FIBER GLASS INSULATION NOT CLASSIFIED AS A HUMAN CARCINOGEN BY IARC

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ABSTRACT
In October 2001, the International Agency for Research on Cancer (IARC) changed their 1987 carcinogenicity classification of fiber glass wool insulation from Group 2b (possibly carcinogenic to humans) to the more favorable Group 3 (not classifiable as to its carcinogenicity to humans). The 2001 decision was based on new animal evidence that the potential carcinogenicity of a synthetic vitreous fiber is directly related to its ability to persist in the lung (biopersistence). Eleven fibers were tested for both carcinogenicity and lung biopersistence. The biosoluble SVFs, such as fiber glass wool insulation, did not cause any malignant or non-malignant disease in rodents even after lifetime exposure to high levels of respirable fiber dust. These animal study results, along with the finding of no exposure related increase in respiratory system cancer in fiber glass manufacturing workers resulted in the downgrading of the IARC classification (Moore et al. 2002).

INDEX TERMS
Inhalation, Respiratory System, Fiber Glass and Wool, Man Made Vitreous Fibers, Synthetic Vitreous Fibers, Carcinogen

INTRODUCTION
Fiber glass (FG) is a synthetic vitreous fiber (SVF). SVFs are amorphous (glassy, vitreous) inorganic fibrous materials manufactured from silica and other inorganic components. In addition to FG, SVFs include several other traditional groups (slag wool, rock wool, stone wool, and refractory ceramic fiber [RCF]) as well as newer compositions that do not fit any of these traditional categories. FG is traditionally divided into two groups: glass wool and continuous glass filament. Glass wools can release respirable fibrous dust; thus, it has been extensively studied for potential respiratory system effects. Continuous filament is manufactured in non-respirable dimensions (diameters >3 μm and very long or continuous lengths); therefore, it is not a concern for respiratory health. Fiber glass wool is used for thermal and acoustical insulation, filtration media, and some specialized application; continuous filament is used primarily for reinforcement of plastics and other materials.

In 1987, IARC (the International Agency for Research on Cancer, an agency of the World Health Organization) evaluated the carcinogenicity of SVFs. IARC concluded that animal studies (mostly abdominal injection studies and some poorly-conducted inhalation studies) provided "sufficient evidence" for carcinogenicity in animals. At the same time, the agency concluded that long term epidemiology studies of FG manufacturing workers provided "inadequate evidence" of carcinogenicity in humans. However, based on the animal evidence, IARC classified fiber glass (and all other SVFs) as "possibly carcinogenic to humans" (Group

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2b) (IARC, 1987). The 1987 IARC findings prompted 14 years of intensive toxicologic research on these fibers, which was completed in the year 2001

In October 2001, in response to significant new findings, IARC re-evaluated the carcinogenicity of SVFs. In a break from the long-time traditional view, IARC acknowledged recent scientific evidence that demonstrates a clear toxicologic difference between standard fiber glass wool insulation (FGWI) and certain durable special purpose fiber glasses (SPFG; e.g., ultra-thin microfibers made from e glass or 475 glass). SPFG are produced in relatively small quantities for specialized applications, such as components of circuit boards or filtration media for liquids. Thus, IARC now recognizes three divisions of FG: FGWI, SPFG, and continuous glass filament (Moore et al., 2002; IARC, 2001).

In the 2001 re-evaluation, the primary focus was on a series of new rodent inhalation studies of 11 SVFs, which showed that the potential carcinogenicity of an SVF was directly related to its biopersistence (ability to persist in the lung). Non-biopersistent (biosoluble) SVFs, such as FGWI, did not cause any malignant or non-malignant disease in rodents even after lifetime inhalation exposure to high levels of respirable fiber dust. After reviewing these new inhalation studies, IARC downgraded the animal evidence for carcinogenicity of FGWI from the 1987 "sufficient" to only "limited."

In 2001, IARC also reviewed the recent updates of the ongoing health studies of FG workers and re-confirmed their 1988 conclusion that the studies provided "inadequate evidence of carcinogenicity to humans." The limited animal evidence coupled with inadequate human evidence resulted in the decision of IARC to reclassify fiber glass wool insulation to Group 3, "not classifiable as to its carcinogenicity in humans." Thus, IARC does not consider FGWI to be a potential human carcinogen (IARC, 2002).

