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Report of The Joint Study Group on Lead

Review of Lead Carcinogenicity And EPA Scientific Policy on Lead

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

EPA-SAB-EHC-90-001

November 21, 1989

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W. 20460

Subject: Science Advisory Board's Review of the Office of Research and Development's (ORD) Draft Assessment Document "Review of the Carcinogenic Potential of Lead Associated With Oral Exposure," (OHEA-C267, July 1988)

Dear Mr. Reilly:

At its November 10, 1988 meeting, the Science Advisory Board (SAB) Executive Committee discussed an inquiry members had received from representatives of the Lead Industries Association, Inc. regarding the proposed classification of lead and lead compounds as "B2" carcinogens in a draft assessment document noted above. The B2 designation identifies a substance as a probable human carcinogen, a term of art generally indicating the presence of sufficient evidence of animal carcinogenicity, and inadequate evidence of human carcinogenicity.

As a result of its discussion, the Executive Committee requested from then EPA Administrator Thomas the opportunity to review the basis for the B2 classification of lead, as well as to examine related issues concerning the Agency's scientific position on lead and lead compounds. An ad hoc Joint Study Group was created, including members of the Executive Committee, the SAB Environmental Health Committee, and the Clean Air Scientific Advisory Committee. Meetings were held in Washington, D.C. on March 31, 1989, and Research Triangle Park, N.C. on April 27 and 28, 1989.

After extensive review, the Study Group agrees with the proposed B2 classification for lead and lead compounds, primarily on the basis of the animal tumor data summarized in the assessment document. It must be stressed however, that given the limited state of our understanding of the mechanisms of lead-induced tumorigenesis and the data gaps involved, and considering the use of high levels of exposure in the critical studies, the B2 classification is not considered to provide a sufficient basis for quantitative risk assessment.

The Study Group also reviewed the manner in which scientific data on lead were utilized by the research, air, and drinking water programs; information from other EPA units was not available. The Group found a generally sound, but not fully consistent, approach for the three program areas noted, but there were some significant issues---target blood lead levels and definition of populations at risk, among others---in which differences were noted. The Study Group recommends that EPA develop a national policy on blood lead level reductions (particularly for children), and that EPA should address environmental exposure to lead on the basis of preventing adverse neurological effects in children. Basing regulatory strategy on the observable neurobehavioral effects in a sensitive human population can avoid problems of rodent-to-man and high-dose-to-environmentally realistic level extrapolations; this approach appears likely to provide an acceptable degree of protection against other adverse effects in the entire population.

Lastly, the Study Group urges the Administrator to undertake positive action to assure the uniform application of scientific data on lead to regulatory decisions by all organizations within the Agency. The mechanisms to accomplish this are beyond the purview of the Joint Study Group, but we regard it as a highly important goal if the Agency is to make sound and consistent decisions concerning lead in the environment.

We appreciate the opportunity to carry out this review, and look forward to your response.

Sincerely,

Raymond C. Loehr

Dr. Raymond C. Loehr, Chairman
Executive Committee
Science Advisory Board

Arthur Upton

Dr. Arthur Upton, Chairman
Joint Study Group on Lead

U. S. ENVIRONMENTAL PROTECTION AGENCY

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ABSTRACT

This report presents the conclusions and recommendations of the U.S. Environmental Protection Agency's Science Advisory Board summarizing a review of the Office of Research and Development's Draft Assessment Document "Review of the Carcinogenetic Potential of Lead Associated With Oral Exposure." The Board's major conclusion is that the proposed B2 classification is appropriate, but that there is not sufficient basis for a quantitative risk assessment. The Board recommends that EPA establish a national blood lead policy, create internal mechanisms to assure that all organizations within the Agency deal with lead-related scientific issues in a sound and consistent manner, and that regulatory strategy be based upon preventing lead-induced neurological in children--a sensitive population.

Key Words: Lead; carcinogenetic; B2; blood lead levels; tumorigenesis.

