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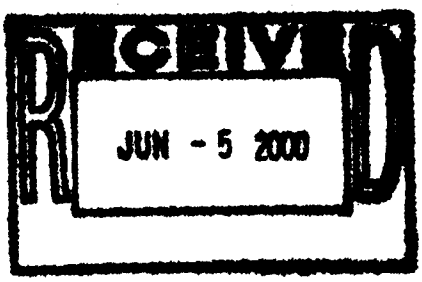

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Re: Comments on Substances Proposed for Listing in the Report on Carcinogens, Tenth Edition

Dear Dr. Jameson:

These comments are submitted on behalf of the Battery Council International ("BCI") in response to the National Toxicology Program's ("NTP") call for public comments on Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens ("RoC"), Tenth Edition.[1] *See* 65 Fed. Reg. 17889 (Apr. 5, 2000).

INTRODUCTION

Nothing has changed since the NTP designated lead acetate and lead phosphate as *reasonably anticipated to be human carcinogens* that would warrant the elevation of these or other forms of lead to the classification of *known human carcinogens*. Epidemiological studies performed to date on occupationally exposed groups are not sufficient to establish the carcinogenicity of lead in humans. This is because the actual compound(s) of lead, the route(s) of exposure, and levels of lead to which workers were exposed have not been reported and potential confounders (*e.g.*, exposure to arsenic, cadmium, antimony, drinking alcohol, and smoking) have not been controlled or isolated by most studies. Indeed, the few studies that have examined potential confounders have not shown an association between lead and cancer. As such, the nomination of lead and its compounds as *known human carcinogens* should be rejected.

[1] BCI is a not-for-profit trade association representing commercial entities involved in the manufacture, distribution sale and reclamation of lead-acid batteries. BCI's members and associate members include manufacturers and distributors of lead-acid storage batteries for automotive, marine, industrial, stationary, specialty, consumer and commercial uses, and secondary lead smelters that reclaim (recycle) the batteries once they are spent. BCI's membership represents more than 99% of the nation's domestic lead-acid battery manufacturing capacity and more than 85% of the nation's lead battery recycling or secondary smelting capacity.

COMMENTS

1. There is Insufficient Evidence of Carcinogenicity from Studies in Humans to Indicate a Causal Relationship between Lead and Cancer

In order for the NTP to designate lead as a *known human carcinogen* it must find that "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to . . . [lead] and human cancer." *See* Report on Carcinogens, Listing Criteria, http://ntp-server.niehs.nih.gov/NewHomeRoc/ListingCriteria.html. This standard requires evidence from "traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues from humans exposed to the substance in question and useful for evaluating whether a relevant cancer mechanism is operating in people." *Id.*

In the case of lead and its compounds the only pertinent evidence of carcinogenicity in humans comes from epidemiological studies of occupationally exposed groups.[2] Most such studies find little in the way of an association between occupational exposure to lead and cancer; the few purporting to report modest excesses generally do not document or report the actual compounds of lead to which exposure occurred, the routes or levels of exposure. Those studies that purportedly found an association between the increased incidence of cancer and lead exposure are further compromised by the fact that employees were exposed to other chemicals, such as arsenic and cadmium and/or regularly used tobacco products or alcohol (all designated by the NTP as *known human carcinogens*).[3]

In 1987 the International Agency for Research on Cancer ("IARC") evaluated lead as a human carcinogen and concluded that there was inadequate evidence for carcinogenicity in

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[2] We note that studies with experimental animals appear to show that some lead compounds (lead acetate and lead phosphate) may be capable of inducing cancer in rodents. The overall pattern of tumor induction combined with a negative profile for genotoxicity has lead many in the scientific community to doubt the relevance of these findings for humans. For example, Goyer (1993) has suggested that carcinomas induced by lead in rodents occur as a consequence of cystic changes in the renal cortex that follows chronic lead nephropathy. Given the susceptibility of the rodent kidney (particularly that of the male rat) to nephropathy, the relevance of the results obtained with animals is questionable.

More recent studies performed on experimental animals (*i.e.*, mechanistic studies of the time and dose-dependent changes that occur in the male rat kidney as a consequence of oral lead acetate administration) support the Goyer rationale that tumor induction in the male rat kidney is preceded by a series of degenerative and hyperplastic changes that are likely unique to the rodent kidney.

[3] BCI notes that a more thorough and critical discussion of the relevant epidemiological studies purporting to show an association between exposure to lead and the incidence of human cancer is available in the comments submitted by the International Lead and Zinc Research Organization. BCI wholeheartedly endorses and incorporates by reference those comments.

humans resulting from occupational exposures to lead – despite the fact that IARC evaluated studies in which lead levels far exceed any realistic exposure. Nonetheless, IARC concluded that the "[e]xcesses of respiratory cancer in these studies were relatively small, showed no clear-cut trend with length of exposure, and could have been confounded by factors such as smoking or exposure to arsenic." *See* Overall Evaluation of Carcinogenicity: An Updating of IARC Monograph vol. 1-42 at 230-232 (1987). New evidence published since 1987 does not change this conclusion. To the contrary, additional evidence has emerged to confirm that confounding factors likely account for any excess cancers reported in epidemiological studies.

