Comments on the Draft Recommendations for Inclusion of Refractory Ceramic Fibers on Annex XIV (Authorisation List)

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Background

The German government has prepared two Annex XV Dossiers[1] leading to the listing of two types of aluminosilicate wools (often termed [RCF] and so identified in the dossiers) as *substances of very high concern* (SVHC) on the Candidate List. ECHA has recommended these entries for inclusion on Annex XIV (the Authorisation List), following a selection / priority ranking process.

I have been involved in research on various aspects of RCF exposure, toxicity, and epidemiology for approximately 20 years and published numerous papers in peer-reviewed journals summarizing these investigations. I have been asked by Unifrax Corp to prepare and submit comments on these two Annex XIV Draft Recommendations.[2]

These comments include; (1) comments on ongoing epidemiological studies, and (2) comments on clinical effects related to RCF exposure. I present summary material relevant to these issues in what follows. These summaries are brief, but fully supported by numerous reports and data published in the peer-reviewed literature.

Epidemiology Studies

As part of its ongoing product stewardship program the RCF industry in both the United States and Europe has sponsored a series of epidemiological studies beginning in 1987 at the University of Cincinnati in the United States and at the *Institute of Occupational Medicine* (IOM) in Europe on occupationally exposed cohorts.[3] This work included evaluation of historical exposures and studies of respiratory symptoms, possible fibrosis, effects on lung function, respiratory tumors, and mortality. These studies have been published in the peer-reviewed scientific literature and also explicitly considered in the United States National Institutes Occupational Health and Safety (NIOSH) Criteria Document. To put these findings in perspective, production workers studied in the

[1] See Annex XV Dossiers available at: http://echa.europa.eu/doc/consultations/svhc/svhc_axvrep_germany_cmr_AlSi_ref_ceramic_fibres_20090831.pdf and http://echa.europa.eu/doc/consultations/svhc/svhc_axvrep_germany_cmr_ZrOAlSi-Ref_ceramic_fibres_20090831.pdf.

[2] The views are my own and do not necessarily represent those of Unifrax Corp or any other manufacturer of RCF.

[3] The European study was actually a collaborative project led by the Institute of Occupational Medicine (IOM) in the United Kingdom, with the Institut National de Recherche et de Sécurité (INRS) and Institut National del'Environnement Industriel et des Risques (INERIS) in France and the University of Köln in Germany. The European study included six RCF plants: two in England, three in France, and one in Germany.

University of Cincinnati cohort have up to 43 years of exposure to RCF (25% of all production workers in the cohort have over 20 years of exposure) and no disease above background rates has been observed.

-Historical Exposures

On average RCF exposures have decreased over the years in both US and European plants. The maximum exposure estimated was approximately 10 fibers per cubic centimeter (f/cc) in one plant in the United States during the 1950s for carding for textile operations;[4] this decreased to less than 1.0 f/cc by the 1990s (Maxim *et al*., 2008; Rice *et al.*, 1997; see also Cowie *et al.* [2001] and contained references for exposures in European plants). Epidemiology results are summarized below for respiratory symptoms, pulmonary function tests, radiological findings, and mortality. The reader should bear in mind that these results reflect occupational exposures that were greater (particularly in the early years) than current exposures, which implies that the potential for adverse health effects will also be reduced in the future.

-Respiratory symptoms

In a US study (LeMasters *et al*., 1998) respiratory symptoms, including chronic cough, chronic phlegm, pleuritic chest pain, shortness of breath, wheezing, and asthma were assessed using the *American Thoracic Society* (ATS) questionnaire. The major finding from the analysis of respiratory symptom questionnaires was dyspnea (shortness of breath). This symptom occurred more frequently among production employees. Specifically, differences in prevalence of these symptoms between production and non-production workers were statistically significant among males for dyspnea 1, dyspnea 2,[5] and "one or more symptoms." Additionally, there were differences in prevalence rates in male production workers compared to non-production workers reporting one or more respiratory symptoms; 29.6% and 11.3% respectively with an adjusted odds ratio of 2.9 [95% confidence interval 1.4-6.2] (LeMasters *et al.*, 1998). Such a finding was to be expected: the authors (LeMasters *et al.*, 1998) concluded:

> "In general, the prevalence of respiratory symptoms here is similar to that reported in other dust-exposed populations."

