

**Utility Solid Waste Activities Group**

c/o Edison Electric Institute  
701 Pennsylvania Avenue, NW  
Washington, DC 20004-2696  
202-508-5645  
www.uswag.org

U S W A G

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**BY FACSIMILE AND ELECTRONIC MAIL**

Dr. C.W. Jameson  
Department of Health and Human Services  
Public Health Service  
National Toxicology Program  
Report on Carcinogens  
MD EC-14  
P.O. Box 12233  
Research Triangle Park, NC 27709

Re: Comments on the Proposed Listing of Lead and Lead Compounds in  
NTP's Eleventh Edition of the Report on Carcinogens

Dear Dr. Jameson:

The Utility Solid Waste Activities Group ("USWAG")<sup>1</sup> provides this response to the National Toxicology Program's ("NTP") request for public comment on the proposed nomination of lead and lead compounds for listing in the *Report of Carcinogens, Eleventh Edition* (the "ROC"). See NTP; Call for Public Comments on Seven Nominations Proposed for Listing in the Report on Carcinogens, Eleventh Edition, 68 Fed. Reg. 62825 (Nov. 6, 2003). For the reasons set forth below, USWAG urges NTP to withdraw its proposed listing of *all* lead and lead compounds as "reasonably anticipated human carcinogens." At a minimum, USWAG respectfully suggests that

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<sup>1</sup> USWAG is an informal consortium of the Edison Electric Institute ("EEI"), the American Public Power Association ("APPA"), the National Rural Electric Cooperative Association ("NRECA") and approximately 80 electric utility operating companies located throughout the country. EEI is the principal national association of investor-owned electric power and light companies. APPA is the national association of publicly-owned electric utilities. NRECA is the national association of rural electric cooperatives. Together, USWAG members represent more than 85 percent of the total electric generating capacity of the United States and service more than 95 percent of the nation's consumers of electricity.

NTP withdraw the broad proposal to categorically list *all* “lead and lead compounds” and instead, refine the proposed listing to target a specific subset of lead constituents for which NTP can demonstrate a reasonable basis for the ROC listing under the pre-established criteria.

As a general matter, USWAG disagrees with NTP’s proposal to classify *all* forms of lead and lead compounds as “reasonably anticipated human carcinogens.” NTP’s proposal violates established criteria for such a listing including, among other things, a showing of credible and sufficient evidence from human or animal studies. The data and analysis presented by NTP do not meet this fundamental showing and, therefore, cannot justify NTP’s wholesale identification of *all* lead and lead compounds as “reasonably anticipated human carcinogens.”

USWAG urges NTP to weigh the substantial and far-reaching implications of any decision to move forward with the listing of lead and lead compounds in its consideration of these comments (and the comments of other interested parties cited herein to which USWAG joins). Many key federal and state environmental regulations (*i.e.*, regulations governing solid and hazardous waste requirements, drinking water standards, and site remediation standards) impose risk-based standards that are subject to modification based on, among other things, information contained in NTP’s ROC. See, *e.g.*, ROC Background Document for Lead and Lead Compounds at A-3 and A-4 (May 8, 2003) (the “Background Document”). USWAG member companies operate hundreds of facilities around the country that perform waste management and site remediation activities that are subject to such risk-based regulations governing lead and lead compounds. A decision by NTP to move forward with this listing, in the absence of adequate science-based justification, threatens to complicate and raise the cost of regulatory compliance without adequate consideration of true public health risks and will serve to divert limited resources from other more significant occupational health and environmental issues.

**I. The NTP Has Failed To Demonstrate That Lead and Lead Compounds Are Reasonably Anticipated Human Carcinogens.**

**A. NTP’s Listing Criteria.**

NTP publishes the ROC pursuant to authority granted by Congress to the Secretary of Health and Human Services under Section 301(b)(4)(A) of the Public Health Services Act, 42 U.S.C. § 241(b)(4)(A). Under established ROC listing criteria, NTP can only list a substance or group of substances as a “reasonably anticipated human carcinogen(s)” if:

- there is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded;

- there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors: (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or
- there is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Annual or Biennial Report on Carcinogens as either a known to be human carcinogen, or reasonably anticipated to be human carcinogen or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

See NTP Revised Criteria for Listing Substances in the Biennial Report on Carcinogens, 61 Fed. Reg. 50499-50500 (Sept. 26, 1996) (the "NTP Listing Criteria").

