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April 16, 2012

Dr. Ruth Lunn
Director, Report on Carcinogens Center
National Toxicology Program
MD K2-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: 12th RoC Listing for Ceramic Fibers

Dear Dr. Lunn:

The HTIW Coalition, formerly the Refractory Ceramic Fibers Coalition (RCFC), submits the following comments on the listing for Ceramic Fibers in the 12th Report on Carcinogens (2011). HTIW Coalition has four member companies, representing virtually 100% of the RCF used in the United States. RCFC was formed in 1992 to focus on product stewardship for refractory ceramic fibers (RCF) and conduct a wide range of health and safety studies, with the purpose of identifying and quantifying risk and protecting manufacturing and customer workers from any potential health risks. HTIW Coalition is the same organization renamed in 2011 to continue this work.

RCFC did not comment previously on the 12th RoC listing for RCF because it Coalition was not aware that the prior listing would be revised. In reviewing the new listing, HTIW has identified several errors and omissions that we would like to bring to your attention. The final Report states that "although not anticipated, factual errors or omissions in this report may be identified after its distribution. If this should happen, these errors or omissions will be addressed by the NTP. Where appropriate, corrections will initially be posted on the NTP RoC Center Web site at http://ntp.niehs.nih.gov/go/roc and then made in the next edition of the RoC" (p. 7).

Our comments are set forth below. We urge you to post them on the RoC website as discussed above. In addition, we note that no RCF information is posted in the portion of the site dedicated to background materials for various substances

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evaluated in the report. We also ask that you create a new category for RCF background materials and post these as public comments for reviewers to examine.

CAS No.

While the listing indicates that no CAS No. has been assigned to RCF, a number has been assigned. It is 142844-00-6 (Person, 2004). It is important to list the CAS No. to differentiate RCF from other fiber products. Accordingly we ask that you add the correct CAS No. to the listing.

Animal Studies

The discussion of cancer studies in experimental animals should clarify that a subsequent review of the maximum tolerated dose (MTD) pathology indicated that the animals' lungs were "overloaded" because of large quantities of non-fibrous particles, and that this overload condition was likely responsible for the disease observed. In fact, evaluation of the aerosol samples used confirmed the presence of significant quantities of particulate matter (Bellmann et al., 2001; Brown et al., 2000, 2005; Mast et al., 2000a,b; Yu and Oberdöster, 2000; Yu et al., 1994a, b, 1995 a, b, 1996). In a later multi-dose animal inhalation study of WHO fibers at 26 f/cc, 75 f/cc, and 120 f/cc a *no observed adverse effect level* (NOAEL) was found at 26 f/cc (Mast et al., 1995; NIOSH, 2006), Health Council of the Netherlands [DECOS], 1995). This level is 50 times the RCFC recommended REG of 0.5 f/cc for humans (Maxim et al., 2008).

Human Studies

Greater weight should be given to the primary findings of the University of Cincinnati (UC) RCF study (LeMasters et al., 2003). In its continuing effort to determine possible human health effects following RCF exposure, RCFC has engaged UC to conduct a long-term medical surveillance study on RCF workers. This continuing study has been in progress for over 20 years, collecting data from respiratory questionnaires, lung function tests, chest X-rays, exposure monitoring, and worker mortality.

The results of this study of RCF plant workers exposed from 1953 to the present have shown:

- No excess mortality related to all deaths, all cancers, or lung cancer
- No statistically significant increase in interstitial findings (fibrosis), and
- No mesotheliomas.

Through 1996, pleural plaques seen on chest X-rays in 2.7% of the workers were associated with RCF exposure (Lockey et al., 1996). Pleural plaques are considered a marker of exposure and not disease. The prevalence of pleural plaques has remained relatively constant over time, perhaps as a result of lower current exposure levels (Utell and Maxim, 2010).

An initial cross-sectional spirometry study revealed lung function decrements in the RCF-exposed cohort that were associated with heavier historical exposures (Lockey et al., 1998). Subsequently, longitudinal studies have revealed no RCF exposure related decrements in lung function associated with current exposure levels (Lockey et al., 2002; McKay et al., 2011).

Thus, this long term epidemiology study continues to demonstrate both an absence of interstitial fibrosis, no increased mortality risk, and no decrement in lung function associated with current exposures.

The discussion in the NTP listing of the urinary cancer finding in this study should be qualified. In the study, the lower 95% confidence limits on the standardized mortality ratios (SMRs) for more than 40 other possible causes were less than 100, meaning that SMRs were not significantly elevated. By failing to mention the large number of other death causes evaluated, the current listing does not acknowledge the possibility that the urinary cancer result might be a "false positive." The 95% confidence limit accepts the possibility that 1 in 20 comparisons will result in false positives. With more than 40 comparisons made, the expected number of false positives would be two. LeMasters et al., (2003) acknowledged this in writing about the reported excess in urinary cancers:

> The confidence intervals for these SMRs are wide, and together with the fact that there are 46 statistical tests reported in Table 2, may indicate a chance finding. Bladder cancer was not an a priori hypothesis and no mechanism has been posited to explain this possible association.

