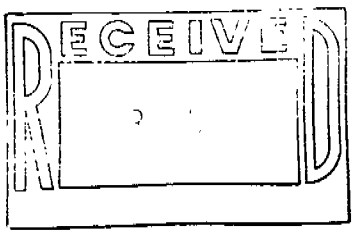

CMA
CHEMICAL MANUFACTURERS ASSOCIATION

April 11, 1989

To: Vinylidene Chloride Producers Group

Re: First Draft of Generic Comments on the
Second Set of ATSDR Toxicological Profiles

Enclosed is a draft report of CMA's comments on the second set of toxicological profiles. Please review this information prior to our May 2nd meeting for possible consideration/inclusion in the VDC Panel's comments to ATSDR.

Please note a meeting has been scheduled for may 2, 1989 at CMA offices from 10:00 a.m. to 3:00 p.m. Please make arrangements accordingly and an agenda will follow shortly. I look forward to meeting with you.

Sincerely,

Barbara Francis

Barbara Francis
Manager
Vinylidene Chloride Program

2501 M Street, NW, Washington, DC 20037 202-887-1100 Telex 89617 (CMA WSH)

SL 062798

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION ON THE SECOND SET OF TOXICOLOGICAL PROFILES

DRAFT REPORT

D R A F T

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION ON THE SECOND SET OF TOXICOLOGICAL PROFILES

DRAFT REPORT

Prepared for

Chemical Manufacturers Association
Washington, DC

Prepared by

ENVIRON Corporation
Washington, DC

March 31, 1989

SL 062800

C O N T E N T S

C O N T E N T S
Continued

I. INTRODUCTION

In the Federal Register of December 20, 1988, 53 Fed. Reg. 51192, the Agency for Toxic Substances and Disease Registry (ATSDR) announced the expected availability of the second 25 draft Toxicological Profiles for review and comment. The notice stated that a 90-day public comment period would be provided for each profile.

These comments are submitted by the Chemical Manufacturers Association (CMA) in response to this request for comments. CMA is a non-profit trade association whose member companies account for more than 90 percent of the total production capacity for basic industrial chemicals in the United States. CMA member companies produce, use, and market many of the chemicals that have been designated for priority consideration under Section 104(i)(2) of CERCLA. Accordingly, CMA is vitally interested in the way in which Toxicological Profiles are developed and the manner in which the data contained in the profiles are selected, evaluated, and presented.

Our present comments do not address ATSDR's specific evaluations of toxicological and epidemiological data for the individual chemicals that are the subject of the second 25 profiles. Instead, the comments focus on generic issues relating to data selection, evaluation, and presentation. Substance-specific comments may be submitted separately by various CMA member companies or Special Program Panels.

This is not CMA's first set of comments relating to the development of Toxicological Profiles. On July 16, 1987, CMA submitted Comments on ATSDR/EPA's First Priority List of Hazardous Substances and Guidelines for Development of Toxicological Profiles. On December 4, 1987, CMA submitted Comments on Approaches to Identifying Critical Data Needs for Establishing Significant Human Exposure Levels. On March 3, 1988, CMA submitted Comments on Generic Issues Raised by the First 25 Toxicological Profiles. Readers of our present

comments may wish to review earlier CMA comments in order to get a more complete picture of CMA's views on related issues.

Our comments on the second 25 Toxicological Profiles are as follows. In Part II, we present general comments on the profiles relating to organization of the profiles and overall use of scientific judgment and interpretation of the available data. In Part III, we discuss the Public Health Statements that constitute Chapter 1 of the profiles and offer suggestions for improving the presentation of information to lay readers. In Part IV, we comment on generic issues in the characterization and presentation of levels of significant exposure. In Part V, we raise issues regarding the content and organization of the health effects review (Chapters 2 in the Toxicological Profiles). In Part VI, we address the need for ATSDR to provide a more thorough and useful discussion of adequacy of the data base as a basis for identifying data needs.

II. GENERAL COMMENTS ON THE TOXICOLOGICAL PROFILES

In reviewing the second set of 25 Toxicological Profiles, CMA recognized a number of changes in the format and content of the toxicological profiles, including reorganization of the health effects review by route of exposure rather than endpoint, modification of the levels of significant exposure graphs (including addition of a table to accompany the graphs), removal of thermometer graphs, and addition of a section on relevance of health effects data to public health. We believe that these and other changes in the Toxicological Profiles clarify the presentation of the health effects data and we commend ATSDR for their continued efforts to revise the profiles in response to comments.

Although the second set of 25 profiles incorporates improvements over the first set of 25, CMA offers the following comments on general format and content of the profiles that would result in more scientifically sound and readable documents.

A. Profiles Should Provide a More Integrated Review of the Data with Better Application of Scientific Judgment

The guidance document to contractors prepared by ATSDR states that the purpose of the Toxicological Profiles is to provide "ATSDR's judgments about whether and at what levels of exposure adverse effects occur," and that "the emphasis in the documents is on providing interpretations of data rather than all of the data themselves." As the guidance document correctly notes, "interpreting data often requires judgment and implicit assumptions that are more a matter of policy than objective science."

