and 6 mo. The authors concluded that wollastonite is less cytotoxic than crocidolite. The authors attributed the “very mild histological reaction” to wollastonite exposure to the short half-time. (The Wagner grades reportedly attained in this study are higher than typically found in inhalation studies, probably as a result of the IT administration. However, even if the assigned grades were biased high, the differences between wollastonite and crocidolite are noteworthy and consistent with results of other studies.)

### KINETIC/MECHANISTIC STUDIES

The modern paradigm for fiber toxicology is summarized in the familiar phrase *dose–dimension–durability*. The durability or biopersistence of a fiber has been shown to be a key determinant of pulmonary toxicity generally and cancer specifically. Fibers that are relatively biopersistent, such as crocidolite and amosite asbestos, result in tumors in animal bioassays; those that are not biopersistent such as certain types of fiberglass, are not animal carcinogens (Hesterberg et al., 1998; McDonald, 1998; Maxim et al., 1999; National Research Council, 2000; Bernstein et al., 2001a, 2001b; IARC, 2002). Bernstein et al. (2001a) summarized matters as, “The biopersistence of fibers longer than 20  $\mu\text{m}$  was found to be a good predictor of the lung burden and early pathological changes in chronic inhalation studies as well as of the tumor response in chronic intraperitoneal studies with fibers” (p. 823). These investigators (Bernstein et al., 2001b) showed that “the biopersistence half-times as determined by intratracheal instillation ( $T_{1/2}$  of WHO fibers or weighted  $T_{1/2}$  of fibers with  $L > 20 \mu\text{m}$ ) and as determined by inhalation (weighted  $T_{1/2}$  of fibers with  $L > 20 \mu\text{m}$ ) are equivalent predictors of the ip results” (p. 870).

The *in vivo* biopersistence of wollastonite has been investigated by two groups of investigators. Warheit et al. (1994a, 1994b) studied the biopersistence of wollastonite and other fibers in *inhalation experiments*. Muhle and colleagues (Muhle et al., 1991, 1994; Bellmann & Muhle, 1994) studied the biopersistence of wollastonite and other fibers by *intratracheal instillation*. Results of these studies were consistent and show that wollastonite is cleared rapidly from the lung.

Warheit et al. (1994a, 1994b) exposed groups of 8-wk-old male Crl:CDBR rats 6 h/day for 5 days to aerosols of wollastonite (NYAD-G, NYCO Minerals) fibers (835 f/ml or 114  $\text{mg}/\text{m}^3$ ). Kevlar fibrils (900–1344 f/ml; 9–11  $\text{mg}/\text{m}^3$ ) were also evaluated in the same experiment. Following exposure groups of 3–4 animals and age-matched controls were evaluated at 0, 24, and 72 h, 1 wk, and 1, 3, and 6 mo postexposure. The inhaled wollastonite fibers were cleared rapidly with a retention half-time of <1 wk. The authors concluded “These data suggest that both inhaled Kevlar and wollastonite fibers have low durability in the lungs of exposed rats, and this may be responsible for the measured differences in toxicity between Kevlar and wollastonite on the one hand, and durable dusts such as silica or crocidolite as-

bestos fibers on the other” (Warheit et al., 1994b, pp. 469–470). Warheit et al. (1994a, 1994b) did not present any data on the relation between fiber length and clearance rate.

Muhle and colleagues (Muhle et al., 1991, 1994; Bellmann & Muhle, 1994) used *intratracheal instillation* to estimate half-times for wollastonite and other fibers. Fibers (known length–diameter distributions) of various coated and uncoated wollastonite (three sources, including India, Eternit, and NYCO Minerals) and other materials were instilled intratracheally into female Wistar rats. After serial sacrifices at 2 and 24 days, and 1, 3, and 6 mo, the fibers were analyzed by TEM and the half-times calculated. Estimated half-times for the wollastonite fibers (length  $> 5 \mu\text{m}$ ) ranged from 15 to 21 days (Bellmann & Muhle, 1994)—values consistent with results of their other studies (Muhle et al., 1991, 1994) of 10–18 days. Among the fibers tested, only xonotlite [ $\text{Ca}_6\text{Si}_6\text{O}_{17}(\text{OH})_2$ ] had a more rapid elimination time (<2 days). Bellmann and Muhle (1994) concluded that “The relatively fast dissolution of the test materials, which are all composed of a calcium silicate base, should minimize the health effects related to respired fibers” (p. 194). They also concluded “The coating of wollastonite in Wollastocoat had no effect on the elimination process” (p. 191).