Other studies, including several cited in LeMasters et al., (2003), support this conclusion.[1]

In our view, it would be appropriate for NTP to qualify the statement about the results of the UC mortality study as follows:

[1] See e.g., Marsh et al. (1996); Chiazzi et al. (1999); Marsh et al. (2001); Stone et al. (2004) Sali et al. (1999); Steenland et al. (2002).

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Since the IARC evaluation, a study (LeMasters et al., 2003) of two refractory ceramic fiber manufacturing plants reported no excesses of lung cancer, mesothelioma, or other causes among 46 possible causes of death. Ongoing work by the primary researchers continues to support these results. The study did report a statistically significant threefold excess of urinary cancer (mainly urinary-bladder cancer) based on five deaths although the confidence interval on the SMR was very broad and the authors surmised that this may be a chance finding.

Risk Assessment

Because human disease has not been associated with exposure to RCF, a risk assessment based on cancer endpoints in humans is impossible. Thus, RCFC commissioned a risk assessment based on the bioassay data from the animal studies described in the listing which were conducted at RCC Laboratories in Geneva, Switzerland during the late 1980's. Sciences International Inc. (SII), a world renowned environmental consulting firm, conducted the risk assessment in 1998 based on the RCF animal studies (SII, 1998). The risk assessment team was led by Dr. Suresh Moolgavkar and utilized the two stage clonal expansion model. (Moolgavkar et al., 1999).

The model looked at fiber lung burden in the animals along with deposition and clearance in both humans and animals, allowing for estimates of risk based on lung burden only. The calculated risk for a 70 year old worker with 30 years of exposure to 1 f/cc was 3.7×10^{-5} (maximum likelihood estimate) for a nonsmoker and 1.5×10^{-4} for a smoker (Moolgavkar et al., 1999).

Using the Moolgavkar work, Turim and Brown (2003) summarized the 95% upper bound risk of excess lifetime lung cancer for nonsmoking workers as:

- 3×10^{-5} for a 1 f/cc exposure
- 1.5×10^{-5} for a 0.5 f/cc exposure
- 0.3×10^{-5} for a 0.1 f/cc exposure.

Separately, Fayerweather et al., (1997) extrapolated rat data to human data using a linearized multistage model and found at exposures of 1 f/cc, the excess lifetime risk of developing lung tumors was 3.8×10^{-5} (maximum likelihood estimate). Subsequently others have modeled animal data yielding similar risk estimates (see e.g., Walker, Maxim and Utell, 2002, Maxim et al., 2003, and NIOSH, 2006).

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Regulations

Clean Air Act. The listing notes that fine mineral fibers are listed as a hazardous air pollutant in the Clean Air Act (CAA). However, a footnote to that listing in the statute reads as follows:

> Includes mineral fiber emissions from facilities manufacturing or processing glass, rock, or slag fibers (or other mineral derived fibers) of average diameter 1 micrometer or less (42 USC 7412(b)(1)).

Pursuant to this footnote, RCF is not covered by the CAA listing because it has an average diameter above 1 micrometer. Accordingly, the CAA reference should be removed from the NTP listing or a clarification that it does not apply to RCF should be added.

NIOSH. In 2006, NIOSH issued a Criteria Document for RCF (#2006-123) after an extensive review of available literature and data both by NIOSH scientists and external experts. NIOSH initially considered adoption of a recommended exposure limit (REL) of 0.2 fibers per cubic centimeter (f/cc) but ultimately elected to adopt 0.5 f/cc REL, consistent with OSHA and the industry's REG as explained below.

Guidelines

The listing should reference the HTIW Coalition Recommended Exposure Guideline (REG) of 0.5 f/cc. As mentioned above, NIOSH has adopted the industry REG as its recommended exposure limit (REL) for RCF. The REG is part of the extensive product stewardship program (PSP) that the industry has developed and implemented through RCFC, now HTIW Coalition. The complete PSP includes many other elements and can be found on the RCFC/HTIW Coalition website. The PSP has been commended by EPA, OSHA, NIOSH, ACGIH, and others for its work on monitoring and reducing exposures through the years, as well as its scientific work. The industry is in its second five-year agreement with OSHA under which OSHA has agreed not to pursue a PEL for RCF as long as the PSP continues to be implemented. Annual reports are provided to OSHA and are available on the RCFC/HTIW Coalition website. The current five-year agreement with OSHA will soon reach its term, and the industry is preparing an updated version of the PSP to present to OSHA as the basis for a new agreement. The updated PSP will be available on our website when it is completed.

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Thank you for considering our comments on the RCF listing in the 12th RoC. We ask that you incorporate them and post them on the RoC website as discussed above. We would be glad to meet with you at your convenience to discuss these issues further.

Sincerely,

[Redacted]

Thomas E. Walters
Business Administrator

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