In 2001, IARC re-confirmed its earlier Group 3 classification for continuous filament and its Group 2B classification for certain durable special purpose glass fibers (composed of e glass or 475 glass) as well as for refractory ceramic fiber. All other SVFs, including FGWI, were re-classified as Group 3.

In the present paper, we summarize the scientific basis for the 2001 IARC decision—the animal study methods, findings, and conclusions.

METHODS

Chronic inhalation studies. Rats or hamsters were exposed in nose-only inhalation tubes to high concentrations of aerosolized, rat-respirable fibers. Exposure was 6 hr./d. and 5 d./wk. for lifetime (rats, 2 yr.; hamsters, 1½ yr.). Exposure aerosols contained approximately 200 F>5/cc (F>5 = fibers >5 μm in length and <3 μm in diameter), including approximately 100 F>20 μm/cc (fibers >20 μm in length). Aerosols were monitored regularly for mass and for numbers and sizes of fibers. At intervals during and after the exposure period, 3-6 rodents were evaluated for lung pathology and for lung fiber burden. Fibers that were evaluated included 9 SVFs (2 SPFG, 2 FGWI, rock wool, slag wool, HT stonewool, RCF, and a nontraditional hybrid fiber) and two types of asbestos (amosite and crocidolite; fiber aerosol concentration was much higher for crocidolite than for the other fibers types). (Studies were reviewed by Hesterberg and Hart, 2001.)

Biopersistence Studies. Rats were similarly exposed to 9 SVFs or 2 asbestos types for 5 days and maintained for up to 1 year post-exposure. Immediately following exposure and at regular intervals thereafter, 6-12 rats were evaluated for lung fiber burden. The weighted clearance

half-times were estimated for fibers longer than 20 μm based on a 2-pool model of lung clearance. Clearance of long fibers was used as an indicator of biopersistence, because these fibers are not subject to macrophage-mediated clearance (they are too long to be engulfed and translocated out of the lower lung by alveolar macrophages). (Details were reported by Bernstein et al., 1997, and Hesterberg et al., 1998).

In Vitro Dissolution Studies. To determine the rate of dissolution of the various fiber types, small webs of each fiber type were placed in cartridges, which were placed in a flow-through system containing simulated lung fluid (a physiological saline solution that mimics the inorganic components of tissue and cell fluids) at near-neutral pH (mimicking extracellular lung fluid) or at pH 4.5 (mimicking fluid of the phagolysosome of macrophages). Effluent from the system was analyzed for solutes. The dissolution rate constant, k_{dis} (mass loss per unit of fiber surface area over time; k_{dis} = ng/cm^2/hr), was calculated based on a constant velocity dissolution model (assuming that all components dissolve at the same and at an unchanging rate). Methods were reported in detail by Zoitos et al., 1997.

Table 1. Lung Clearance and Pathogenicity of Fibers in Rodents and In Vitro Dissolution. For clearance and pathogenicity studies, rodents inhaled high levels of airborne fiber. For in vitro dissolution studies, fibers were subjected to physiological saline in a flow-through system.

Fiber		**Lung Clearance** of Long Fibers[a]	**Pathogenicity** Chronic Inhalation		**In Vitro Dissolution** [b]
		$WT_{1/2}$ Days	**Lung Fibrosis**	**Thoracic Tumors**	pH 7.4 (pH 4.5)
Amosite	Asbestos	418	+	+	<1
Crocidolite	Asbestos	817	+	+	<1
MMVF32	E Glass, SPFG	79	+	+	9
RCF1	Refractory	55	+	+	3
MMVF33	475 Glass, SPFG	49	+	+/- [c]	12
MMVF21	Rock Wool	67	+	-	20
MMVF10	901 FGWI	14.5 [d]	-	-	300
X607	Hybrid Fiber	9.8	-	-	990
MMVF11	FGWI	9	-	-	100
MMVF22	Slag Wool	9	-	-	400
MMVF34	HT Stonewool	6	-	-	59 (1010)

Based on Hesterberg and Hart, 2001, and Hesterberg et al., 2002.

Abbreviations for Table 1: $WT_{1/2}$ = weighted clearance half-time; k_{dis} = ng/cm^2 hr; FGWI = fiber glass wool insulation; SPFG = Special Purpose Fiber Glass; minus sign (-) = no fibrosis or no elevated tumor incidence.

[a] Fibers longer than 20 μm.