Figure 3 shows the IT half-times (fibers with length  $\geq 5 \mu\text{m}$ ) for wollastonite, several synthetic vitreous fibers (SVFs), and crocidolite asbestos as reported by Muhle et al. (1994). As can be seen, the wollastonite fibers are cleared very rapidly, a finding with important implications for the toxicity and carcinogenicity of these fibers.

### DISSOLUTION RATE STUDIES

Protocols for measurement of the *in vitro dissolution rate* (rate constant  $K_{\text{dis}}$  typically measured in units of  $\text{ng}/\text{cm}^2/\text{h}$ ) of fibers in simulated lung fluid are well established (see, e.g., Potter & Mattson, 1991; Zoitos et al., 1997; Eastes & Hadley,

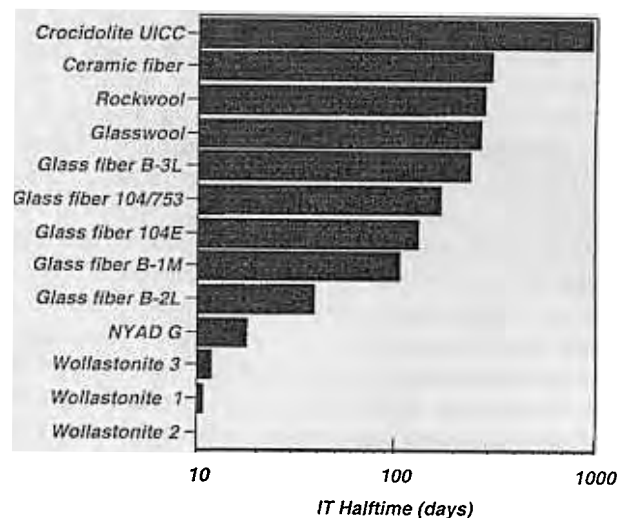


FIG. 3. Half-time (days) based on number of fibers ( $\geq 5 \mu\text{m}$ ) for wollastonite, several SVFs, and crocidolite (Muhle et al., 1994).

1996; Maxim et al., 1999).  $K_{dis}$  has been shown to correlate well with in-vivo measurements of  $T_{1/2}$  (Maxim et al., 1999). To date no estimate of  $K_{dis}$  has been published for wollastonite. However, the wollastonite  $K_{dis}$  has been measured by at least one laboratory. Potter (2004) measured the  $K_{dis}$  for wollastonite (NYCO Minerals with median diameter 10  $\mu\text{m}$ ) as  $520 \pm 56 \text{ ng/cm}^2/\text{h}$ . Using the empirical relation for SVFs developed by Maxim et al. (1999) between in vitro  $K_{dis}$  and in vivo  $T_{1/2}$  inhalation measurements ( $T_{1/2} = e^{5.8} K_{dis}^{-0.7}$ ) would result in a predicted value of 4 days for  $T_{1/2}$  (based on Potter's measured value of  $K_{dis}$ ) for wollastonite compared to the <1 wk actually measured by Warheit et al. (1994a, 1994b)—in remarkably good agreement.

Eastes and Hadley (1996) analyzed the relation between dissolution measurements of  $K_{dis}$  and fibrosis/tumors for SVFs. They developed a mathematical model of fiber carcinogenicity and fibrosis in inhalation and intraperitoneal experiments in rats. They concluded, "The mathematical model presented and tested here has been found to predict the diseases that occur in rats exposed to large doses of fibers both in inhalation and in intraperitoneal experiments. The model suggests that synthetic vitreous fibers with a dissolution rate constant of 100  $\text{ng/cm}^2/\text{h}$  or more would not result in fibrosis in a well-conducted, RCC-type animal inhalation study at MTD. To induce tumors, a fiber would have to be much more durable. This model provides a tool for the assessment of the potential health effects of untested fibers" (p. 341). Maxim et al. (1999) analyzed published bioassay data for SVFs and showed that an empirical  $K_{dis}$  threshold for fibrosis was 55, rather than 100. The estimated  $K_{dis}$  for wollastonite (520) is well in excess of either threshold, suggesting that wollastonite is unlikely to produce fibrosis or be carcinogenic in animal tests.

## OTHER STUDIES

Wollastonite toxicity has also been investigated using in vitro methods. Although interesting and potentially useful, the state-of-the-art of fiber toxicology is not sufficiently well developed at present to use these as the sole basis for carcinogen classification.

