September 28, 2009

Dr. Ruth Lunn
Director, RoC Center
NIEHS
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Re: Comments of Unifrax I LLC on the RoC Expert Panel's Recommendations on Listing Status for Glass Wool Fibers and the Scientific Justification for the Recommendations, 74 Fed. Reg. 40598 (August 12, 2009)

Dear Dr. Lunn:

Unifrax I LLC, a manufacturer of Refractory Ceramic Fiber (RCF) and other manmade mineral fibers, supports the RoC Expert Panel Recommendation that synthetic vitreous fibers with a length less than 15 micrometers or a Kdis coefficient greater than 100 ng/cm2/h are not reasonably anticipated to be human carcinogens. Scientific support for the Panel recommendation is summarized below.

Unifrax products are high temperature insulation materials that produce energy savings up to 40% or more in industrial furnace and other applications. In these times, it is particularly important to encourage use of such materials where they can be used safely. For over 20 years, Unifrax and our fellow members of the Refractory Ceramic Fiber Coalition (RCFC) repeatedly have been commended for our dedication to product stewardship and workplace health protection. Since the late 1980's, RCFC and its member companies have developed and implemented a comprehensive Product Stewardship Program (PSP) to control potential workplace and other exposures to RCF. The RCFC PSP has been endorsed on various occasions by both OSHA and NIOSH.

One of the primary elements of the PSP involves research to develop new soluble fiber products that retain a high insulation capacity but reduce potential human risk by dissolving more quickly in the lung. To date, Unifrax and other RCFC members have developed several such products. All of these products have a Kdis coefficient greater than the 100 ng/cm2/h cutoff point recommended by the Expert Panel.

The well-established role of fiber biopersistence in the potential biological activity of fibers played an important role when IARC evaluated the animal data with respect to insulation glass wool. As noted by IARC:

> Increasing emphasis has been placed on clearance and retention of MMVFs in discussing the mechanistic data in risk assessment for adverse health effects induced by fibres (McClellan, 1977). This is partly because the biopersistence of fibres has been shown to play an important role in the effects on health of manmade and other mineral fibres.[1]

This recognition by IARC is also consistent with the conclusion drawn by the National Research Council (NRC): "The potential hazard posed by a given MVF is directly related to its ability to persist in the lung long enough to cause chronic disease.[2]

Both the RoC Background Document (BD) for Glass Wool Fibers and a substantial body of additional research indicate that fibers with a Kdis coefficient exceeding 100 are unlikely to cause adverse human health effects. The BD notes that "Dose, dimension, and durability have been termed the three Ds, all of which are important in determining the carcinogenicity of fibers (see Section 5.3)" (p. 11). As reported in BD Tables 4-9, 5-7, 5-9, and 5-10, fibers with Kdis coefficients exceeding 100 almost never produce significant tumor rates.[3] The BD also notes:

> The *in vivo* clearance of fibers > 20 μm in length from the lungs of F344 rats has been reported to result from the dissolution of the fibers in extracellular fluid at approximately the same rate as the dissolution rate (kdis) measured in simulated lung fluid *in vitro*, a process that depends on the chemical composition of the fibers (Eastes and Hadley 1995, Eastes *et al.* 1995). The predicted dissolution rates were similar for inhalation studies of MMVF10 and MMVF11 glass fibers, MMVF21 rock wool, MMVF22 slag wool, and crocidolite asbestos (Eastes and Hadley 1995) and for intratracheal instillation studies of MMVF10 and MMVF11 glass fibers and three experimental glass fibers, X7779, X7753, and X7484, with kdis values of 2, 100, and 600 ng/cm2 per hour, respectively (Eastes *et al.* 1995). For fibers < 20 μm in length they proposed that physical removal occurred bymacrophage-mediated process that did not differ by fiber type. The authors also reported that computer simulations of fiber clearance based on these processes