ATSDR's recognition of the importance of data interpretation is also highlighted in the guidance on completing worksheets as part of the process of preparing the profiles. The guidance document points out that interpretation of study results is "the core of both the Tox Profiles and the

effort to set priorities for research," and that judgments about study quality and validity call for the reviewers toxicological expertise.

CMA believes that many of the Toxicological Profiles fall short of ATSDR's directive by failing to provide adequate application of scientific judgment in the analysis and interpretation of the complete data base for the profiled chemicals.

While this observation does not apply to all Toxicological Profiles, review of many of the profiles provides examples that indicate that sound scientific judgment was not always brought to bear in the the evaluation and presentation of study data and that available data were not adequately synthesized to permit development of consistent conclusions reflecting weight-of-evidence judgments. For example, to illustrate this point, we note the following examples: selection of LOAELs in the Public Health Statement that are not consistent with data summarized in the Health Effects chapter (see Section III.A.1 of comments); criteria for conversion of gavage doses to levels in the diet and drinking water that ignore scientific precedent (see Section III.A.3); failure to relate toxicity information by dietary and drinking water routes of administration (see Section III.A.3); inconsistencies between ATSDR MRLs and regulatory standards (see Section III.C); inconsistencies among acute, intermediate, and chronic MRLs for the same chemical (see Section IV.C); and scientifically ambiguous application of the term "cancer" (see Section IV.D).

CMA's generic review of the profiles suggests the need for additional senior level review of the Toxicological Profiles by trained toxicologists who can provide a level of data synthesis and interpretation beyond that reflected in many of the profiles. CMA recognizes that such review may require the allocation of additional resources for preparation of the Toxicological Profiles. Because the ATSDR profiles are rapidly becoming key government profiles for health professionals and the informed public, however, it is all the more important that

these resources be committed in order to achieve the purpose of these profiles.

B. Profiles Should Be Reorganized so that the Health Effects Chapter Follows Chapters Presenting Relevant Background Information

CMA believes that reorganization of certain chapters of the Toxicological Profiles would provide a more logical and useful presentation of information in the profiles. In particular, the chapters presenting physical and chemical information (Chapter 3), production, import, use, and disposal information (Chapter 4), and potential for human exposure (Chapter 5) should immediately follow the more general Public Health Statement, where the information contained in these sections would help orient the informed reader of the nature of the substance being reviewed and likelihood for exposure.

Knowledge of chemical identity and physical-chemical properties are critical to an understanding of a substance's likely biological properties and behavior in the environment. For instance, chemicals with a relatively low molecular weight and high lipid solubility can be absorbed more readily from water through the skin. For a chemical with very low water solubility, exposure via drinking water would not be expected to be significant. Accordingly, one would not expect to see any toxicity testing of that substance via drinking water exposure. Chemicals with a low vapor pressure would not be expected to pose a significant exposure via inhalation. Information on the production, import, use and disposal of a substance would provide an indication of the potential extent of environmental contamination and the likely conditions under which exposure could occur. Information contained in the chapter on potential for human exposure would indicate the likelihood that adverse effects may be associated with different routes of exposure.

In general, reorganization of the profiles with chapters related to chemical indentity, physical-chemical properties and

potential for human exposure preceding the health effects chapter would put into perspective the nature of the available toxicity testing and whether lack of data for certain exposure pathways more likely reflects a data need or an unlikely pathway of exposure.

Furthermore, chemical profiles are traditionally organized with background information preceding a discussion of health effects. In the U.S. EPA's Health Assessment Documents, chapters on physical-chemical properties; sampling and analytical data; sources in the environment; environmental fate, transport, and distribution; and environmental levels and exposure precede a discussion of the health effects associated with the profiled chemical. Similarly, the International Agency for Research on Cancer (IARC) monographs present chemical and physical data and production, use, occurrence, and analysis information prior to the section on toxicity data. We would suggest that ATSDR consider a similar organization of chapters in their profiles.

C. A Brief Executive or Scientific Summary Would Provide a Valuable Overview of the Profile

The Toxicological Profiles provide a summary of exposure and toxicity information on the substance being reviewed in the Public Health Statement. The Public Health Statement, however, is intended to communicate to the lay public essential information about the chemical being reviewed and is not intended to be used as a technical summary. CMA believes that the Toxicological Profiles would benefit from the inclusion of an executive or scientific summary directed toward public health professionals or other readers of the document looking for a more technical summary than is provided in the Public Health Statement. We suggest placing this summary immediately after the Public Health Statement. This executive summary should present a succinct review of physical-chemical data; production, import, use and disposal data; potential for human

exposure; health effects data; analytical methods; and regulations and advisories.

Because of the many subsections in the Toxicological Profiles, it is difficult at present to readily identify critical information characterizing the nature of the hazard posed by the substance being profiled. A good executive summary would provide a valuable overview of a chemical's toxicity and exposure potential and would help direct an informed reader to more detailed reviews of the topics of concern in the body of the profile.

II. PUBLIC HEALTH STATEMENT

A. ATSDR Should De[illegible]e Clearly and Unambiguously the Data and St[illegible]es Selected for the Human and Animal Health Effects Tables

The Public Health Statements, including the Health Effects Tables, are expected to be widely read by the lay public. It is especially important that the information provided be presented in a clear and concise manner that is easily understood by the lay reader. With these points in mind, some general issues of format and presentation are addressed in the following pages.

