Refractory ceramic fibres (RCF)

by Hartwig Muhle PhD and Kyle Steenland PhD

Citation for most recent IARC review

IARC Monographs 81, 2002

Current evaluation

Conclusion from the previous Monograph:
Refractory ceramic fibres are possibly carcinogenic to humans (Group 2 B).

Exposure and biomonitoring

RCFs are produced by melting a combination of predominantly alumina (Al_2O_3) and silica (SiO_2).

Exposure intensity in the small U.S. cohort (n=942), the only existing cohort with epidemiologic data, was relatively low (<10 fb/ml maximum in 1950s, dropping to <0.6 fb/ml by the late 1980s) (LeMasters et al., 2003), especially in comparison for example to historical asbestos exposures which resulted in excess lung cancer (intensity 10-100 fb/ml) (Hodgson and Darnton, 2000, Berman and Crump, 2008). Cumulative exposures in this cohort were low (average approximately 40 fb/ml months, by the end of 2000).

NIOSH has estimated that there were about 30,000 U.S. workers exposed to ceramic fibers in the 1980s.

Maxim et al. (2008) and Rice et al. (2004) have summarized exposures in the United States since the late 1980s. The current recommended level (ACGIH) is 0.2 fb/ml. Finnish data indicates most current levels in production are low (0.01-0.29)(Linnainmaa et al., 2007), although peaks occurred in maintenance work (0.01-14.2 fb.ml. Ontario construction workers in the early 2000s generally had low RCF exposures (Verma et al., 2004) although some exceeded the ACGIH recommended level.

Cancer in humans

(*inadequate***,** Vol 81, 2002)

There are no new data on cancer in humans since the 2002 Monograph 81, although it appears that the Working Group at that time had a preliminary draft of a manuscript which published a year later (LeMasters et al., 2003). Results in the published manuscript differ only slightly from the Monograph results; lung cancer shows no excess (SMR 0.78) but the cohort (n=942) and the numbers of lung cancer deaths (n=9) are small, hence few firm conclusions can be drawn. A review of all death certificates and medical records for 35% of the deceased found no mention of mesotheliomas. There was a significant (at the $p<0.05$ level) excess of bladder cancer death based on only 3 deaths (SMR=5.0). This may have been a chance finding given the lack of a priori evidence. This cohort also shows an exposure-related excess of pleural plaques, with adjustment for asbestos exposure (asbestos exposure was apparently common, often far in the past, but prevalence data are not presented) (Lentz et al., 2003). ORs for plaque among 652 current and former workers by quartile of cumulative fiber-months/cm^3 were 1.0, 1.0, 7.7 (0.9-67), 22 (2.9-180), by quartile of exposure (0-2, 3-16, 16-51, >51 fiber-months/cm^3) (observed plaques 0,1, 6, 14 by quartile). Results using estimated cumulative dose to the lung were similar. Plaques are biomarkers of fiber (usually asbestos) exposure, but here may reflect RCF exposure. Their presence in this cohort may suggest increased subsequent risk of lung cancer of mesothelioma. There was also a dose-related increased in damage to lung function, for either FEV or FVC (Lockey et al., 1998)

There is a small European convenience cohort of ceramic fiber production workers (n=774), but there are no cancer data on this cohort. There was some evidence of lung function damage in relation to increased ceramic fiber exposure (Cowie et al., 2001). There was a relation between pleural plaques and time since last exposure to ceramic fibers.

Cancer in experimental animals

(*sufficient***,** Vol 81, 2002)

No new carcinogenicity assays have been performed since the last evaluation since 2002.

Mechanisms of carcinogenicity

Respirability (the fraction of inhaled fibres reaching the alveolar region) is an important aspect of fiber pathogenicity (ILSI Working Group, 2005). Surface charge and hydrophilicity, as well as adsorbed finishes and other physical and chemical factors, determine whether fibres can be easily dispersed or will agglomerate into larger, non respirable masses.

For respirable fibres tested in rodent bioassays, the dose, dimensions, durability in the lung, and in some cases surface reactivity of the fibres have been identified as critical parameters

related to adverse health effects. Fiber length is hypothesized to be a major determinant of pathogenicity: fibers that are not efficiently cleared or altered by physicochemical processes (e.g. breaking, or leaching) are termed biopersistent. Fibres that are too long to be completely phagocytized by macrophages are cleared less efficiently if the fiber type shows a high biopersistence. Refractory ceramic fibres have the potential to interact with target cells in the lungs or to be translocated to the interstitium or the pleura where they may cause disease. Chronic inhalation assays used in man-made vitreous fibres in rodents have correlated fiber length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma (ILSI Working Group, 2005).

Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalyzing generation of reactive oxygen species (ROS) resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired (reviewed in Institute of Medicine, 2006). In addition to direct clastogenic and aneuploidogenic activities that may be induced to target cells in lungs, persistent inflammation and macrophage activation can secondarily generate additional ROS and reactive nitrogen species (RNS) that can indirectly induce genotoxicity in addition to intracellular signaling pathways, stimulation of cell proliferation. There are indications that RCFs acting by a similar mechanism. Somatic gene alterations were induced by refractory ceramic fibres in mesothelial cells (Andujar et al., 2007).