In parallel European studies, Burge *et al*. (1995) concluded that current exposures to both inspirable dust and respirable fibers were associated with dry cough, stuffy nose, eye and skin irritation, and breathlessness. Trethowan *et al.* (1995) concluded that statistically significant increases were noted in the prevalence of dyspnea (both grades) with increasing cumulative exposure. Cowie *et al.* (2001) analyzed chronic bronchitis, breathlessness, recurrent chest illness,[6] and pleuritic chest pain as a function of recent and cumulative exposure. Calculated odds ratios were greater than one for each of these, but

[4] This was a maximum and involved relatively few workers. Typical exposures were beneath this level.

[5] Dyspnea grade 1 included all grades of shortness of breath upon exertion. Dyspnea grade 2 included all grades of shortness of breath upon exertion, excluding shortness of breath when hurrying on the level or walking up a slight hill.

[6] Recurrent chest illness was defined as a positive response to the question "During the past 3 years have you had any chest illnesses that have kept you off work?" if the worker reported two or more chest illnesses.

only statistically significant for recurrent chest illness OR = 1.48 (95% CI 1.11 to 1.96) with cumulative exposure.[7] However, the authors noted that the "prevalence in the study group was low."

-Pulmonary function results

The US cross-sectional study of pulmonary function (LeMasters *et al.,* 1998) reported no statistically significant findings for FEV_1/FVC or FEF_{25-75}. For men, there was a statistically (but not clinically) significant decline in forced vital capacity (FVC) for current and past smokers of 165 mL and 156 mL, respectively. There was no significant decline among non-smokers.

Forced expiratory volume in one second (FEV_1) showed a statistically significant decline (135 mL) only for men who were current smokers. Thus, only those men who worked in RCF production and smoked showed a decline in FVC and FEV_1.

A later longitudinal analysis of 361 male production workers who provided 5 or more spirometry tests did not show further declines between the initial test and the final test (Lockey *et al.,* 1998). The authors noted that no further declines might reflect the fact that exposures have decreased over the years. An expansion of the longitudinal study included current and former workers (n = 1,396) followed for up to 17 years. Similar to the findings from the earlier study, no consistent decline was observed longitudinally with exposure to RCF (McKay, *et al*., 2011).

In Europe, an initial study (Trethowan *et al.,* 1995) found no association between RCF exposure and lung function in non-smokers. However, there was a significant association between FEV_1 and cumulative exposure in past smokers and a non-significant trend for cumulative exposure and FVC for current and past smokers. In the follow-up study (Cowie *et al.,* 2001), the effects were slightly smaller than those seen in 1987 but there were mild decrements in FVC and FEV_1 associated with estimated cumulative RCF exposure but only for male current smokers. In addition, there was no reduction in diffusing capacity for carbon monoxide related to exposure, another sensitive test of lung function measured by these investigators.

-Radiological findings

The radiological investigation of workers in the US cohort exposed to RCF revealed a statistically significant increase in the prevalence of pleural plaques. Specifically, pleural changes were seen in 27 workers (2.7%). Results from the cumulative exposure analysis demonstrated a significant elevated *odds ratio* (OR) of 6.0 [95% confidence interval 1.4 to 31.0] (Lockey *et al.,* 2002). The prevalence of parenchymal abnormalities did not differ from workers exposed to other types of dust (Lockey *et al.,* 1996; 2002). Pleural plaques are regarded as a marker of exposure rather than a disease or precursor of disease. Pleural plaques do not cause pain, reduced lung function, and do not progress to either fibrosis or tumors.

[7] The OR for recurrent chest illness was not significantly associated with recent (1987 to 1996) exposure, however.

The European study of Cowie *et al.* in 2001 found no association between category 1/0+ opacities and exposure. A weak association between category 0/1+ small opacities and cumulative exposure to RCF was suggested, but not clearly established. Pleural changes, after adjustment for age and past exposure to asbestos showed some (but not statistically significant) evidence of a relation with time since first exposure to RCF.