1. The Criteria for the Selection of the Data in the Tables Must Be Made Apparent

In the guidance documents to contractors, ATSDR provides the following instruction with regard to the content of the Human and Animal Health Effects tables to be included in the Public Health Statement: "Develop tables that present dose/response data in a form that is easily understood by the public. These tables are for illustrative purposes. There is no need to put all species, durations, or effects in them."

CMA believes that these tables would be more useful if specific criteria were developed for the purpose of determining what data are selected for presentation. Although it appears that ATSDR generally presents duration- and route-specific Lowest-Observed-Adverse-Effect Levels (LOAELs) in the tables, this is not explicitly stated and is not true for all profiles. For example, Table 1-8 of the Public Health Statement for Organic Mercury (Long-Term Exposure) lists a level of 1.7 ppm in food (0.08 mg/kg/day) as causing kidney disease; however Table 2-3 (Levels of Significant Exposure to Organic Mercury-Oral) cites a LOAEL for "less serious" renal effects of 0.015 mg/kg/day. It is not clear why the

latter (lower) value was not converted to a level in food and included in Table 1-8.

ATSDR should develop and explicitly state the criteria to be applied for determining which data are included in the Human and Animal Health Effects tables. This would improve the consistency of the profiles and result in the presentation of information that is more useful and meaningful to the reader.

ATSDR should also provide the literature reference for the data that are presented in the Human and Animal Health Effects tables. It is currently difficult for the reader to identify the studies on which these data are based. The reader must refer to the "Discussion of Health Effects by Route of Exposure" and identify the studies from which data were converted to levels in food and water. It is important that even the lay reader be able to readily identify the studies on which the data in the tables are based.

2. Exposure Levels Should Be in Units of mg/kg/day, Not Dietary Concentrations, Which Cannot Be Compared Across Species

In expressing levels of substances in food and water, ATSDR should use units of mg/kg/day instead of media-specific concentrations (e.g., ppm). Because of interspecies differences in factors such as average daily food and water intake (per unit of body weight), dietary concentrations are not comparable across species. Table 1 illustrates this point by showing the doses (in mg/kg/day) that are equivalent to 1 ppm of a substance in the diet of different species, including humans. The values in the tables are averages. An example of the lack of comparability is apparent in the estimated doses for a mouse (0.150 mg/kg/day) and man (0.025 mg/kg/day) equivalent to a dietary level of 1 ppm, which differ by a factor of 6. In the first set of 25 Toxicological

TABLE 1

Approximate Relation of Parts Per Million in Diet to mg/kg/day

Animal	Weight in Kilograms	Grams Food Consumed Per Day (Liquids Omitted)	Type of Diet	1 ppm in Food Equals, in mg/kg/day
Mouse	0.02	3	Dry	0.150
Rat, young	0.10	10	chow	0.100
Rat, older	0.40	20	diets	0.050
Guinea Pig	0.75	30		0.040
Rabbit	2.0	60		0.030
Dog	10.0	250		0.025
Cat	2	100	Moist	0.050
Monkey	5	250	semi-solid	0.050
Man	60	1500	diets	0.025

Adapted from: Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. The Association of Food and Drug Officials of the United States. 1965.

Profiles, ATSDR expressed exposure levels in the Public Health Statement in units of mg/kg/day; CMA believes that the Agency should return to this practice.

If ATSDR chooses to continue to express exposure levels as dietary concentrations, conversions from other units must be made as accurately as possible. The conversion factors used for this process are currently not provided by ATSDR in the profiles (see discussion in IV.C). Thus, there is no way for the reader to check the accuracy of ATSDR's conversion of doses in mg/kg/day to media concentrations (e.g., ppm). This is an important omission that could be easily rectified by ATSDR.

3. ATSDR Should Adhere to Scientific Precedents for Relating Exposures by Gavage, Drinking Water, and Dietary Administration

In ATSDR's guidance document for contractors, the agency provides guidelines for the conversion of exposure values from animal studies into food or water concentrations for presentation in the health effects tables of the Public Health Statement. The agency provides the following instructions to contractors:

> "a. Food or feeding study data should be converted to levels in food only.
>
> b. Water or drinking water data should be converted to levels in water only.
>
> c. If there are no food/feeding or water/drinking water studies for that exposure duration, gavage studies can be converted to levels in food when oil was used as the vehicle (lipophilic) or to levels in water when an aqueous vehicle was used (hydrophilic)."

These guidelines ignore a long history and regulatory precedent for using data from toxicology studies in which animals were exposed via feed to estimate equivalent concentrations in drinking water. There are many

instances where regulatory agencies (e.g., USEPA and FDA) and expert scientific bodies (e.g., the National Academy of Sciences, NAS) have used toxicity data from feeding studies to estimate safe exposure levels in drinking water. Table 2 provides a number of examples where this procedure has been followed by the U.S.EPA and NAS to derive safe drinking water concentrations of various substances.