IARC (1997) summarized these studies as of 1996. Generally speaking, these studies indicated that wollastonite caused cellular level effects, but these were less than those observed with various types of asbestos. For example, Pailles et al. (1984) exposed cultures of rabbit alveolar macrophages to chrysotile, wollastonite (NYCO Minerals, 98%  $\leq 8 \mu\text{m}$  length), and latex beads at concentrations ranging from 50 to 250  $\mu\text{g/ml}$ . The authors found that chrysotile was cytotoxic whereas wollastonite was far less cytotoxic. Aslam et al. (1992) compared the cytotoxic effects of three samples of wollastonite (Kemolit ASB-3, Kemolit-N, and Kemolit A-60 manufactured by Wolchem Ltd., Udaipur, India) with those of chrysotile (supplied by Andhra Pradesh Mining Corporation Ltd. Hyderabad, India). Dust suspensions were added to the red blood cell suspensions and effects were noted. Compared to the chrysotile samples, the wollastonite samples had a smaller hemolytic potential and caused less lipid peroxidation in the erythrocytes. The authors concluded, "Therefore it is likely that wollastonite samples, which are less toxic in vitro

than the chrysotile, may account for the lower incidence of fibrosis among workers occupationally engaged in the wollastonite industry" (p. 30).

Other studies have been published since the IARC review was written—with similar results and conclusions. For example, Macdonald and Kane (1997) compared the mesothelial cell proliferation induced by wollastonite (NYAD 1250, NYCO Minerals) and UICC crocidolite. Macdonald and Kane (1997) included crocidolite in the study because it is both biopersistent and carcinogenic. Wollastonite was included because of its low biopersistence and the negative bioassay results of Pott et al. (1987) and McConnell et al. (1991). Macdonald and Kane established a dose-response relationship between the number of fibers delivered to the parietal peritoneal lining, inflammation, and mesothelial-cell proliferation induced by intraperitoneal injection of crocidolite fibers in mice. Persistence of these inflammatory and proliferative responses depended on persistence of fibers at the target tissue. Intraperitoneal injection of wollastonite fibers induced an early inflammatory and proliferative response that subsided after 21 days. In contrast, the number of fibers recovered from tissue digests had not declined 6 mo after injection of crocidolite asbestos. The authors concluded that their results "support the hypothesis that biopersistent fibers cause persistent inflammation and chronic mesothelial cell proliferation" (p. 180).

Governa et al. (1998) tested wollastonite fibers (NYAD from NYCO Minerals, length and diameter distribution given in Figure 4) in vitro for their ability to produce reactive oxygen species (ROS) with two different systems: a cell-free reactive mixture containing deoxyribose, and a polymorphonuclear (PMN) leukocyte suspension. The test article was well characterized in terms of chemical composition and dimensions. (See Figure 4 for the marginal distributions of wollastonite fiber diameter and length as determined from scanning electron microscopy [SEM] measurements of 1000 fibers.) Compared with asbestos, wollastonite fibers produced higher ROS levels both in the PMN suspensions and in the cell-free reactive mixtures. However, a large amount of these ROS were not hydroxyl radicals. The authors concluded, "On the surface of wollastonite fibers there are functionalities able to generate ROS of which a large amount [sic] are not hydroxyl radicals. Since asbestos toxicity is mainly due to hydroxyl radical generation . . . we share the opinion of Nejjari et al. (1993) and Aslam et al. (1995) that wollastonite fibers are probably less toxic than asbestos fibers" (pp. 36–37).

## EVIDENCE REGARDING SURFACE TREATED WOLLASTONITE

As noted earlier, some wollastonite is treated with various agents (typical concentrations 0.5–1%) to improve its properties for certain applications. These surface-treated wollastonites have not been studied extensively. However, Bellmann and Muhle (1994) have studied the biopersistence of surface-treated wollastonite (WOLLASTOCOAT 1001 and 1005, NYCO Minerals) and found that these materials had half-times similar to those of the untreated materials also tested (NYAD G and NYAD