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1.0 EXECUTIVE SUMMARY

At its November 10, 1988 meeting, the Science Advisory Board (SAB) Executive Committee discussed an inquiry members had received from representatives of the Lead Industries Association, Inc., regarding the proposed classification of lead and lead compounds as "B2" carcinogens in a draft assessment document (Review of the Carcinogenic Potential of Lead Associated With Oral Exposure, OHEA-C267, July 1988) produced by the Office of Research and Development's (ORD) Office of Health and Environmental Assessment (OHEA). The B2 designation identifies a substance as a probable human carcinogen, a term of art generally indicating the presence of sufficient evidence of animal carcinogenicity, and inadequate evidence of human carcinogenicity.

As a result of its discussion, the Executive Committee moved to request from the EPA Administrator the opportunity to review the basis for the B2 classification of lead. It also recommended that the review take into consideration related issues concerning the Agency's scientific position on lead and lead compounds. Since many of the same issues were already being addressed by the Office of Air Quality and Standards (OAQPS), the latter Office requested that the SAB postpone its review of the OAQPS position on lead until after the Board had resolved the carcinogenicity question. An ad hoc Joint Study Group was created, including members of the Executive Committee, the SAB Environmental Health Committee, and the Clean Air Scientific Advisory Committee. Meetings were held in Washington, D.C. on March 31, 1989, and Research Triangle Park, N.C. on April 27 and 28, 1989.

As a result of its review, the Study Group supports the proposed B2 classification for lead and lead compounds, primarily on the basis of the animal tumor data summarized in the review document. Although there are some uncertainties and anomalies in the interspecies data, the high incidence of kidney tumors resulting from large cumulative doses of lead in rats and mice of both sexes in many independent experiments provides "sufficient" evidence of the carcinogenicity of lead in laboratory animals. In addition, it is appropriate to conclude that lead is genotoxic, although we do not have a full understanding of how this property may relate to its tumorigenic effect. It is also noteworthy that the available epidemiological data are inadequate for evaluating the potential carcinogenicity of lead.

It must be stressed moreover, that given the unknowns noted above, and considering the very high levels of exposure in the critical studies, the B2 classification may not provide a sufficient basis for quantitative risk assessment.

This report also provides a detailed analysis of issues

raised by the OHEA document, as well as recommendations for further improvements. The Study Group also reviewed the manner in which scientific data on lead were utilized by the research, air, and drinking water programs: information on other EPA units was not available. The Group found a generally sound, but less than fully consistent, approach for the three program areas noted, i.e., there were some significant issues--target blood lead levels and definition of populations at risk, among others--in which differences were noted. These issues are addressed in detail below.

The Study Group recommends that EPA develop a national policy on blood lead level reductions (particularly for children), and that EPA should address environmental exposure to lead on the basis of preventing adverse neurological effects in children. Basing regulatory strategy on preventing the observable, well documented neurobehavioral effects in a sensitive human population does not raise the unresolved methodological problems of rodent-to-man and high-dose-to-environmentally realistic level extrapolations; this approach can also be expected to provide an acceptable degree of protection against other adverse effects in the entire population. In order to achieve these policy goals, the Agency should conduct further research to obtain mass-balance data on lead in the environment and its fluxes to routes of exposure to the human population.

Lastly, the Study Group urges the Administrator to undertake positive action to assure the uniform application of scientific data on lead to regulatory decisions by all organizations within the Agency. The mechanisms to accomplish this are beyond the purview of the Joint Study Group, but we regard it as an highly important goal if the Agency is to make sound and consistent decisions concerning lead in the environment.

2.0 APPROACH

To accomplish the desired review, the Executive Committee recommended the formation of a Joint Study Group on Lead, the members of which would be drawn from the Executive Committee, the Clean Air Scientific Advisory Committee (CASAC), the SAB Environmental Health Committee, and other sources of expertise, as appropriate.

The charge to the Joint Study Group directed it to:

> ".... perform a 'broad spectrum' review of lead-related health effects and exposure issues which cut across EPA organizational lines. To accomplish this, the Group will assess the scientific information concerning lead now available to the Agency, and determine if it is being applied in a sound and consistent manner to

standard setting and other regulatory decisions throughout the Agency."