It is also possible to estimate equivalent concentrations in food based on data from toxicity studies in which animals were exposed to an agent in drinking water. For some chemicals, the available data indicate that concentrations of a substance administered in a liquid should not be directly converted to levels in food (or vice versa). In such cases it may be possible to apply a specific factor (e.g., that may account for differences in bioavailability) to the data that would allow for the conversion to be made. An example of the use of a bioavailability factor is discussed later in this section.

As previously noted, ATSDR provides specific criteria in the guidance to contractors for converting from gavag studies to food and water concentrations in the absence of toxicity studies using food and drinking water exposures. CMA disagrees with these criteria in two respects: 1) gavage data should be used to estimate food and drinking water concentrations, regardless of whether the agent is lipophilic or hydrophilic; and 2) the conversion from gavage dose to food and drinking water concentrations should take into account factors such as differences in bioavailability, and should not necessarily assume direct equivalence between the gavage dose and media concentration.

Table 12 provides two examples of cases in which gavage studies with lipophilic agents (administered in corn oil) were used to develop acceptable levels in

TABLE 2
Examples of Drinking Water Criteria Derived from Feeding Studies and Gavage Studies With Oil Vehicle

Chemical	Drinking Water Criteria	Route of Administration*	Reference
Aldicarb residues	proposed RMCL[a]	Feed	50 FR 46985[c]
Cadmium	proposed RMCL	Feed	50 FR 46065
Carbofuran	proposed RMCL	Feed	50 FR 46986
Lindane	proposed RMCL	Feed	50 FR 46997
Methoxychlor	proposed RMCL	Feed	50 FR 46999
Monochlorobenzene	proposed RMCL	gavage in corn oil	50 FR 47000
Pentachlorophenol	proposed RMCL	Feed	50 FR 47002
2,4,5-TP	proposed RMCL	Feed	50 FR 47005
Dichloroacetonitrile	SNARL[b]	gavage in corn oil	NAS 1987, Drinking Water and Health, Vol. 7

*For study upon which criteria was based.
[a]RMCL = Recommended Maximum Contaminant Level
[b]SNARL = Suggested No-Adverse-Effect Level
[c]All Federal Register citations are from November 13, 1985

drinking water. ATSDR should acknowledge the considerable precedent for using gavage data to estimate drinking water exposure levels and change its procedures accordingly.

As stated above, CMA believes that ATSDR should convert gavage data to equivalent levels in food and water, taking into account bioavailability and other relevant factors. It is known that for some agents (e.g., those that strongly adsorb to food) the bioavailability is less when administered in food than when administered in a liquid vehicle. For example, in its Ethylene Dibromide (EDB) Position Document 4 (Sept. 27, 1983), the U.S. EPA acknowledged the expected reduction in the bioavailability of EDB administered in feed (as opposed to gavage). In this document, EPA derives a cancer potency factor for EDB in food by multiplying a gavage-based potency factor for EDB by a factor (0.59) that would account for its reduced bioavailability in feed. This factor was computed using data from studies conducted on another halogenated compound, dibromochloropropane (DBCP). It is very likely that a literature search would identify other documented examples of differences in the bioavailability of a substance administered in food as opposed to a liquid vehicle. When such information is available, ATSDR should use it to more accurately convert gavage data to the equivalent food or drinking water concentrations.

4. Durations of Exposure Must Be Made Unambiguous

ATSDR should also be more accurate in providing information on the duration of exposure, especially with regard to inhalation data. In most of the health effects tables for inhalation exposure, the total length of the study was provided under the heading "Duration of Exposure." It is not possible for the reader to determine whether or not this exposure was intermittent or continuous during the study period. If the exposure in

question was intermittent (e.g., 8 hrs/day, 5 days/wk), as is true with most inhalation studies, this information should be provided.

B. ATSDR Should Define Clearly and Unambiguously the Term Minimal Risk Level (MRL)

If ATSDR is going to use the term minimal risk level (MRL) in the Public Health Statement, it should be clearly defined. The current usage of the term could be easily misunderstood by the lay reader. The profiles include the following statement in Section 1.6 of the Public Health Statement: "Should a person be exposed to [X] at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur." Although this statement is true, it could lead the lay reader to assume that exposure to a substance at or slightly above the MRL is likely to result in adverse health effects. The truth is, because of the manner in which they are derived, exposures at or slightly higher than the MRL are very unlikely to present a public health risk. This should be made clear to the reader. CMA previously made this point to ATSDR in Comments of the Chemical Manufacturers Association on Generic Issues Raised by the First 25 Toxicological Profiles, submitted on March 3, 1988. We continue to believe that the current usage of the term MRL in the toxicological profiles is likely to be misunderstood by the lay reader.

Section 1.6 of the profiles also contains the following statement with respect to MRLs: "Since these levels are based on information that is currently available, there is always some uncertainty associated with them." This is an ambiguous statement and suggests that the uncertainty associated with MRLs is based only on the use of currently available data. In fact, the greatest source of uncertainty in the derivation of most MRLs is the use of data from laboratory animals to predict acceptable exposure levels for humans. The "currently available data" may be quite extensive for a given chemical, and not the major source of uncertainty. A generic statement

regarding the source of uncertainty for MRLs is inappropriate. If ATSDR is going to continue to develop and present MRLs in the Toxicological Profiles; rather, the uncertainties associated with each one should be considered on a case-by-case basis.