[1] IARC Monograph 81, p. 255.
[2] National Research Council, *Review of the U.S. Navy's Exposure Standard for Manufactured Vitreous Fibers* (2000), p. 33
[3] Only one study, Miller et al. 1999(b), is listed as producing a significant tumor rate for a fiber with a Kdis coefficient above 100 (129 for MMVF10; see Tables 4-9 and 5-8). That was an IP study. The authors note that the IP approach is aimed at obtaining "a relatively quick and repeatable comparison of potential hazard among different fibre types" and may not be suitable for deciding whether a fiber should be considered a potential human carcinogen (p. 165). As discussed further below, others have concluded that the disease-limiting Kdis coefficient is much higher in IP studies.

> agreed well with *in vivo* measurements of fibers remaining in the lung up to a year after exposure (p. 193).

Other studies confirm that fibers with a Kdis coefficient exceeding 100 are unlikely to be harmful. For example, Estes and Hadley (1996) concluded:

> [I]t would be very unlikely to observe any disease after this exposure to a fiber with a kdis of 100 ng/cm2/h or higher . . . It would appear from these considerations that to be free of respiratory disease in a state-of-the-art, RCC-type rat inhalation study at MTD, an insulation wool fiber should have a dissolution rate constant of 100 ng/cm2/h or higher.[4]

The authors note that "the data . . . also suggest that the no-disease limiting Kdis is much higher for the intraperitoneal injection studies than for the inhalation studies" (p. 337).

Similar results are reported in Maxim et al. (1999):

> Numerous papers have been written on the relevance of Kdis values for assessing the hazard/risk posed by SVFs. Before discussing relevant results, it should be noted that Kdis (based on an in vitro measurement) correlates well with in vivo measurements of biopersistence. For example, as discussed at length below, Kdis correlates with the estimated half-life of long (>20 pm) fibers as measured in short-term inhalation studies . . . Thus, in principle, Kdis can be used as a surrogate for in vivo measurements. In this report, measurements of both . . . are available for the fibers under study. Results are presented for both measures . . . Based on these data, use of Kdis thresholds of 17 (for tumors) and 55 (for fibrosis) results in no misclassification. Simply put, no fiber with a Kdis $\geq$ 17 has resulted in increased tumors in rats and no fiber with a Kdis $\geq$ 55 has produced fibrosis in a chronic rat inhalation study.[5]

This is confirmed in a comprehensive list of tested fibers and Kdis values provided in Table A-1 of Maxim et al 2006.[6] Similar data are reported in a 2005 paper prepared by a working group of the International Life Sciences Institute.[7]

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[4] Estes & Hadley, "A Mathematical Model of Fiber Carcinogenicity and Fibrosis in Inhalation and Intraperitoneal Experiments in Rats." Inhalation Toxicology, 8:323-343, 1996 (p. 339).
[5] Maxim et al., "Hazard Assessment and Risk Analysis of Two New Synthetic Vitreous Fibers." Regulatory Toxicology and Pharmacology 30: 54-74, 1999 (p. 57).
[6] Maxim et al., "The Role of Fiber Durability/Biopersistence of Silica-Based Synthetic Vitreous Fibers and Their Influence on Toxicology." Regulatory Toxicology and Pharmacology 46, 42-62 (2006).
[7] "Testing of Fibrous Particles: Short-Term Assays and Strategies." Inhalation Toxicology, 17:497–537 (2005)(Figure 5).

Unifrax and RCFC take pride in their continuing commitment to development of soluble fiber products that retain superlative insulation properties while reducing potential hazards from human exposure. The scientific literature discussed above has led us to believe that the Kdis coefficient is an accurate predictor of potential human health risk. We believe that the available literature fully supports the recommendation of the Expert Panel in this regard, and we urge NTP to adopt the Panel's recommendations in preparing the RoC.

Please contact me with any questions or comments you may have with respect to our position or these issues in general.

Sincerely,

Dr. Dean Venturin

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