Specifically, the Joint Study Group was requested to review:

1. The weight of evidence classification of lead and lead compounds as carcinogens, as discussed in the ORD Office of Health and Environmental Assessment document entitled 'Evaluation of the Potential Carcinogenicity of Lead And Lead Compounds

2. The Supplement to the 1986 Addendum to the 1986 Air Quality Criteria Document for Lead, and the document entitled 'Review of The National Ambient Air Quality Standards for Lead: Assessment of Specific And Technical Information' (OAQPS draft staff paper)

3. The consistency of the proposed regulations for lead in drinking water with previously reviewed and approved data, studies, and analyses.

4. Other relevant issues which may be identified by the Joint Study Group, CASAC, or the SAB Executive Committee.

The Joint Study Group met twice--first on March 30, 1989 with the primary purpose of reviewing the OHEA document on carcinogenicity; and again on April 27-28, 1989, sitting jointly with the CASAC, to address the broader aspects of the Executive Committee charge.

3.0 REVIEW OF THE WEIGHT OF EVIDENCE CLASSIFICATION AS A B2 CARCINOGEN

With the availability in March, 1989, of an updated document from OHEA on the carcinogenicity of lead and lead compounds, the Joint Study Group met in Washington, D.C. on March 31 to review the weight of evidence classification of the carcinogenicity of lead.

After detailed briefings from Staff Officials of the ORD, comment from a representative of the Lead Industries Association and extensive discussions, the Study Group broke into subgroups to focus on specific aspects of the relevant issues--animal toxicity data, epidemiology, potency, and mechanisms of lead carcinogenicity. Subsequently, the Study Group met again in plenary session, at which time there was further discussion of each issue, with detailed suggestions to Agency staff for improvement of the document.

The most significant suggestions for improvement related to the interpretation of certain critical studies, the omission

few relevant publications, and the failure to exploit the available human data for deriving upper bound estimates of carcinogenic potency. These issues not withstanding, the consensus of the Study Group was that the main conclusion of the document--i.e., that the weight of evidence was sufficient to support a B2 classification for the carcinogenicity of lead -- is correct.

3.1 DETAILED FINDINGS

3.1.1 Animal Tumor Data. In more than 20 separate studies, lead acetate or lead subacetate administered chronically at relatively high concentrations in the diet has been observed to cause an elevated incidence of kidney tumors in rats and mice. In a few experiments, the repeated administration of lead phosphate by intraperitoneal injection, subcutaneous injection, or skin painting also has been observed to cause comparable tumorigenic effects in mice and rats. On the other hand, experiments in which lead acetate or other lead compounds have been administered similarly to hamsters, rabbits, monkeys, and dogs have not demonstrated tumorigenic effects in these species, but the results are inconclusive in view of the small numbers of animals exposed and/or the limited duration of exposure and/or follow-up.

The animal studies are definitive in demonstrating the carcinogenicity of soluble lead salts at relatively high dose levels for rodents. However, most of the studies were conducted more than 10 years ago. In the large majority of these studies, the group sizes were small, and the majority of the results were under-reported in respect to the strain of animal used, the survival of test and control groups, and the presence or absence of competing risks. Also, the absence of age-adjusted analyses complicates the interpretation of non-renal tumors (such as gliomas or reticulum cell sarcomas).

Partially unresolved questions include: (1) tumorigenicity of lead for species other than the rat and the mouse; (2) the forms of lead that produce renal tumors (lead itself and organic lead compounds have not been studied adequately); (3) the effectiveness of the inhalation route of exposure, which has not been studied as yet in animals; (4) the susceptibility of prenatal and postnatal age groups, which have not been studied adequately; (5) the possible effects of dietary variations; and (6) the kinetics of turnover of lead in trabecular and cortical bone.

In addition to the above points, it also should be emphasized that we currently do not understand the mechanism of kidney tumor induction by lead, nor, despite the caveats above, can we explain the general absence of such tumors at lower levels of exposure --albeit levels which are several times higher than

humans are typically exposed to in the environment. Consequently, it is not clear how one would extrapolate the observed effects in rats to estimate the carcinogenetic effects of low-level exposures to humans.

Also noteworthy is the fact that the renal tubular carcinomas associated with lead administration differ from those produced by other substances and associated with hyaline droplet formation (alpha 2u globulin-related). Rats and mice of both sexes are affected by lead, and focal droplet formation, cellular degeneration, and cast formation are not reported. The lead-related lesions differ, too, from those typically produced by analgesic drugs, which include papillary necrosis and tumors of the renal pelvis rather than of tubular epithelium.