As previously discussed in Section III.A.1, we believe that data presented in the Human and Animal Health Effects tables should be referenced. A literature reference should b provided in conjunction with an MRL so that the reader can easily identify the data on which the MRL is based.

C. Data Tabulated in the Public Health Statement Should Be Evaluated in Light of Other Regulatory Guidelines and Standards

Section 1.7 of the Public Health Statement discusses regulatory standards and guidelines that have been developed by the federal government. No attempt is made to discuss these values with respect to data presented in the health effects tables. This is especially important with respect to MRLs. CMA has noted a number of cases where the MRL for a specific chemical is significantly lower than the comparable federal standard or guideline. This is an important omission; the reader might logically conclude that considerable health risks are associated with exposures at these levels (i.e., those associated with the relevant standards and/or guidelines).

An example of the situation noted above can be seen in the Public Health Statement for 1,2-dichloropropane. In Table 1-1 of this profile, an MRL (long-term) for inhalation exposure is listed at 6 ppb. This is approximately four orders of magnitude lower than the Permissible Exposure Limit (PEL) of 75 ppm (75,000 ppb) that was established by OSHA. The OSHA PEL is cited in Sections 1.6 and 1.7 of the profile and is described in Section 1.6 as a concentration that OSHA "feels is acceptable for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect." Another example of a

significant discrepancy between an MRL and a federal guideline can be seen in the Toxicological Profile for Mercury. In table 1-7 of the Public Health Statement, a short-term MRL of 0.00027 ppm is listed for organic mercury in drinking water (equivalent to an average intake in an adult of approximately 0.00054 mg/day). However, ATSDR states in Section 1.7 that "The EPA estimates that for an adult of average weight, exposure to 0.021 milligrams (mg) of inorganic or organic mercury per day in food or water is unlikely to result in any harm to health." The EPA guidance level is approximately two orders of magnitude greater than the MRL.

Similar discrepancies can be seen in other profiles as well. The reader (especially the lay reader) cannot be expected to reconcile such differences in exposure levels that are both designed to be protective. CMA believes that this is an example of how the inclusion of "minimal risk levels" in the Public Health Statement may cause the lay reader to be unnecessarily alarmed. If ATSDR continues to include MRLs in the Public Health Statements, discrepancies with respect to regulatory standards and guidelines must be discussed.

D. ATSDR Should Be More Precise and Avoid Overgeneralizations in The Discussion of Health Effects

In Section 1.4 of the toxicological profiles, "How Can [X] Affect my Health," ATSDR should use more precise language and avoid overgeneralizations. For example, this section often includes a description of effects in animals that have been observed at "high" or "low" doses. The reader is unable to judge the significance of high and low dose exposures in animals with respect to typical human exposure levels. Low dose exposures in animal studies (especially carcinogenicity bioassays) are likely to correspond to unusually high doses in humans. It would be logical for the lay reader to conclude that "low doses" in animal studies are equivalent to typical "low doses" in human, even though they may differ by orders of magnitude.

In "Comments of the Chemical Manufacturers Association on Generic Issues Raised by the First 25 Toxicological Profiles" submitted on March 3, 1988, CMA suggested that Section 1.4 be combined with Section 1.6 ("What Levels of Exposure Have Resulted in Harmful Health Effects?") into a single section. CMA continues to believe that this would be a useful practice that would help prevent misinterpretation by the reader. If ATSDR continues with the present format, clarifying statements such as the following should be used in Section 1.4: "the levels of [profiled chemical] to which the animals were exposed in this study were approximately [factor] times higher than those to which humans are typically exposed."

In an attempt to discuss the health effects of a substance in language that is understandable to the lay reader (Section 1.4), ATSDR must be careful not to mak overgeneralizations. This is especially true with regard to the potential carcinogenicity of a substance. For example, in Section 1.4 of the Toxicological Profile for Phenol, ATSDR states that "...cancer has been shown to occur in mice when phenol is applied to the skin." A review of the relevant data in Chapter 2 of the profile indicates that this statement is misleading. In the discussion it is noted that the application of phenol to the skin of mice for extended periods caused an increase in the incidence of papillomas (benign tumors). ATSDR also refers to a study in which "One fibrosarcoma was observed [in mice] after 52 weeks of exposure to phenol alone." We would not expect the results of this second study to be s tistically significant, although no study det ls are provided in the Toxicolog cal Profile to permit such a determination.

In Section 1.4 of the same profile, ATSDR states that "When it [phenol] is applied in combination with certain chemicals known to cause cancer, more cancer occurs than when the other chemicals are applied alone." This statement is also misleading. In the Health Effects review (Chapter 2), ATSDR discusses two studies in which phenol was applied in combination with the known carcinogen 9,10-dimethyl-1,2-

benzanthracene (DMBA), resulting in apparent tumor promotion. A more recent study was also cited in which phenol, applied in conjunction with the carcinogen benzo[a]pyrene, did not cause an increase in tumor incidence. The statement quoted above is misleading in that it suggests that phenol has been shown to be a promoter when used in combination with more than one initiating chemical. In fact phenol has had this effect only when applied in conjunction with one chemical, DMBA. When applied in conjunction with benzo[a]pyrene, phenol did not have this effect.