[b] Dissolution rate constant, k_{dis} = ng/cm^2/hr

[c] +/- indicates tumorigenicity in hamsters (one mesothelioma in 83 animals) but not in rats.

[d] Biopersistence is for MMVF10.1, which is longer and thinner than the original MMVF10 that was used for chronic studies.

RESULTS

Results of the chronic and biopersistence rodent inhalation studies and the in vitro dissolution studies are summarized in Table 1. A relationship between fiber durability, both in vitro and

in the lung, and pathogenicity is readily apparent in these data. The less biopersistent fibers (FGWI, X607, slag wool, and HT stonewool, $WT_{1/2}$ values 5-14.5 days) also dissolved rapidly in vitro (k_{dis} >100 ng/cm^2/hr) and caused no irreversible lung disease. These non-biopersistent fibers caused only transient lung irritation that would be expected following inhalation of large amounts of any innocuous dust. On the other hand, the more biopersistent fibers (asbestos, SPFG, RCF, and rock wool; $WT_{1/2}$ >40) were fibrogenic and all but rock wool also caused respiratory cancer in the rodents.

FGWI was clearly less biopersistent than SPFG: $WT_{1/2}$ values were 9-15 days for FGWI vs. 49-79 days for SPFG. In vitro dissolution was also more rapid for FGWI than for SPFG: K_{dis} values were 100-300 for FGWI vs. 9-12 for SPFG.

Asbestos fibers were 5- to 80-fold more biopersistent than the 9 SVFs: $WT_{1/2}$ values were 400-800 days for asbestos but 9-80 days for the SVFs. In vitro dissolution was negligible for both asbestos types, and both were fibrogenic and carcinogenic in the rodents.

DISCUSSION

Although lung fibrosis and cancer have both been observed in rodents following chronic exposure to high levels of certain durable SVFs, it should be noted that there has been no evidence that these effects in humans as a result of occupational exposure to any form of SVF. Respiratory health has been monitored in SVF manufacturing workers from the 1940's to 1993 in very large, ongoing morbidity and mortality studies. These studies conclude that the respiratory health of SVF workers is similar to that of local control groups of people that do not work with fibers (Weill et al., 1983; Hughes et al., 1993; Marsh et al., 2001).

In 1987, IARC recognized two categories of fiber glass: fiber glass wool (insulation and special purpose fibers were not differentiated) and continuous glass filament. After noting the lack of human or animal evidence of carcinogenicity for continuous filament, IARC originally classified this material as Group 3, "not classifiable as to its carcinogenicity to humans," and this classification was re-confirmed in the 2001 review. IARC originally classified all forms of fiber glass wool as Group 2B, "possibly carcinogenic to humans," based on limited animal evidence and insufficient human evidence of carcinogenicity.

In reviewing the post-1987 animal studies in October 2001 (Table 1), the IARC panel noted the clear differences between FGWI and durable SPFG (e.g., e glass and 475 glass microfiber) in both biopersistence and pathogenicity, and, for the first time, made a distinction between these two very different types of fiber glass. For SPFG, IARC retained the Group 2B classification, "possibly carcinogenic to humans." However, due to the thorough and meticulous studies conducted between 1987 and 2001, which demonstrated no fibrosis or elevated tumor incidence in animals chronically exposed to FGWI, IARC reclassified this material as Group 3, "not classifiable as to its carcinogenicity to humans," based on limited evidence of carcinogenicity in animals and in inadequate evidence in humans.

The saga of SVF research, evaluation and classification, followed by new research, re-evaluation and re-classification, is a success story for industry, independent researchers, and scientific review agencies. All three entities functioned in concert to protect and inform the public and to develop more knowledge about materials that perform important functions in today's world. After the discovery that chronic inhalation exposure to asbestos fibers is associated with the development of thoracic cancers and fibrogenic lung disease, chronic inhalation of all dusts, including many that had previously been considered innocuous, was viewed with concern. Because many SVFs can release respirable *fibrous* particles, these

materials were of special concern. Research was initiated by both public health agencies and the SVF industry. The early research was reviewed by IARC, SVFs were classified as possible carcinogens, and industry launched another round of research at independent laboratories. The new research prompted a new, more accurate classification of these materials. The new classification has prompted responses from both industry and regulatory agencies. Industry has moved to reformulate fibers for decreased biopersistence and to decrease human exposure to those fibers that require greater durability for their special applications.

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