In spite of the above uncertainties, the high incidence of kidney tumors resulting from (admittedly) large cumulative doses of lead in rats and mice of both sexes in many independent experiments provides "sufficient" evidence of the carcinogenicity of lead in laboratory animals. Thus the data justify the B2 classification of lead as a carcinogen but are limited with respect to support for a quantitative risk assessment.

3.1.2 Epidemiology. Results of the published human studies on lead fall short of satisfying even the "limited evidence" criteria for carcinogenicity. Relatively few epidemiological studies of quality have dealt with this ubiquitous and familiar agent. The Agency should make a major effort to support innovative studies of long-term outcomes of human exposure to lead. Such efforts should include population-based, as well as industry-based, studies and should be designed to assess environmentally distributed lead compounds in relation to cancer risks.

Most of the U.S. population was exposed to increasing concentrations of lead in air and food during the period 1925-1975, primarily owing to the use of lead in fuel additives; since then, the inputs of lead have diminished dramatically. During the same period, millions of workers have had significant occupational exposures. In addition, many thousands of children living in deteriorated housing ingested large quantities of lead, particularly from lead-based paints and high-lead content solder in the plumbing system, as well as from lead particulate matter associated with automobile traffic. Those surviving the acute effects retain elevated body burdens. As a result of these exposures, there is an extensive literature on blood lead levels in both occupationally exposed workers and children examined in community screening programs. Furthermore, there is an extensive data base on blood lead levels in the populations of selected U.S. cities since the 1950s, as well as a large population-based sample in the NHANES II (National Health and Nutrition Survey) study performed in the period 1976-1980. The latter extends

the time when the usage of lead in gasoline peaked to a time when it had since dropped by more than 75%. Because blood lead is a marker of lead intake, although not of the body burden--especially in population studies of on-going exposure--an analysis of kidney cancer trends during the past six decades in relation to changes in population mean blood lead levels might have some ability to show whether upper-bound estimates of carcinogenic potency extrapolated from animal bioassay data were realistic. Analyses of bone lead may increase the precision of dosimetry. Other points along the exposure-response continuum might also be established from those occupational cohorts for whom exposure histories were available. Such analyses would not be capable of determining whether kidney cancer was caused by lead, but might be capable of establishing an upper bound for plausible risk estimates. Thus, the data available in the open literature on blood lead in various populations could be analyzed for trends in relation to trends in kidney cancer incidence.

In addition, EPA should not reject out of hand the quantitative risk assessment approach based on animal data, although this approach involves many uncertain assumptions concerning species differences in lead adsorption and organ distribution, i.e., that people and rats have similar responses to comparable dose levels. It also assumes that high-level exposure can be extrapolated to low-level situations.

Other quantitative risk assessments have been made in the past, using rodent databases no better than, nor even as good as, the existing database for lead.

3.1.3 Potency. Assessment of the potency of lead as a potential human carcinogen involves a series of extrapolations, for which a number of methodologies can be used. The Agency has often selected the upper confidence bound of the linearized multi-stage model as the default model for potency estimations applicable to lower levels of potential risks. This default model assumes that there is no threshold to the response. The evidence that a threshold model would be more appropriate for lead is considered to be ambiguous by most of the Joint Study Group, but there is consensus that the linearized multi-stage model fails to take into account much relevant information, including pharmacokinetic data and measures such as time-to-tumor.

Ideally, the potency extrapolation model should employ best estimates of biologically available lead dose, based upon pharmacokinetic modeling. A question that may not be readily answerable at this time, however, is whether blood lead levels, kidney lead levels, cancer-related bone lead levels, or renal lead clearance rates would be the preferred measures of delivered dose. Nevertheless, the wealth of pharmacokinetic data on lead available from studies in humans and rats should be used, insofar

as possible, in defining the carcinogenic dose in rats and in making comparisons with humans. When possible, moreover, it would appear prudent to compare studies on the basis of mg/kg/day, i.e., the rate of exposure, rather than on the basis of total cumulative exposure, divided by an arbitrary net body weight and time for exposure. Physiologically-based pharmacokinetic models should be useful in such comparisons.

