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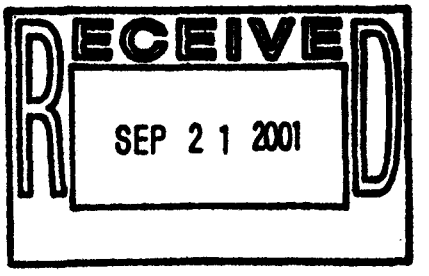

Dr. C.W. Jameson
National Toxicology Program
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

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

Dear Dr. Jameson:

These comments are submitted on behalf of the Battery Council International[1] (BCI) in response to the National Toxicology Program's (NTP) call for public comments on 16 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Eleventh Edition 66 Fed. Reg. 38430 (Jul. 24, 2001).

INTRODUCTION

Epidemiological studies performed to date on occupationally exposed groups are not sufficient to establish the carcinogenicity of lead in humans. This is because studies showing a positive correlation between lead and cancer have not evaluated the actual compound(s) of lead, route(s) of exposure, and levels of lead to which workers have been exposed. Nor have these studies controlled for potential confounding (e.g., exposure to arsenic, drinking alcohol and smoking). Indeed the few epidemiological studies that have examined potential confounding have not shown an association between lead and cancer. As a result, the NPT's nomination of occupational exposure to lead and its compounds as known human carcinogens cannot be supported.

[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 battery manufacturing capacity and more than 89% of the nation's lead battery recycling or secondary smelting capacity

COMMENTS

1. There is Insufficient Evidence of Carcinogenicity from Epidemiological Studies of Humans in Occupational Settings to Justify the Elevation of Lead and its Compounds to the Designation of Known Human Carcinogens

According to the NTP, its decision to nominate occupational exposure to lead or lead compounds for inclusion in the 11th Report on Carcinogens is based upon recently published data that indicate an excess of cancers in workers exposed to lead. As I discuss further below, the latest findings from multiple studies do not support the NTP's suggestion that recent studies indicate occupational exposure to lead or its compounds pose excess cancer risk.[2]

In order for the NTP to designate occupational exposure to lead and its compounds as *known human carcinogens* 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." 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.[3] Most such studies find little in the way of an association between occupational exposure to lead and cancer. Those few studies purporting to report modest excesses generally do not document or report the actual compounds of lead to which exposure occurred or the routes or levels of exposure. Those studies that purportedly found an association between the increased incidence of cancer and lead

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

[3] BCI notes that studies with experimental animals appear to show that some lead compounds (lead acetate and phosphate) may be capable of inducing cancer in rodents. The overall pattern of tumor induction combined with a negative profile for genotoxicity of the male rat has led 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 follow 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 at best.

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.

exposure are further compromised by the fact that the subjects of those studies (exposed employees) were exposed to other chemicals, such as arsenic and/or regularly used tobacco products or alcohol (all designated by the NTP as *known human carcinogens*).

In 1987, the International Agency for Research on Cancer (IARC) evaluated lead as a human carcinogen and concluded that there was inadequate evidence of carcinogenicity in humans resulting from occupational exposures to lead – despite the fact that the IARC evaluated studies in which lead levels far exceeded 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." 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 likely accounts for any excess cancers reported in epidemiological studies.

Most of the major epidemiological studies 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 found limited evidence to support the hypothesis of a causal connection with lead exposure. Fu and Boffetta noted that most of the studies showing a positive correlation did not take into account potential confounding such as other occupational exposures, smoking and dietary habits. For example, the relative risk observed for lung cancer (RR 1.29) was comparable to that expected in studies lacking correction for confounding exposures to cigarette smoking.

The increased incidence of stomach cancer that was reported in some of the studies in the meta-analysis was noted by Fu and Boffetta to be inversely related to socio-economic status and to vary as a function of dietary and other lifestyle factors. The incidence of stomach cancer also was suspected to be associated with occupational exposures to other substances in the workplace.

In the case of bladder cancer, elevations of observed cancer appear likely to be the result of publication bias since only four of 14 studies reviewed presented results for bladder cancer. Given the known association between bladder cancer and cigarette smoking, lifestyle confounding in those four studies was judged probable by Fu and Boffetta. Finally, the study authors noted that a non-statistically significant increased risk of kidney cancer was evident in their meta-analysis. Based upon the relatively small number of tumors observed, Fu and Boffetta concluded, however, that the evidence was "still inadequate to either confirm or rule out an association between kidney cancer and exposure to lead."

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 confounding and/or the presence of other carcinogens in the workplace.

It is for this reason that the Agency for Toxic Substances and Disease Registry (ATSDR) stated in its 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." Toxicological Profile for Lead: Update 1999, Agency for Toxic Substances and Disease Registry, at 114.

Since the conduct of the Fu and Boffetta meta-analysis, data has become available from new studies and/or from updates of existing cohort mortality studies. These more recent studies indicate that there is little reason to suspect lead is a human carcinogen. A recent review of more recent studies by Steenland and Boffetta (2000) concludes that "[o]verall, there is only weak evidence associating lead with cancer." Indeed, these studies strongly suggest that the associations between lead and cancer are due to confounding.

For example, a study by Englyst et al (2001), which involved an analysis of excess mortality at a Swedish copper smelter with a small volume of lead production as a co-generation product, found that arsenic exposure, not lead exposure, was strongly associated with the development of lung cancer. An earlier study by Lundstrom, et al. (1997) had reported a relationship between lead exposure and the incidence of lung cancer. Upon further investigation 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. These workers had exposure to several substances other than lead, including arsenic, copper and diesel exhaust. In contrast to the earlier Lundstrom paper, which concluded that a dose-dependent correlation between lead and lung cancer was evident in this cohort, the more recent study concludes that "arsenic exposure, which occurred among these workers, is probably a main contributing factor to the development of lung cancer."

A case control study also has just been completed at this smelter. The study is not yet published, but does suggest a strong interaction between arsenic and cigarette smoking for the incidence of lung cancer in the lead cohort. A relationship between lead exposure and lung cancer was not found. These findings are presently in preparation for publication.

Another 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 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 was not causally related to lead.

Given the failure of existing epidemiological studies to control for confounding 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 occupational exposure to 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 (215) 619-7886 or BCI's Washington Counsel, Edward L. Ferguson, at (202) 383-6930.

Sincerely,

[redacted]

Timothy J. Lafond
Chairman,
BCI Environmental Committee