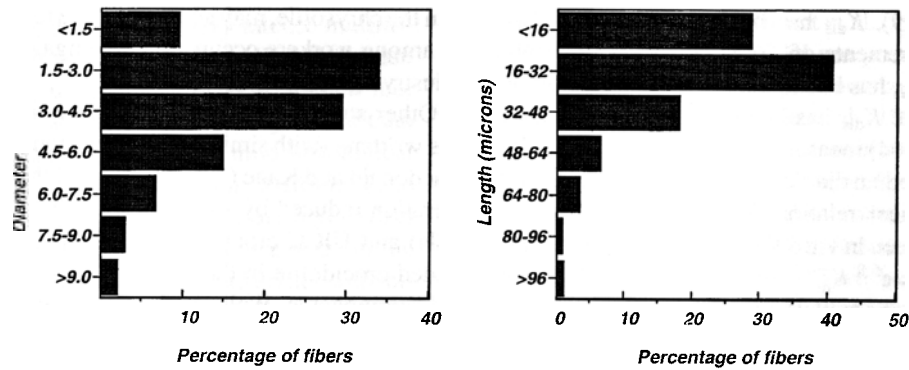


FIG. 4. Marginal distribution of fiber diameter (left) and length (right) for NYAD wollastonite sample (1000 fibers) as determined by scanning electron microscopy (SEM) used as test article in Governa et al. (1998) study.

1250)—all samples tested cleared rapidly (half-times between 18 and 22 days). In view of the critical role of biopersistence in fiber toxicity, this study is noteworthy and demonstrates that these coatings (at least at the concentrations typically used) would not have an impact on the pathogenicity of wollastonite.

#### CONTAMINATION AND COEXPOSURE

As with any mineral product, wollastonite deposits contain various other substances. Even though these may be segregated and/or removed in the beneficiation process, the chemical composition of the finished product(s) can vary as can the composition and quantity of byproducts and wastes.

As noted in the summary of human studies, some of the occupationally exposed cohorts were also exposed to other substances (e.g., calcite, crystalline silica and tremolite), of which some are potentially toxic and carcinogenic. Crystalline silica and tremolite, for example, are both classified in IARC Group 1 (agents carcinogenic to humans). Such coexposure confounds the interpretation of these studies.

The presence of impurities may also confound the interpretation of animal studies and is potentially problematic unless the test material is well characterized in terms of its source, composition (including trace contaminants), length–diameter distribution (and length–diameter distribution of the aerosol for inhalation experiments). As noted, deposits of natural wollastonite typically contain other minerals or contaminants, which may include toxic contaminants, such as crystalline silica and various types of asbestos (see, e.g., Simandl et al., 1999). Contamination has occurred even in the New York wollastonite deposits (Anonymous, 2002; CNX marketlink, 2002; Simandl, 2003), where traces of tremolite were found in a localized area in this deposit. Upon this discovery, NYCO Mineral, Inc., strengthened and expanded its product stewardship program, carefully segregated the contaminated materials, tested wollastonite ore being processed, and conducted airborne testing to ensure that workplace concentrations were in compliance with applicable occupational exposure limits and other environmental requirements. Furthermore, all ore released from the mine is ND (nondetect)

for asbestiform tremolite as tested using the TEM technique. The stewardship program is ongoing and will continue throughout the working lifetime of the mineral deposit. However, this incident also serves to illustrate the point that careful characterization is required for test materials used in animal experiments.

#### SUMMARY AND CONCLUSIONS

Natural wollastonite is a valuable industrial mineral used in diverse applications in plastics, ceramics, metallurgy, paint, and friction products. Domestic production of wollastonite (approximately 130,000 MT in 2000) is significant, but small (4.8%) in comparison to glass wool and mineral wool. NIOSH estimated that approximately 70,000 workers in diverse occupations were potentially exposed to wollastonite in 1981–1983. This upper bound estimate has not been updated, but is likely to be smaller at present.

Wollastonite is produced in several grades, broadly separated into powder (low aspect ratio) and acicular (high aspect ratio) materials. These grades share many physical properties (e.g., density, alkalinity, and coefficient of thermal expansion) but differ in terms of the length and diameter distribution of the particles/fibers.

Because some wollastonite particles/fibers are respirable, are similar to the lengths and diameters that have been identified as having greatest biological activity, and (in part) because some applications involve asbestos replacement, numerous studies have been made of the toxicology and epidemiology of wollastonite. It is convenient to group these studies into four broad classes: (1) cellular/mechanistic, (2) biopersistence, (3) animal (cancer and other), and (4) human.

Most of the cellular/mechanistic studies (whether in vitro or in vivo) show that wollastonite is capable of producing potentially adverse effects (e.g., cytotoxicity, inflammation, and mesothelial cell proliferation) but also demonstrate that these effects are transient and significantly less toxic than is produced by various forms of asbestos.