If the carcinogenicity of lead is assumed to be associated with the lead ion itself, the question of the comparative carcinogenic potency of the various inorganic lead salts should be addressed in relation to their respective bioavailability and delivered (internal) doses. Also, as pointed out in the OHEA document, appropriate allowances for age and nutritional status need to be included.

Although numerous physico-chemical properties of lead influence its biokinetics during absorption via the respiratory or gastro-intestinal routes, the anion to which lead is bound in the external environment does not necessarily remain associated with the ligand that transports it to the target organ. Divalent lead binds reversibly to various inorganic or organic ions, e.g. proteins, which transport it to target tissues. It is Pb^{++}, rather than the molecular complex in which it is found in the external environment, that is responsible for the toxic effects of lead. Since the mechanism through which lead acts as a carcinogen is not resolved, the way in which its biodistribution may influence its carcinogenicity remains to be determined.

Also, the ORD report needs to recognize more clearly that daily exposures are cumulative and, for humans, must be integrated over decades. This is particularly important because internal stores of lead can be mobilized and redistributed, for example, from bone to other target organs during pregnancy and lactation, or because of osteoporosis.

3.1.4 Mechanism of Lead Carcinogenicity. Although the animal data indicate lead to be carcinogenic, they raise a number of questions about the underlying mechanisms and their generality. The primary question, perhaps, is why the kidney is the most susceptible rodent target organ. Indeed, the bulk of the evidence implicating lead as a potential human carcinogen depends upon this site of action in rodent species. A subsidiary question that arises as a result is: do the tumors in rodents develop in part from systemic toxicity? Such a question is posed by the large doses typical of those causing tumors in the lead carcinogenicity studies. For example, 1% lead acetate in the diet corresponds to a dose as high as 800 mg/kg daily. This value contrasts markedly with the amount demonstrated to induce neurobehavioral effects -- a fraction of 1 mg/kg.

Unfortunately, lead tissue levels are typically absent fro-

the reports addressing carcinogenicity, so that comparisons are largely speculative, especially given the many variables determining bioavailability and toxicokinetics. The kidney, however, is one of the documented targets of lead toxicity. It remains to be determined, therefore, if renal damage, or impaired renal function is a necessary precursor to tumor expression. For example, kidney tumors might be postulated to arise from a combination of cellular damage and impaired function, leading ultimately to elevated lead concentrations in kidney tissue that might be sufficient to damage DNA. Reports on carcinogenicity have also largely ignored measures of heme synthesis, an important endpoint for lead toxicity. These processes could be related to tumor production.

Another potential contribution of systemic effects could also result from the joint consequences of lead kinetics and aging. With advanced age, bone mass declines, and lead previously stored in bone is released. Concurrently, nephrons are lost, so that advanced age may offer an especially sensitive period for systemic toxicity to be translated into tumorigenesis.

Although such proposed toxicological mechanisms are highly speculative, they help to emphasize the uncertainties in converting the available animal data into a coherent estimate of human hazard, and, finally, into human risk.

In addition, there is substantial evidence for the genotoxicity of lead. While the data do not provide a mechanistic understanding of carcinogenesis, they add weight to the assessment of lead as a potential carcinogen. The ORD document contains a discussion of genotoxic mechanisms; however it tends to over-emphasize relatively preliminary data on the induction of protein kinase C activity as a mechanism of lead carcinogenicity. Effects of lead added <u>in vitro</u> on the activity of this enzyme in endothelial cells may be relevant, but this is not yet known. It cannot be assumed that all inducers of the enzyme are carcinogenic--the enzyme is also implicated in neural transmission.

The discussion also omits two other possible mechanisms: the ability of lead at relatively high concentrations (mM) to cause breaks in DNA, and the potential displacement by Pb^{++} of Zn^{++} on so-called DNA finger loops (DNA-binding proteins which appear to regulate gene expression through their conformation-specific binding to specific genes, including some proto oncogenes).

Thus, while it is appropriate to conclude that lead is genotoxic[1], it is not presently known how this property may relate mechanistically to tumorigenesis in the kidney or any other organ. The data do not in themselves provide a scientific basis for any specific model for risk assessment, or for a judgment that lead is a promoter rather than an initiator of carcinogenesis.