CMA is concerned that misleading statements such as those cited above could cause lay readers unnecessary alarm. This is especially true with regard to a substance such as phenol that is found in many commonly used products.

IV. LEVELS OF SIGNIFICANT EXPOSURE

In general, the tables and figures in the Health Effects chapter of the Toxicological Profiles provide an adequate presentation of the available data on levels of exposure that may produce adverse effects. The format of the Levels of Significant Exposure figures provide a qualitative review of a large body of data represented by various species and toxicological endpoints. However, because the Toxicological Profiles are not intended to provide an in-depth evaluation of all the available data for each chemical, there is a need to carefully define terms used to describe potentially significant exposure levels. Also, the criteria by which the most important studies are identified and the procedures for deriving Levels of Significant Exposure should be described in detail in the text. These steps would serve to minimize any misinterpretation of the information presented in the figures.

A. Definitions of "Less Serious" and "Serious" LOAELs Should Be Provided in the Text, including Criteria for such Characterization of Effects

The concept of "less serious" and "serious" health effects from exposure to a chemical is very useful in evaluating the potential risk to humans and subsequently identifying and choosing an appropriate risk management policy. Because the characterization of the seriousness of the response is clearly a subjective process, a framework of criteria for determining the relative significance of an effect is required. While the Toxicological Profiles adequately state the intent in classifying Lowest-Observed-Adverse-Effect-Levels (LOAELs), no definitions or criteria for identifying "less serious" and "serious" effects are provided. As a result, it may be difficult to interpret the significance of these distinctions.

In particular, the term "less serious" may carry a connotation of being not serious if not more precisely defined. For example, isophorone can be characterized as a sensory irritant in both humans and mice. One study reported

that a 5 minute exposure to 27.8 ppm isophorone produced a 50% decrease in the respiratory rate (RD_{50}) of mice. Although a 50% response represents a significant effect, this concentration was reported in the Toxicological Profile as a LOAEL for "less serious" respiratory effects in mice because it was the lowest effect level that was clearly indicated in the study. Alarie (1984)[1/] has described the RD_{50} concentration in mice as a level that would likely be intolerable to humans even for short periods of time. Such an exposure may represent significant hazard to humans, particularly those who may be sensitive to the effects of inhaled irritants; e.g., asthmatics. Short-term exposure to isophorone at concentrations which produce effects such as mild sensory irritation that are reversible may be characterized as "less serious." However, it seems inappropriate to present a 50% effect level as LOAEL because more serious or permanent effects may become evident and would add to the uncertainty in extrapolating from one species to another.

Development of well-defined criteria for determining the relative seriousness of effects would provide more consistency in identifying significant levels of exposure. A description of these criteria in the Toxicological Profiles would benefit those who will use these documents to evaluate the health risk associated with exposure to these chemicals.

1/Alarie, Y. 1984. Establishing threshold limit values for airborne sensory irritants from an animal model and the mechanisms of action of sensory irritants. In advances in modern environmental toxicology, Vol. VIII, Occupational and industrial hygiene: concepts and methods, a symposium in honor of Theodore F. Hatch, eds., N.E. Esmen and M.A. Mehlman. Princeton, NJ: Princeton Scientific Publications.

B. Criteria for Determining the Reliability of LOAELs Presented in the Figures Should Be Provided in the Text

In some of the Toxicological Profiles, a sentence often appears at the end of the section for a given health effect by a given route of exposure stating that all reliable LOAELs are presented in the "Levels of Significant Exposure" tables and figures. However, no explanation is provided as to how the reliability of these values was established. The purpose of the Toxicological Profiles is to summarize and interpret the available toxicological and epidemiological data on a chemical and not to present detailed descriptions of each study. Thus, the reader does not have the information necessary to critically evaluate each study and must rely on ATSDR's assessment of the quality of the data. However, no criteria are presented which would indicate the process by which "reliable" LOAELs were identified and whether these values were selected in a consistent manner.

Detailed criteria should be developed for the identification of "reliable" LOAELs to be included in the tables and figures that present "Levels of Significant Exposure". This process would presumably be tied closely to the critical evaluation of the available literature as discussed in Chapter V. A description of the criteria applied in the selection of "reliable" LOAELs should be included in the Toxicological Profile for each chemical.

. The Minimal Risk Level (MRL) Should Be Clearly Defined in the Text, including Criteria that a Study Must Meet before an MRL Can Be Derived

On July 16, 1987, CMA submitted Comments on ATSDR/EPA's First Priority List of Hazardous Substances and Guidelines for Development of Toxicological Profiles. In those comments, CMA suggested that ATSDR should not make policy judgments with regard to the level of exposure to a chemical that is deemed to be safe or presents a "minimal risk" to humans. Rather, ATSDR should simply summarize and interpret the toxicological and

epidemiological data to identify levels of exposure that are known to cause adverse health effects and to identify any uncertainties associated with these levels. Risk managers can then use this information to estimate levels of significant human exposure.