## **B. The NTP Has Failed To Demonstrate That Lead and Lead Compounds Meet The NTP Listing Criteria.**

NTP's nomination of lead and lead compounds for listing in the ROC is overly broad and does not meet established ROC listing criteria. In particular, NTP has failed to adequately justify the proposed listing with (1) credible evidence from studies in humans that lead and lead compounds are carcinogens, (2) data from animal studies that provide sufficient evidence of carcinogenicity under specific NTP Listing Criteria, or with (3) a showing that lead and lead compounds belong to a well defined, structurally-related class of substances known or reasonably anticipated to be human carcinogens.

### **1. There Is No Credible Evidence That Lead and Lead Compounds Are Human Carcinogens.**

NTP's proposal to list lead and lead compounds as "reasonably anticipated human carcinogens" is based a series of flawed human studies which fail individually and collectively to provide credible evidence of human carcinogenicity. To the contrary, the studies relied on by NTP tend to confirm a lack of causal connection between lead exposure and cancer. In those few instances cited by NTP where statistical increases in cancer were noted, the data is accompanied with an acknowledgement of serious and fundamental flaws and limitations that preclude reliance on the studies as a basis for an ROC listing decision.

For example, the key human studies cited by NTP in the Background Document fail to establish any dose-response relationship between exposure to lead compounds and cancer. See Comments of International Lead Zinc Research Organization (ILZRO) (Sept. 29, 2003, Sept. 24, 2001 and June 2, 2000). ILZRO's Comments detail how study after study relied on by NTP fail to establish an increase incidence of cancer with elevated levels of lead exposure in a variety of occupational exposure scenarios. See, e.g., ILZRO Comments documenting lack of exposure/dose response in the following

studies: Wong and Harris (2000), Antilla et al. (1995 and 1996), Gehardsson et al. (1995). In the rare instance that a dose-dependent relationship between lead exposure and cancer was suggested in a human study cited by NTP (*i.e.*, Lundstrom et al. (1997)), ILZRO correctly points out that more detailed follow-up investigations have since documented that the elevated cancer levels reported in Lundstrom et al. (1997) were in fact attributed to exposure to other known carcinogens, not lead. ILZRO Comments pp. 4-5 (Sept. 29, 2003) *citing* Englyst et al. (2001).

The human studies cited by NTP in support of its listing proposal contain other serious weaknesses, including a failure to support questionable assertions of lead uptake (Stauber et al. (1994)) and consistently inadequate documentation of facts relied on to establish subject exposure histories (Antilla et al. (1995), Cocco et al. (1999), and Lundstrom et al. (1997), Selevan et al. (1985) and Wong and Harris (2000)). See, *e.g.*, ILZRO Comments pp. 4-9 (Sept. 29, 2003) and pp. 3-6 (Sept. 24, 2001). Most, troubling, however, is the consistent failure of the studies to account in any meaningful way for overriding confounding factors such as smoking, and significant, documented occupational exposure of study subjects to other known carcinogens. See, *e.g.*, ILZRO Comments pp. 4-8 (Sept. 29, 2003) and pp. 4-6 (Sept. 24, 2001) (documenting serious confounding factors in Lundstrom et al. (1997), Wong and Harris (2000), Lustberg and Silbergeld (2002), and Englyst et al (2001)).<sup>2</sup>

The substantial cumulative weaknesses documented in the underlying data compiled by NTP on lead and lead compounds go far beyond a mere suggestion of alternative causation. The weaknesses in the human studies call into question the veracity of the underlying data relied on by NTP. These concerns were raised by several members of the NTP ROC Subcommittee at the meeting on October 14, 2003 in Washington D.C. One member of the Subcommittee stated that human studies cited by NTP had “overwhelming weaknesses” and called into question NTP’s conclusions in the Background Document. This member concluded that evidence of carcinogenicity was either not present or possibly so weak so as to be undetectable in studies. Two other Subcommittee members agreed that epidemiological evidence was “unconvincing” and that it was speculative at best to apply animal study findings for lead acetate and lead phosphate to all lead compounds. In voting to approve the listing, however, the Subcommittee never resolved these important concerns.

USWAG respectfully submits that it is improper for NTP to move forward with such a broad a listing decision when, as here, the underlying data are consistently flawed with uncertainties, limitations and confounding factors. In summary, the

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<sup>2</sup> Likewise, the data generated by these and other studies also cast doubt on the meta-analysis of these studies performed by Fu and Boffetta (1995) and Streenland and Boffetta (2000), which are also cited by NTP. The qualified findings in the meta-analysis studies speak to the unreliable nature of the underlying data. See, *e.g.*, Background Document at 67-68 (recognizing that the underlying studies fail to provide sufficient evidence for assessment of exposure-response relationships and that the confounding factor of smoking alone “dwarfs that which could be expected from lead exposure based on available evidence”).

underlying data fail to meet the NTP Listing Criteria for “credible” evidence of human carcinogenicity caused by exposure to lead and lead compounds.