4.0 REVIEW OF OTHER ASPECTS OF THE STUDY GROUP'S CHARGE

On April 27-28, 1989, the Study Group met jointly with the CASAC at Research Triangle Park, N.C. to address other issues driving from its charge--particularly those issues which cut across EPA organizational lines. On April 27, the Study Group participated in the CASAC discussion of two major lead-related documents ("Review of the National Ambient Air Quality Standards for Lead: Assessment of Scientific and Technical Information" (OAQPS Draft Staff Paper, March, 1989), and the ORD document, "Supplement to the 1986 EPA Air Quality Criteria for Lead-Volume 1 Addendum (pages A1-A67), March 1989), as identified in item (2) of the specific charge. On April 28, the CASAC and the Joint Study Group received briefings from representatives of EPA regulatory program offices (the Office of Toxic Substances (OTS) and the Office of Drinking Water (ODW)) and discussed issues of lead toxicity, exposure/risk, and cross-Agency consistency in technical approaches to lead regulatory questions, with particular attention to the ODW's recently proposed regulation on permissible lead levels.

Detailed discussion of each issue follows.

4.1 Review of ORD and OAQPS Documents The detailed findings and recommendations on these documents are contained in the CASAC Closure Letter (EPA-SAB-CASAC-90-002, November, 1989). It is relevant to note here however that the CASAC concurred with the general modeling framework presented in the OAQPS report and endorsed the use of the biokinetic model in children under six years of age, and the use of the disaggregate approach in adults. The CASAC cautioned that these modeling predictions were not valid for pregnant women and their fetuses due to a lack of information on this subpopulation. The use of the biokinetic model for metals other than lead was not recommended.

4.2 Lead Toxicity

4.2.1 Definition and Comparison of Different Adverse Effects Adverse effects of toxicants are typically scored by the intensity or severity of effects, or by the number of individuals

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[1]Zelikoff et al, "Genetic Toxicology of Lead Compounds" Carcinogenicity, Vol 9, pg 1727-1732, 1988.

affected. For example, it is customary to estimate the numbers of cases of cancer that may be induced in the population by a given exposure to a carcinogenic agent. With neurotoxicants, however, a different problem is posed; e.g., the health risks resulting from low-level exposure to lead are probably reflected most clearly by a shift in the distribution of IQ test scores. For example, a blood lead level of 10 µg/dl (compared, say to 3 µg/dl) may shift the mean intelligence test score by 5% (from a score of 100 to a score of 95); such a shift in a population of 100 million would reduce the number of individuals scoring above 130 from 2.3 million to 0.99 million, and, in parallel, would increase the number of individuals scoring below 70 correspondingly. Furthermore, everyone would be affected, so that the risk should be expressed in terms of a shift in the distribution of IQ scores in the population. Analyses based on the median underestimate the total impact.

Hence, it would be informative in comparing the risks of the two end-effects to estimate the percentage of children at the extremes of the distribution of intelligence test scores (below, say, 70 and above 130), who would be affected by the projected shifts in the mean. Such an approach would indicate consequences stemming from any specific choice of a targeted blood level. It would also avoid the use of such terms as "level of concern," which, to some readers, might imply support for a threshold even though no such position is proposed.

Similarly, the total public health impact of relatively small displacements of blood pressure levels by lead might also be expressed more clearly if stated in terms of shifts in distribution within the whole population.

4.2.2 Mechanisms and Dose-Response Models. The rich source of information that exists on the experimental neurotoxicity of lead is highly relevant in: (1) supporting the human studies remarkably well, providing confirmation of observations in the absence of the confounding variables inevitably present in human populations, and (2) providing the mechanistic basis for developing health-based goals for reducing toxicity.

Particularly relevant are the recent studies on neurobehavioral dysfunctions associated with low-dose lead exposure in primates.[2] Also relevant are recent mechanistic studies, based on inferences from neuroscience, on the critical events in neurogenesis within the late fetal and early neonatal periods, during which lead may have irreversible effects. Taken together, these experimental data are the basis for proposing

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[2] Rice, D. C. and Karpinski, K. F. "Lifetime Low-level Exposure Produces Deficits in Delayed Alternation in Monkeys," Neurotoxicol. Teratol., 10:207-214, 1988

that there is likely to be no threshold for lead neurotoxicity, at least within the contemporary range of blood lead levels (i.e., 1-10 µg/dl).