In comparing the European findings with a study conducted in the US, pleural plaques were observed in the RCF manufacturing cohort in the US and associated with cumulative exposure to RCF (Lockey *et al.*, 2002) and biopersistence (Lockey et al, 2012). The European study of Cowie *et al.* (2001) also found some evidence of a relationship between RCF latency and pleural plaques but not with duration or intensity of exposure to RCF. Neither the most recent US study (Lockey *et al.*, 2012) nor the earlier European study demonstrated evidence of parenchymal or interstitial disease.

-Mortality

In 2003 LeMasters *et al.* reported results of a study on the mortality of workers exposed to RCF in the United States. Current and former male workers employed between 1952 and 2000 at two RCF manufacturing plants were followed to investigate any possible excess in mortality.

There was no significant excess mortality related to all deaths (SMR[8] = 69.8), all cancers (SMR = 94.2), malignancies (SMR = 78.8) or diseases of the respiratory system (SMR = 106.8) including mesothelioma.

LeMasters *et al.* (2003) also employed Cox's proportional hazards model (adjusted for age and race); *this did not show elevated risk with cumulative RCF exposure* (risk ratio 0.99, 95% CI = 0.85 – 1.16). A parallel analysis that lagged exposure by 10 years led to similar conclusions.

The authors of the mortality study (LeMasters *et al.* 2003) provide an extensive discussion of the strengths and weaknesses of the study. Limitations of the study were the relative youth of the cohort and its small size. At the time the analysis was prepared the mortality analysis had a 95% power to detect a 2-fold increase in all deaths and all cancers and a 40% power to detect a 2-fold increase in lung cancer. The mortality analysis is ongoing, which will increase the statistical power over time.

In an earlier analysis of Walker *et al.* (2002) designed to explore the statistical power of the mortality study indicated that the experience of lung cancer mortality in the RCF cohort was statistically incompatible with the hypothesis that RCF was as potent as amphibole asbestos assuming identical cumulative exposure to the cohort. However, the possibility that RCF was as potent as chrysotile asbestos could not be excluded.

[8] SMR means standard mortality ratio, which compares the mortality in the occupationally exposed group with that of a reference population. An SMR of 100 means that the mortality in the exposed group is identical with that of the exposed population.

Summary

The results of the epidemiology studies in the United States and Europe (published in peer-reviewed scientific journals) can be summarized briefly[9] as:

- Historical exposures were greater than those found at present.
- Exposure to RCF resulted in the development of certain respiratory symptoms, particularly shortness of breath, but this was regarded as anticipated and similar to results found in other dust-exposed populations.
- Exposure to RCF resulted in statistically (but not clinically) significant decrements in certain lung function indicators among current or past smokers in a cross-sectional study. However, later longitudinal studies did not demonstrate further decreases in lung function.
- Exposure to RCF resulted in an increase in the prevalence of pleural plaques, which do not result in pain, impair pulmonary function, or progress to either fibrosis or tumors.
- Exposure to RCF did not result in the development of interstitial fibrosis.
- Exposure to RCF did not result in incremental lung cancer or any mesotheliomas.

Clinical Interpretation:

From a clinical perspective, it is appropriate to note that production workers in the University of Cincinnati cohort have up to 43 years of exposure to RCF (25% of all production workers in the cohort have over 20 years of exposure) and no disease above background rates has been observed. In the many years of worker surveillance, no increased incidence or prevalence of respiratory disease has been detected. Furthermore, the recent study showing no accelerated rate of loss of lung function over 17 years further confirmed that the industry exposure limit of 0.5 f/cc protected workers from lung inflammation and interstitial fibrosis. If fibrosis were occurring at a subclinical level (that is, in the tissue but not yet seen on x-ray), one would have expected lung function to decrease at a rate more rapid than in non-exposed, healthy individuals. This did not occur.

With the epidemiological data collected over the past 20 years, the studies demonstrate that with adequate controls, RCF poses a low risk for development of respiratory disease. The RCF industry is mindful of the limitations of these (and other) studies and believes that continued prudence in handling RCF is justified as reflected in the industry's product stewardship program. And the industry remains committed to continuing these studies. Nonetheless, these results are viewed as encouraging; they certainly neither justify listing RCF as a SVHC nor the inclusion on the Authorisation List.

[9] A more comprehensive summary can be found in a manuscript submitted by Utell and Maxim (2010).

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