Most of the major epidemiological studies that have been conducted since the 1987 IARC Monograph have been summarized by Fu and Boffetta (1995) in a critical review that included a meta-analysis of case control and cohort studies. The review noted that modest elevations of cancer were evident at sites such as lung, stomach, bladder and kidney, but that most of the studies did not take into account potential confounders such as other occupational exposures, smoking, and dietary habits. Furthermore, without controlling for these confounding factors, a causal relationship between lead and the increased incidence of cancer could not be established.

Studies conducted since the Fu and Boffetta review have continued to display the same inconsistent and doubtful pattern of results that characterize earlier studies. In all, the significance of any observations linking exposure to lead with the increased incidence of cancer are extremely limited due to the probable influence of lifestyle confounders (*e.g.*, smoking, drinking alcohol, etc.) and/or the presence of other carcinogens in the workplace.

For these reasons the Agency for Toxic Substances and Disease Registry ("ATSDR") stated in the most recent update of the Toxicological Profile for Lead (1999) that the studies reporting an association between lead and cancer "are not sufficient to determine the carcinogenicity of lead in humans." *See* Toxicological Profile for Lead: Update 1999, Agency for Toxic Substances and Disease Registry, at 114. Indeed, two studies completed since 1997 strongly indicate that associations between lead and cancer are likely due to confounding.

The first study involved an analysis of mortality at a Swedish copper smelter with a small volume of lead production as a co-generation product. An earlier study by Lundstrom, et. al. (1997) had reported a dose-dependent relationship between indexes of cumulative lead exposure and the incidence of lung cancer for workers at the smelter. Upon further analysis of the mortality from lung cancer, it was discovered that a substantial proportion of the lung cancers reported in the Lundstrom study occurred in maintenance workers, builders and truck drivers who worked in all departments of the facility and hence had exposure to a number of other substances, such as arsenic and copper. Given the exposure to these other substances, and the fact that a number of cancers reported earlier were not in lead smelter workers, the authors of the Lundstrom study now caution that it cannot be used to support a causal relationship between lead exposure and the increased incidence of lung cancer.

The second study by Wong and Harris involved an update of a large cancer mortality study of employees in battery production plants and lead smelters in the United States. The study reports a deficit of kidney cancer and a statistically significant deficit in bladder cancer mortality. A disproportionate excess of stomach cancer was observed among foreign-born

workers from countries that have a higher rate of stomach cancer than is present in the United States. Thus, the excess stomach cancer is likely a product of confounding factors and not exposure to lead. Likewise, a small increase in lung cancer was observed on the order of that expected to be found in databases (such as the earlier study) that did not correct for confounding by smoking. Moreover, the risk of lung cancer was found to increase as workers' overall exposure to lead decreased. Thus, the failure of lung cancer incidence to correlate with exposure duration or intensity strongly suggests that it is not causally related to lead.

Given the failure of existing epidemiological studies to control for confounders such as exposure to other carcinogenic compounds and to correlate increased lead exposures to the increased incidence of cancer, a causal relationship between lead exposure and an increased cancer risk cannot be established.

CONCLUSION

For the foregoing reasons, the nomination of lead and its compounds to be designated as *known human carcinogens* should be rejected. If you have any questions on these comments, please do not hesitate to call me at (414) 228-2745 or BCI's Washington Counsel, Edward L. Ferguson, at (202) 383-6930.

Sincerely,

Timothy J. Lafond
Chairman,
BCI Environmental Committee

References

1. Fu, H. and Boffetta, P. (1995). Cancer and Occupational Exposure to Inorganic Lead Compounds: A Meta-Analysis of Published Data. Occup. Environ. Med. 52: 73-81.

2. Gerhardsson, L., Hagmar, L., Rylander, L., Skerfving, S. (1995). Mortality and Cancer Incidence Among Secondary Lead Smelter Workers. Occup. Environ. Med. 52: 667-672.

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4. International Agency for Research on Cancer, Overall Evaluation of Carcinogenicity: An Updating of IARC Monograph vol. 1–42. IARC Monograph Eval Carcinog Risks Hum.; update, 1-42: 230-232 (1987).

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6. Wong, O. and Harris, F. *(in press)*. Cancer Mortality Study of Employees at Lead Battery Plants and Lead.

7. Agency for Toxic Substances and Disease Registry, Toxicological Profile for Lead; Update (1999).