The use of mechanistic data in risk assessment is a long established practice for carcinogens. The mechanistic data on lead call for an approach in assessing neurobehavioral effects that goes beyond the customary practice of applying standard uncertainty factors to LOAELs (Lowest Observed Adverse Effects Level) or NOAELs (No Observed Adverse Effects Level) in developing a health-based goal for neurotoxins. Thus, mechanistic models for risk assessment deserve to be explored in this context.

4.3 Risk and Exposure

4.3.1 High-Risk Subpopulations. The most vulnerable populations may differ with respect to common sources of lead. With regard to exposure to lead in dust and drinking water during early life, for example, sensitive populations vary for several reasons. Mobility and normal hand-to-mouth activity make the 12-36 month old most sensitive to lead in dust. By contrast, water requirements are highest from birth to three months of age, primarily because of high growth rate, high metabolic rate, and age-dependent differences in renal function. Therefore, three months should be selected as the critical age for a drinking water lead standard. At the geriatric end of the age spectrum other considerations apply. For these reasons careful consideration of age differences must be given in assessing the risk of toxicity of lead from each source.

4.3.2 Exposure-Dose Relationships. The mother-fetal unit represents a particularly sensitive population; however, one should not focus exclusively on this population. There are data sets on fetal tissue that could be used to address this question, particularly the work reported by Barlthrop, et al[3]. In addition, research is now in progress on Australian populations near lead smelters which should provide some of the data that are needed.

The multi-media model should be of such a nature as to recognize that the age of the sensitive group may change with the medium. That is, water may be the most important route of exposure at three months; later on, dust. The amounts of time spent indoors and outdoors also vary greatly with age and should, therefore, be considered also.

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[3]Transfer of Lead to The Human Fetus, Barlthrop, D., Barland, L., Ed, in Mineral Metabolism In Pediatrics, pgs 135-151. Davis Publishing, Philadelphia PA, 1969.

speciation is important in distinguishing organic lead from inorganic lead and from metallic lead in terms of kinetics. It is suspected, however, that subspeciation within the inorganic group may not be relevant. The influence of particle size and absorption characteristics also must be considered, as well as the nature of the salt.

In further studies to correlate exposure with blood levels, efforts should be made to obtain as much information as possible regarding the exposure conditions, by whatever route(s), in order to define the relative source contributions more adequately.

4.4 Cross-Agency Consistency on Lead Exposures and Their Health Effects--OAQPS, ODW, And OHEA. The Study Group received a comprehensive briefing, as well as extensive background documentation, from the ORD Environmental Criteria And Assessment Office (ECAO) and OAQPS staff on issues relating to exposure by all routes, toxicokinetics, and health effects including neurobehavioral, developmental, cardiovascular, and carcinogenic effects. It also received a brief oral presentation on drinking water issues from ODW staff, and had an opportunity to ask questions about consistency and differences between the scientific and regulatory considerations affecting approaches to health protection used for ambient air and drinking water. By contrast, there was neither background documentation nor on-site representation from the offices dealing with lead in pesticides and toxic substances, solid waste, superfund, or emergency response. Thus, the extent of consistency and coordination among these offices and the air, drinking water, and research programs within the agency could not be determined fully. This was particularly unfortunate, since human exposures to lead from sources associated with the programs not reviewed may rise.

The following summary, while incomplete for the reasons stated above, indicates some important differences in the procedures followed by OHEA, OAQPS, and ODW.

4.4.1 Health Effects Data Used to Support Regulatory Actions. All three groups consider neurobehavioral effects in infants and young children to be the most important basis for regulatory action. OHEA and ODW give more prominence to potential carcinogenicity than OAQPS. On the other hand, OAQPS and ODW give consideration to cardiovascular effects, while OHEA did not. One cause for differences may lie in the data base utilized. It was also noted that many of the papers used by OHEA to support their analysis of carcinogenic potential would not meet the acceptance criteria for standard-setting for the NAAQS. All three agreed on the use of blood lead as an indicator of exposure and as a surrogate index of health effects.