Combination effects

Granular breakdown products of refractory ceramic fibres which are produced at the preparation of a rat respirable fraction of RCF1 show a higher deposition and retention in lungs of rats compared to fibres. The granular particles may partly act by the same adverse effects in lungs like chronic inflammation and induction of fibrosis (Davis, 1996; Bellmann et al., 2001). A mixed fibrous and non-fibrous dust exposure may have led to combination effects in the chronic rat inhalation experiments published by Mast et al., 1995.

Research needs and recommendations:

Combination effects of RCF and granular, low biosoluble particles should be investigated. The presence of granular dust retained in lungs could significantly aggravate effects of inhaled fibres (Davis, 1996)

The impact of fiber length on carcinogenicity should be investigated. Fibres longer than 20 µm are supposed to be more carcinogenic than fibres in the range between 5 and 10 µm.

The validity of dose response data in rats after inhalational exposure is potentially questionable as there are indications that the sensitivity of this assay is relatively low. This can be concluded from inhalation experiments with asbestos in rats compared to results in the asbestos epidemiology (Muhle and Pott, 2000, Wardenbach et al., 2005). More sensitive models for investigating carcinogenicity of man-made fibres should be developed

Further follow-up of the United States cohort is recommended, and mortality follow-up is currently planned. Incidence follow-up would be useful. However it is unlikely that this

small cohort will yield important results until many more years of follow-up. Mortality to date is 13% for this relatively young cohort. Follow up for cancer mortality or incidence in the European cohort would also be useful.

Selected relevant publications:

Andujar P, Lecomte C, Renier A, et al. Clinico-pathological features and somatic gene alterations in refractory ceramic fiber-induced murine mesothelial reveal mineral fiber-induced mesothelioma identities. *Carcinogenesis* 2007; 28: 1599-1605.

Bellmann B, Muhle H, Creutzenberg O, Ernst H, Brown RC, Sebastien P. Effects of nonfibrous particles on ceramic fiber (RCF1) toxicity in rats. *Inhal Toxicol* 2001; 13: 877-901.

Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. *Crit Rev Toxicol* 2008; 38 Suppl 1: 49-73.

Cowie HA, Wild P, Beck J, et al. An epidemiological study of the respiratory health of workers in the European refractory ceramic fiber industry. *Occup Environ Med* 2001; 58: 800-810.

Davis, J.M. Mixed fibrous and non-fibrous dust exposures and interactions between agents in fiber carcinogenesis. IARC Scientific Publications No. 140, (Ed. A.B. Kane et al.) 1996; 127-132.

Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg* 2000; 44: 565-601.

ILSI Working Group on Testing of Fibrous Particles. Short-Term Assays and Strategies. *Inhal Toxicol* 2005; 17: 497-537.

Institute of Medicine. Asbestos: Selected Cancers. Washington, DC: The national Academic Press. 2006

LeMasters GK, Lockey JE, Yiin JH, Hilbert TJ, Levin LS, Rice CH. Mortality of workers occupationally exposed to refractory ceramic fibers. *J Occup Environ Med* 2003; 45: 440-50.

Lentz TJ, Rice CH, Succop PA, Lockey JE, Dement JM, LeMasters GK. Pulmonary deposition modeling with airborne fiber exposure data: a study of workers manufacturing refractory ceramic fibers. *Appl Occup Environ Hyg* 2003; 18: 278-88.

Lockey J, Levin L, LeMasters GK, et al. Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. *Am J Respir Crit Care Med* 1998; 167: 1226-1233.

Linnainmaa M, Kangas J, Mäkinen M, Metsärinne S, Tossavainen A, Säntti J, Veteli M, Savolainen H, Kalliokoski P. Exposure to refractory ceramic fibres in the metal industry. *Ann Occup Hyg* 2007; 51: 509-516.

Maxim LD, Allshouse J, Fairfax RE, Lentz TJ, Venturin D, Walters TE. Workplace monitoring of occupational exposure to refractory ceramic fiber--a 17-year retrospective. *Inhal Toxicol* 2008; 20: 289-309.

Mast RW, McConnell EE, Anderson R, et al. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. *Inhal Toxicol* 1995; 7: 425-467.

Muhle H, Pott F. Asbestos as reference material for fibre-induced cancer. *Int Arch Occup Environ Health* 2000; 73: S53-S59.

Rice CH, Levin LS, Borton EK, Lockey JE, Hilbert TJ, Lemasters GK. Exposures to refractory ceramic fibers in manufacturing and related operations: a 10-year update. *J Occup Environ Hyg* 2005; 2: 462-473.

Verma DK, Sahai D, Kurtz LA, Finkelstein MM. Current man-made mineral fibers (MMMF) exposures among Ontario construction workers. *J Occup Environ Hyg* 2004; 1: 306-318.

Wardenbach P, Rödelsperger K, Roller M, and Muhle H. Classification of man-made vitreous fibres: Comments on the revaluation by an IARC working group. *Regul Toxicol Pharmacol* 2005; 43: 181-193.