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Dr. Mary S. Wolfe
Executive Secretary
RoC Subcommittee
National Toxicology Program
P.O. Box 12233
A3-07
Research Triangle Park, NC 27709

RE: COMMENTS CONCERNING THE REPORT ON CARCINOGENS BACKGROUND DOCUMENT FOR LEAD AND LEAD COMPOUNDS

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Dear Dr. Wolfe:

Ethyl Corporation, a manufacturer of lubricant and fuel additives and a supplier of the gasoline lead additive, tetraethyl lead, welcomes the opportunity to comment on the "Lead and Lead Compounds" report [hereafter the "Report"]. Accurate and appropriate classification of chemical compounds, metals, and biological agents as carcinogens is a valuable informational tool that protects public health and makes the workplace environment safer. Inappropriate classification diverts attention and resources from meaningful public and occupational health issues to ones of less significance. Thus an inappropriate classification is counterproductive to the National Toxicology Program's

goal and worse creates confusion about what exposures constitute a real threat of causing cancer. In the case of lead and lead compounds, the Report concluded:

> *The evidence is consistent with the hypothesis that lead is modestly carcinogenic to humans. This evidence is strongest for lung cancer, for which a largely consistent association has been demonstrated with occupations and industries entailing lead exposure, as well as with indices of individual lead exposure, including job history and biological monitoring. Evidence also suggests an association between lead and stomach cancer. However, the observed associations generally are sufficiently weak that they could be due at least partially to confounding ...* [Report p. 75 (emphasis added)]

"Largely consistent association," "suggests an association," and "associations are weak" – caveat and qualification, cloak the anemic conclusion "that lead is modestly carcinogenic to humans." What is a "modest" carcinogen? The criteria for listing agents that appears on p. xi defines "Known to be Human Carcinogens" and "Reasonably Anticipated to be Human Carcinogens," but "modest" does not appear among the definitions. If the authors of the Report must so equivocate in their conclusion, then the underlying evidence must at best be ambiguous. **Uncertainties, confounding, and cohort limitations associated with the reviewed studies do not provide a sound scientific basis for listing lead and lead compounds as either "known" or "reasonably anticipated" human carcinogens. In 1987 the International Agency for Research and Cancer (IARC) listed lead as possibly carcinogenic to humans. The Report offered no compelling results or data to indicate going beyond the 1987 IARC finding.**

Uncertainties and limitations of the data regarding a lead–cancer connection are presented below. Highlighted first are issues with the human cancer studies followed by a discussion of the meta-analyses reports. In a final section, corrections to factual errors regarding tetraethyl lead are offered.

Human Cancer Studies

- **Co-exposure to known carcinogens may explain any increased cancer incidence among workers.**

Table 3-1 provides a summary of human epidemiological studies of lead exposure. Twenty of the 37 studies listed in the table involve an occupational cohort, where exposures to various carcinogenic agents may occur. Smelter and battery workers in particular are exposed to nickel and arsenic, as well as lead. The discussion in the Report does highlight difficulties in assessing co-chemical exposures and notes that results are scattered. In some studies elevated respiratory cancers are reported. In others no elevation was found or inconsistent trends were reported. Conclusions from two studies listed in the table highlight the problem of co-exposure to known carcinogens.

Lundstrom in a study of primary smelter workers concluded:

> *The increased risks were probably due to interactions between lead and other carcinogenic exposures, including arsenic. Further study is required concerning such possible interactions before a role in the induction of lung cancer can be ascribed to lead.* [Lundstrom et al, "Cumulative Lead Exposure in Relation to Mortality and Lung Cancer Morbidity in a Cohort of Primary Smelter Workers," Scand J Work Environ Health 1997, 23(1) 24-30.]

Anttila in a study of 20,700 workers "suggested" that exposure to "engine exhaust" might also have a role in cancer risk.

> *The results suggest that exposure to lead increases the risk of lung cancer. Co-exposure to engine exhaust and lead may be associated with the risk.* [Anttila et al, "Excess Lung Cancer Among Workers Exposed to Lead," Scan J Work Environ Health 1995, 21, 460-469.]

Note: the data were not sufficiently robust to allow Anttila to conclude lead was a carcinogen, but to rather suggest it was, and then a co-exposure was cited to further explain the risk.

- **No increased risk of lung or stomach cancer was found in a study of smelter workers.**

  A study of 1,388 smelter workers by Cocco reported the following conclusion:

  > *No excess risk of stomach cancer and lung cancer was observed in this cohort.* [Cocco et al, "Mortality of Italian Lead Smelter Workers," Scand J Work Environ Health 1997, 23, 15-23.]