4.4.2 Target Values for Blood Lead. Both OAQPS and ODW have identified 10-15 µg/dL as the area in which adverse health

effects have been observed. However, no threshold has been demonstrated.

4.4.3 Population at Risk. OAQPS, ODW and OHEA agree that children are the population of primary concern (for neurobehavioral effects). However, there appear to be some differences in the age range for primary concern.

4.4.4 Percentage of Population Exceeding Blood Lead Limits. ODW specifies protection of 95% of the population from exposure to lead in water > 20µg/L. The Study Group estimated that 20 µg/L would correspond to a blood lead level of 8 µg/dL in children with no other sources of lead exposure. OAQPS is considering a NAAQS in the range of 0.5 to 1.5 µg/m^3 maximum monthly average. A monthly NAAQS between 0.5 and 1.5 µg/m^3 would keep more than 99.9% of the non-pica children, living without lead-paint hazards near the Dallas and E. Helena smelters, below a blood lead level of 15 µg/dL, while a NAAQS of 0.5 µg/m^3 would protect 99.97% of affected children from reaching a blood lead of 15 µg/dL and keep 98.8-99.0% below 10 µg/dL (OAQPS Staff Paper p. IV-24), with most of the blood lead attributable to non-inhalation sources. An exact comparison is not possible, but clearly a NAAQS at or below 1.5 µg/m^3 is considerably more conservative than the proposed MCL for drinking water.

4.4.5 Exposure Models. The exposure model developed by OAQPS is being used by ODW and OHEA. What is not clear is how an acceptable total blood lead of 10 or 15 µg/dL is allocated to each source of exposure. For example, as lead dispersion from the operation of incinerators and from the leaching of landfills increases, will the allocations allowed for drinking water decrease? (Systematic evaluation of the distribution of blood lead levels by census tract might be useful in defining the contributions by various sources.) It is also not clear whether the models are being used in a uniform fashion. For example, are there differences in the coefficients for bioavailability? Other questions that need to be pursued further are the various programs approaches to sampling and analysis issues, statistical analyses, time-activity-patterns, dietary factors, etc.

4.4.6 Risk-reduction Strategies. It is recognized that different strategies are needed to reduce ambient air and drinking water exposures, and that the more site-specific exposures associated with waste disposal and transportation spills need still different approaches. The development of an Agency-wide risk reduction strategy for lead would benefit from a study of the cost-effectiveness of various means of reducing population blood lead levels.

5.0 RECOMMENDATIONS

The Study Group strongly recommends that EPA develop a

national policy on the reduction of blood lead levels in children specifically, and all people in general, since current general population blood lead levels are with the range in which adverse health effects have been observed. They are attributable to numerous sources and exposures by multiple routes, and are, for many people, within a range associated with demonstrated and substantial health effects. It is also strongly recommended that the Agency obtain mass-balance data on lead in environmental media and people for past, current, and future exposures. These data would provide information on source strengths, pathways, fluxes, bodily uptake and retention, etc., to guide the implementation of a cost-effective risk reduction strategy.

EPA should assess environmental exposure to lead in terms of the risk of adverse neurological effects in children. With this approach, no extrapolations from animal to man, or from extremely high to environmentally realistic exposure levels are required. Well documented neurobehavioral effects are observed in humans, and at exposure levels close to those of regulatory concern. Effective regulation of such exposures should insure that blood lead levels remain low enough to limit most risks to most of the adult population for these and other adverse effects.

Finally, the Joint Study Group recommends that the EPA Administrator take action to assure that all components within The Agency are employing consistent scientific approaches to deal with lead-related issues, and working from equivalent, up-to-date, information bases. We believe that our review contributes to this goal, but, because several organizations did not participate in the effort, we are unable to draw any conclusions about the over-all level of integration. To the best of our knowledge, no mechanism to bring about such coordination now exists, nor is it within the purview of the Joint Study Group to suggest one, but we regard this need as vital if the Agency is to carry out its regulatory responsibilities vis-a-vis lead in a technically sound and consistent manner.

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[4] M.A. Smith, L.D. Grant, and A.I. Sors, "Lead Exposure and Child Development--An International Assessment," Kluwer Academic Press, 1989, Boston, Mass.