The in vivo biopersistence studies indicate that wollastonite is cleared rapidly from the lung with halftimes varying from less

than 1 wk (inhalation) to 10–21 days (intratracheal instillation). *These half-times are less than those for many other mineral fibers, including glass wool and mineral wool, for which inhalation bioassay studies (and very large epidemiological studies) are negative.* Biopersistence is recognized as a major determinant of toxicity and carcinogenicity. The relatively low biopersistence of wollastonite is the major reason why, a priori, wollastonite is unlikely to be carcinogenic in humans.

Nearly all of many animal studies (intrapleural, intraperitoneal, intratracheal, and inhalation) of wollastonite *have been negative in terms of fibrosis and cancer.* Two exceptions are the intrapleural study of Stanton and colleagues (1972, 1981), which resulted in an excess of pleural sarcomas compared to controls, and a short-term intratracheal instillation study of Cambelová and Juck (1994), which produced adverse effects (e.g., increase in lung wet weight, lipid content, and hydroxyproline levels) indicative of possible fibrosis. Both of these studies have limitations. The Stanton study did not adequately characterize the source of the wollastonite—which may have been contaminated with asbestiform minerals—and, moreover, the wollastonite was dispersed in hardened gelatin, which may have altered the otherwise low biopersistence of the test material. The study of Cambelová and Juck (1994) has also been criticized and deemed (McConnell, 1995) not to be relevant for determining the potential health effects of wollastonite in humans.

Several negative long-term animal studies have been reported (e.g., McConnell et al., 1991; Pott et al., 1987, 1989; Muhle et al., 1991; Rittinghausen et al., 1991). In principle, the McConnell et al. (1991) study is particularly relevant, because it was an inhalation study. Some reviewers (IARC, 1997) noted that the concentration of long wollastonite fibers used in the inhalation study of McConnell et al. (1991) may have been less than the maximum tolerated dose (MTD) and therefore that the study lacked statistical power.

IARC (1997) classified the evidence of carcinogenicity in experimental animals as *inadequate*, meaning that the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations. IARC (1997) carefully considered the Stanton and Cambelová and Juck results in reaching this conclusion, and we believe that it is noteworthy that the more recent (1997) IARC review changed its original assessment of the animal studies from limited evidence to inadequate evidence.

A more recent review by NOHSC (Douglas, 2001) evaluated the animal data more definitively, concluding that there was *sufficient evidence for the non-toxicity and non-carcinogenicity of wollastonite fibers in experimental animals.*

There have been several epidemiological studies on wollastonite, including mortality and morbidity studies on occupationally exposed cohorts. The authors of a morbidity study of workers in a Finnish wollastonite quarry (Koskinen et al., 1997) noted that their “observations did not produce any evidence indicating that long-term exposure to wollastonite causes parenchymal fibrosis of the lungs” (p. 46). This study found some work-

ers with pleural plaques, but noted, “As the risk of contracting plaques was not related to the duration of wollastonite exposure, the cause of the plaques remains unclear” (p. 46). A mortality study of the Finnish cohort (238 workers) resulted in SMRs less than 1.0 for all causes, malignant neoplasms, and cancer of the lung and bronchus. Morbidity studies of a cohort of workers in a wollastonite mine in New York State showed changes in certain spirometry measures and pneumoconiosis in 3% of the workers. Reviewers of these studies noted that (Merchant, 1990) “Occupational exposure to wollastonite results in a non-specific increase in bronchitis, reduced lung function, and limited evidence of pneumoconiosis” (p. 291) and (Lockey, 1996), “wollastonite has a low level of toxicity but very well may cause pleural and interstitial changes at exposure levels that are unusually high” (p. 340). Both IARC (1997) and NOHSC (Douglas, 2001) concluded that there was inadequate evidence in humans for the carcinogenicity of wollastonite. In evaluating the epidemiological data, it is important to keep in mind that historical exposures were greater than present OELs. It is also important to note the limited statistical power of these studies as reflected in the width of the confidence intervals discussed earlier.

Since the IARC and NOHSC reviews, additional studies have been published that, in our judgment, are consistent with their assessments. All things considered, the most persuasive evidence for the probable lack of pulmonary fibrogenicity and carcinogenicity of wollastonite is the absence of any adequate positive study (epidemiological or animal) and its extremely low biopersistence.

This said, it is prudent to continue product stewardship efforts involving the analysis of ore samples to ensure that there is no contamination by asbestos and that there is continued adherence to published OELs at all stages of mining, beneficiation, processing, and use.

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