- **An overview of selected studies cited in the Report highlight the lack of consistent data to support classification of lead and lead compounds as human carcinogens.**

  Mixed outcomes regarding cancer were reported for glassworkers and co-exposure to other metals and lack of control for smoking and diet were noted. [The Report, p. 53]

Studies of miners were confounded with the probability of exposure to dusts and radon in addition to lead. Overall, no significant increase in the incidence of cancer was reported, but a significant increase in liver cancer was reported. [The Report, p 53]

Studies on mixed workers in Finland reported a slight increase in respiratory and lung cancer, when the moderate lead exposed group was compared to the low exposure group. Surprisingly, the high exposure group showed a lower cancer incidence, implying a protective role for lead exposure! The hypothesis offered to explain this odd result was that cumulative lead exposure rather than peak lead exposure is the controlling factor in cancer incidence. Average duration of exposure for the moderate lead exposure group was 22.3 years and 19.3 years for the highest lead exposed group. Three years difference between the two groups, who each had two decades of exposure, does not appear meaningful. [The Report, p. 54]

The above results serve to highlight the ambiguities associated with lead studies and emphasize the uncertainty associated with using these studies to classify lead as a human carcinogen. In fact, the state of the evidence is far more consistent with a classification of lead, as it is presently categorized, as a possible human carcinogen, rather than a known human carcinogen.

Meta-analyses of Lead Studies

The risk of lung cancer due to cigarette smoking dwarfs that which could be expected from lead exposure based on any available evidence. [The Report, p. 67]

The above quote was taken from a section of the paper discussing shortcomings of the lead studies used in meta-analyses. Confounding due to smoking, co-exposure to other carcinogens, insufficient data to determine an exposure-response relationship, and variability among the studies in controlling for other potential cancer risk factors are among the challenges to be overcome in obtaining meaningful and defensible results in reviewing this body of evidence. On pages 67-69, the Report discusses the strength of the association between lead exposure and lung cancer. The discussion of weaknesses and strengths accentuates the ambiguity of the data used to classify lead and lead compounds as "modestly" carcinogenic to humans. Missing from this discussion of lead is the clarity associated with the statement regarding cigarettes and cancer – the cancer risk from smoking "dwarfs" any risk from lead. Even in the meta-analyses, confounders are present and associations are weak and the classification of lead as even a "modest" human carcinogen is justified by lengthy explanations rather than a clearness, in contrast to the case with cigarettes. With evidence this inconclusive, the Report's findings should be reconsidered and reclassification deferred until and unless stronger support is available.

Corrections to Factual Errors Regarding Tetraethyl Lead

Page 2 of the Report states that lead emissions from gasoline additive is historically "the" primary source of lead in environment. Emissions from gasoline lead

are one of the anthropogenic sources of lead in the environment along with lead paint pigments, uncontrolled emissions from primary and secondary smelters, combustion of coal and oil for home heating, lead pipes and other lead construction products, lead wheel weights, lead plasticizing agents, and a host of other historical lead containing products and uses. These are a few of the anthropogenic sources and, of course, lead occurs naturally in soil and thus crustal weathering is a source of human exposure to lead.

Page 3 states that tetramethyl lead (TML) is used for aviation gasoline and racecar fuel. To our knowledge, TML is no longer manufactured anywhere in the world.

Page 30 states that "organic lead compounds continue to be present or actively deposited in the soil." Correction and context are needed here. First, regarding any meaningful human or ecological exposure, organic lead compounds are not present in the U.S. atmosphere. The combustion products, namely inorganic lead, are exhausted from propeller-driven aircraft that are fueled by gasoline containing tetraethyl lead (TEL). TEL remains the best option for achieving the octane required for taking-off and landing safely. Second, this application represents a very narrow and limited use and any inorganic lead fall-out from it, as demonstrated by decades of lead in air data, is making no significant contribution to soil lead levels.

On page 32, the now very dated NHANES II chart showing the relationship between leaded gasoline and blood lead levels is presented. The authors are remiss in not

citing a few of the numerous publications from the 1990's showing a continuing decline in blood lead levels – long since the peak of leaded gasoline usage in the U.S. The continuing decline in blood lead levels points to other exposure sources than leaded gasoline alone.

Ethyl Corporation thanks the subcommittee for the opportunity to comment and again states our key position that:

Uncertainties, confounding, and cohort limitations associated with the reviewed studies do not provide a sound scientific basis for listing lead and lead compounds as either "known" or "reasonably anticipated" human carcinogens. In 1987 the International Agency for Research and Cancer (IARC) listed lead as <u>possibly</u> carcinogenic to humans. The Report offered no compelling results or data to indicate going beyond the 1987 IARC finding.

Sincerely,

Jerry M. Roper

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