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September 10, 1997

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MDWC-05
P.O. Box 12333
Research Triangle Park, NC 27709

Dear Dr. Jameson:

It has come to our attention that the National Toxicology Program (NTP) is currently accepting comments regarding the possible reclassification of cadmium and cadmium compounds as substances Known to be a Human Carcinogen in its upcoming *Report on Carcinogens*. Recent work carried out by Dr. Thomas Sorahan and associates at the University of Birmingham, Birmingham, UK – which is included for your consideration – would suggest that elevating cadmium and its compounds to this category is unwarranted.

Recent deliberations over the human carcinogenic potential of cadmium and compounds has been driven by epidemiological studies conducted by Thun et al. which reported an increased incidence of lung cancer in workers employed in a U.S. cadmium production facility. However, a well known limitation of the Thun et al. study is its failure to account for worker exposure to other confounding variables, namely arsenic. While follow-up studies by Stayner et al. and Lamm et al. attempted to compensate for arsenic exposure, they too were limited by their reliance on the same ambiguous exposure estimates as used in the Thun et al. work.

All of the past studies have utilized the cadmium exposure data developed by Smith et al. for each department within the plant. This information was then combined with work history data extracted from summary personnel records to determine the cumulative cadmium exposure for each employee. Unfortunately, the summary personnel records contained only sparse information on the workers' actual job assignments and thus could lead to misclassification of the exposure groups to which they were assigned.

Estimating the potential exposures based on job histories by department rather than by general work areas also prevents one from assessing the potential importance of exposure to other carcinogens such as arsenic that were present in the plant. This is due to the fact that the exposure to arsenic is much higher in departments involved in the initial processing of the raw material. Therefore, it becomes necessary to collect job history data by general work areas within the plant rather than simply by department in which the employee worked. This was acknowledged by Stayner et al. when they concluded that it is "impossible to fully discount the potential influence of exposure to arsenic" until such time that a more detailed information on exposures becomes available.

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The lack of detail in assessing workers' exposures in these previous studies prompted Sorahan and Lancashire to construct a new exposure matrix utilizing the departmental exposure developed by Smith et al. but refining the job histories by painstakingly extracting the number of hours each worker spent at various jobs within a department from detailed information on job histories contained in time sheet books. The information on job histories contained in these books was judged to be far more accurate than the general personnel records because they became the basis on which the company calculated the individual workers' pay check. By establishing this detailed job-exposure matrix, the authors were able to investigate possible relationships between lung cancer, cadmium exposure and arsenic exposure. The findings of this study were quite striking. To quote the authors, "A significant positive trend was found for risk of lung cancer and cumulative exposure to cadmium received in the presence of high exposure to arsenic, but not for cumulative exposure to cadmium received in the absence of high exposure to arsenic."

The authors go on to note that the definitive interpretation of this study is difficult and that it is difficult to disassociate the specific roles of cadmium and arsenic in inducing lung cancer. Lung cancer may be the result of arsenic exposure at this facility. Alternatively, an interaction between arsenic and cadmium could be producing the mortality excess observed. The report suggests that exposure to cadmium alone, or at least to less soluble forms of cadmium, either lack carcinogenic activity for humans or the effects cannot be detected due to low potency.

The results of this paper mirror those published last year by Sorahan et al. in a comparison of two copper-cadmium alloy facilities. One facility had an excess of lung cancer while a second facility had a statistically significant deficit of lung cancer. The primary difference between the two facilities was the presence of arsenic in the occupational environment of the facility found to have an excess of lung cancer cases.

We appreciate the opportunity to provide these comments regarding the classification of cadmium and cadmium compounds and respectfully request that these new studies be incorporated into the docket for consideration.

Sincerely,



Craig J. Boreiko, Ph.D.
Manager, Environment and Health

The following journal articles were attached to Craig J. Boreiko's comments. Due to copyright infringement laws we cannot display them. We listed the citations for your information.

National Toxicology Program
Report on Carcinogens Group

Smith TJ, Anderson RJ, Reading JC. 1980. Chronic cadmium exposure associated with kidney function effects. *Am J Ind Med* 1:319-337.

Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. 1985. Mortality among a cohort of U.S. cadmium production workers – an update. *J Natl Cancer Inst* 74(2):325-333.

Stayner L, Smith MA, Thun M, Schnorr T, Lemen R. 1992. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann Epidemiol* 2:177-194.

Lamm SH, Parkinson M, Anderson M, Taylor W. 1992. Determinants of lung cancer risk among cadmium-exposed workers. *Ann Epidemiol* 2:195-211.

Sorahan T, Lister A, Gilthorpe MS, Harrington JM. 1995. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med* 52(12):804-812.

Sorahan T, Lancashire RJ. 1997. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. *Occup Environ Med* 54(3):194-201.