The derivation of "minimal risk levels" (MRL) is a risk management decision, and therefore, should not be presented in the Toxicological Profiles. However, if ATSDR determines that it should attempt to estimate levels of significant human exposure such as MRLs, then a complete and unambiguous definition of the term should be provided in the Discussion of Health Effects by Route of Exposure (Section 2.2). The only operational definition of an MRL appears in the Glossary. A concept as important and easily misinterpreted as a "minimal risk level" for humans requires a more prominent and complete discussion in the main body of the Toxicological Profile.

The MRL, as defined in the glossary, is an estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (non-cancerous) over a specified duration of exposure. This definition suggests that exposure to a chemical at the MRL involves some degree of risk for health effects. In fact, exposure at the MRL or even at slightly higher levels is likely to present no health risk to humans. Thus, the current use of the term "minimal risk level" by ATSDR could easily be misinterpreted, particularly by the lay reader. A clear and unambiguous definition of the MRL and its intended use should be presented in both the Public Health Statement and the Health Effects discussion. This should also include a discussion of the uncertainties associated with the derivation and use of such a term.

The definition provided in the Health Effects chapter should include the criteria for selecting the most appropriate study for deriving an MRL. Without an understanding of the criteria, the reader may have difficulty interpreting the MRLs. For example, the acute (0.005 mg/kg/day) and intermediate (0.001 mg/kg/day) MRLs derived for pentachloro-

phenol are 6 and 30 times less than the chronic MRL, respectively. One would expect the level of acceptable exposure to vary inversely with length of exposure. The acute MRL was derived from a study in mice which reported a LOAEL for serious developmental effects while the intermediate and chronic values were based on doses which produced hepatic effects in rats. Therefore, species and site differences may prevent the direct comparison of the acute value with the long-term MRLs for pentachlorophenol.

The inconsistency between the intermediate and chronic MRLs is less apparent because both are based on hepatic effects observed in rats. However, closer inspection of the relevant animal studies reveals that the intermediate MRL was derived from a LOAEL for less serious effects in rats exposed to technical grade pentachlorophenol in their diet (Kimbrough and Linder 1978). The chronic MRL, on the other hand, was obtained from a study in which NOAEL was determined in rats exposed to a 90% pure preparation of pentachlorophenol in feed (Schwetz et al. 1978). Much of the discussion of the toxic effects of ingested pentachlorophenol in animals (Section 2.2.2.2) deals with the uncertainty introduced by impurities in the test chemical such as dioxins and dibenzofurans. Several studies are described which demonstrate that technical grade preparations with higher levels of impurities are more toxic to rats over the same dose ranges than preparations with higher purity. Nevertheless, the MRLs were derived from studies in which pentachlorophenol of different purities were used with no explanation as to why these studies were chosen. This approach is particularly confusing since there seems to be sufficient data to enable comparisons of pentachlorophenol with similar chemical purity.

The above discussion demonstrates an inconsistent approach in developing MRLs that may result in their misinterpretation. These values are based on both NOAELs and LOAELs for different toxicity endpoints, with varying seriousness of effects, obtained from different species. The lay reader is not likely

to distinguish MRLs on these bases, yet such distinctions must be made if these values are to be used properly in estimating human risk. Essential to this understanding is a knowledge of the criteria used to establish MRLs and explanations where these criteria were not applied.

Explanation should also be provided where no MRL was derived for certain chemicals or for certain routes and durations of exposure. For example, no MRLs were derived for phenol by any route of exposure. While the "Levels of Significant Exposure" figures present several NOAELs and "reliable" LOAELs for inhalation, oral, and dermal routes of exposure, apparently none of the studies were considered by ATSDR to be appropriate for estimating MRLs. Discussion should be provided as to why these studies are not adequate if that is the case, particularly since USEPA has reported an RfD for chronic oral exposure to phenol. In ATSDR's guidelines, contractors are directed to omit MRLs if a value different from USEPA's RfD would be more appropriate. In those instances, a boilerplate statement "The ATSDR, in consultation with the EPA, is evaluating this database for development of a minimal risk level" is to be presented in the discussion for that effect. No such statement appears for phenol; therefore, an explanation should be provided indicating why MRLs were not derived.

In the Toxicological Profiles, the procedure for deriving an MRL from a NOAEL or LOAEL is briefly described in the footnotes of the Levels of Significant Exposure tables. The lay reader is not likely to be aware of the accepted use of safety factors and other dose adjustments used to estimate risk levels for human exposure from animal studies. For example, the statement "dose adjusted for intermittent exposure" is not defined and probably would not be understood by the average layperson. A more complete description of the procedure, perhaps with an example, should be provided in the text and should include a discussion of the use of safety factors and other dose conversions.

Factors for converting dosages in mg/kg/day to ppm in food and water should also be provided in the text. Assuming 70 kg as the body weight for an adult male, the daily food consumption factor used by ATSDR seems to be 3.5 kg/day for most calculations which convert a daily oral dose to a concentration in food. This value is high for a daily consumption rate that does not include liquid. The FDA traditionally uses an average of 1.5 kg/day dry food and 2 liters/day liquid for adult males in its food additive safety evaluations. If the 3.5 kg/day apparently used by ATSDR includes the ingestion of 2 liters (2 kg) of water per day, this factor would be inappropriate for converting from an oral dose to the concentration in food only.