2. Data From Animal Studies Do Not Support The Proposed Listing Of Lead and Lead Compounds Under NTP Listing Criteria

In 1981, NTP listed two individual lead compounds (lead acetate and lead phosphate) as “reasonably anticipated human carcinogens.” These listings were based on animal studies that found increased incidence of tumors in the kidney’s of rodents exposed to lead acetate and lead phosphates. See Summary of Animal Studies in NTP Background Document at pp. 103-113. However, the rodent studies which formed the basis for NTP’s prior listing of these two compounds do not provide an adequate basis under established criteria for listing *all* lead and lead compounds in the ROC. In particular, the lead acetate and lead phosphate rodent studies (or any other animal study cited by NTP) fail to demonstrate the requisite “combination of malignant and benign tumors (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset.

In the Background Document, NTP concedes that, while studies involving lead acetate and lead phosphate show evidence of carcinogenicity in rat kidneys, “other lead compounds have not been associated with carcinogenicity in rats.” Background Document at p. 113. Moreover, the pattern of tumor induction in rats exposed to lead acetate and lead phosphate in these studies combined with a largely negative profile for genotoxicity has cast serious doubt over the relevance of these rodent studies to humans. See ILZRO Comments p. 1 (Sept. 29, 2003) *citing* Goyer, R. (1993).

Moreover, NTP has not presented evidence of any additional animal studies (beyond the rat studies cited as a basis for the previous listing of lead acetate and lead phosphate) that demonstrate an increased incidence of malignant or a combination of malignant and benign tumors in multiple species or at multiple tissue sites, or by multiple routes of exposure, or to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Accordingly, under NTP Listing Criteria, animal studies do not support NTP’s proposed listing of *all* lead and lead compounds in the ROC as “reasonably anticipated human carcinogens.”

3. Lead and Lead Compounds Do Not Belong To Any Well Defined, Structurally-Related Class Of Substances Known Or Reasonably Anticipated To Be Human Carcinogens.

NTP’s Background Document does not assert that lead and lead compounds belong to a “structurally-related class of substances known or reasonably anticipated to be human carcinogens.” To the contrary, the chemical description of lead compounds in the Background Document recognizes the many different chemical forms and properties of lead compounds. See Background Document at pp. 2-16. The physical and chemical properties of lead compounds (*e.g.*, solubility, reactivity) differ greatly from compound to compound which, in turn, results in significant differences in the

bioavailability and other pharmacokinetic properties among various forms of lead constituents. *Id.* NTP has failed to produce evidence that the limited animal and human studies presented in the Background Document (that involve exposure to limited forms of lead compounds via primarily inhalation and ingestion) provide a valid basis for listing *all* lead compounds, in all exposure scenarios, as anticipated carcinogens. Therefore, NTP cannot assert that lead compounds belong to a well defined structurally-related class of chemicals known to cause cancer.

The significantly different chemical properties among the wide range of lead compounds is one of the compelling reasons for NTP to withdraw or modify its proposed blanket listing of *all* lead and lead compounds. The substantial differences in the mobility and bioavailability of lead and the wide variety of potential exposure scenarios demand a more precise treatment of public health risks by NTP. See, *e.g.*, ILZRO Comments at pp. 1-2 (Sept. 29, 2003) (many forms of leads have been shown to have very limited bioavailability) *citing* Cotter-Howells and Thornton (1991) and Maskall et al. (1995).

### **CONCLUSION**

For the reasons discussed above, and for the reasons set forth in the comments of the other interested parties cited herein, USWAG respectfully urges NTP to withdraw its nomination of *all* lead and lead compounds for listing in the ROC as “reasonably anticipated human carcinogens.” At a minimum, USWAG requests that NTP step back from the broad categorical listing of *all* “lead and lead compounds” and instead, adopt a more precise, targeted approach in developing its listing proposal. NTP should limit the listing to a narrowly-defined subset of lead constituents for which NTP can clearly demonstrate a reasonable basis for each constituent under the established criteria.

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If USWAG can be of further assistance to EPA in this effort or can respond to any questions, please contact the USWAG Executive Director, James Roewer (202-508-5645) (jim.roewer@uswag.org).

Very truly yours,

Signature

Joseph E. Shefchek  
Chairman, Utility Solid Waste Activities Group