The intermediate oral MRL of 3 mg/kg/day for isophorone was converted to an equivalent concentration in food of 107 ppm. For a 70 kg man, this conversion would require a food consumption rate of 1.96 kg/day. This value is not consistent with the factor used to convert oral MRLs to equivalent concentrations in food for some of the other chemicals evaluated by ATSDR (e.g. pentachlorophenol, toluene, 1,2-dichloroethane, 1,1,2-trichloroethane). Thus, the procedure for converting dosages to equivalent concentrations should be described, including documentation for the appropriate conversion factors.

D. Cancer Effect Levels (CELs) Should Not Be Presented in the Toxicological Profiles

The Cancer Effect Levels (CELs) are not adequately defined in either the Public Health Statement or the Health Effects summary. As defined in the Glossary of the Toxicological Profile, a CEL is "the lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control." For this second group of 25 chemicals profiled by ATSDR, as well as for most recognized and potential carcinogens, no relationship has been established

between exposure level and carcinogenic effect in humans. Therefore, the CELs reported in the Toxicological Profiles represent essentially LOAELs for carcinogenic (or tumorigenic) effects observed in laboratory animals exposed to a given chemical.

These values, as presented, provide no information to the reader as to the cancer risk for humans exposed to the same chemical and in fact, cannot be used by themselves for such a purpose. Safety factors and dose conversions cannot be applied to a CEL obtained from animals to obtain a "minimal cancer risk level" for humans as is currently done for non-cancer effects. Current models for estimating human cancer risk from animal data require a well-defined dose-response relationship as well as other input factors to perform low dose extrapolations. The results of such modeling procedures are the only values relevant in estimating the human cancer risk associated with exposure. The q_1^* obtained from the linearized multistage model used by EPA is reported, when available, in the Toxicological Profiles.

The CEL may not be useful even for identifying the most sensitive bioassay to use in a risk modeling procedure. Factors such as species, number of animals, number of dose levels, route of exposure, duration of exposure, percent mortality, etc. are more important in selecting an appropriate study for estimating human risk than the lowest dose level at which tumors were observed. Therefore, because the CEL provides no useful information in terms of risk assessment and because of the potential for misinterpretation, CMA feels that CELs should not be presented in the Toxicological Profiles.

If ATSDR determines that the CEL relays some necessary information to the reader, then the meaning and intended use of these values should be unambiguously defined in the text of the Health Effects chapter. ATSDR should clearly state that CELs derived from animal studies do not represent values extrapolated to human exposure. Therefore, the CEL is not representative of the human cancer risk from exposure to the

chemical or even of human exposure concentrations. In fact, humans are likely to be exposed to chemicals at much lower environmental levels than those used in animal studies. Therefore, the cancer risk to humans is likely to be very small and may be non-existent.

The broad application of the term "cancer" could easily be misunderstood by the lay reader. For example, dermal CELs were derived from two studies which reported that phenol promoted the carcinogenic effects of dimethylbenzanthracene (Boutwell and Bosch 1959; Salaman and Glendenning 1957). These studies demonstrated that control mice painted with phenol only developed papillomas (benign skin tumors) and only one fibrosarcoma (malignant tumor) in an unreported number of mice. ATSDR should distinguish between benign and malignant tumor-types because the lay reader is not likely to be familiar with medical pathology terms such as papilloma, fibrosarcoma, etc. Furthermore, both studies reported severe skin irritation in the mice painted with high concentrations of phenol (20%). No tumors were observed in mice exposed to 5% phenol (Salaman and Glendenning 1957). Therefore, the tumor response observed in these mice may have been due to the severe skin damage induced by the application of very high concentrations of chemical and not to any direct tumorigenic activity of phenol itself. Thus, the lack of critical evaluation of the available data as well as an ambiguous application of the term "cancer" may serve to mislead the reader with regard to the actual health risk posed to humans by chemicals that have produced an increased incidence of tumors when tested in experimental animals.

E. Estimated Upper-Bound Human Cancer Risk Levels Should Not Be Presented in the Levels of Significant Exposure Figures

The presentation of the estimated upper-bound human cancer risk levels in the same figure with the non-cancer significant exposure levels often results in a cluttered format that can be difficult to interpret. A y-axis spanning many orders of

magnitude is required to include dose levels ranging from the very small human exposure levels associated with 10^{-4} to 10^{-7} cancer risk levels to very high acute exposure levels. This scale results in a qualitative presentation of the data that may be greatly distorted. The size of the symbols representing the significant exposure levels may cover tens, hundreds, or even thousands of mg/kg/day and may result in values for different effects or durations of exposure as being more similar than they actually are.

Placement of the estimated upper-bound human cancer risk levels opposite the dose scale with the figure key in between makes it difficult to identify exposure levels with the corresponding cancer risk estimates. Because these figures may be viewed in the absence of the corresponding text and because of the importance of the data as representing levels of significant exposure, the information must be presented as clearly as possible. CMA believes that the human cancer risk estimates with the corresponding dosage estimates should be presented in a separate figure or table. This would permit th dose scale to be expanded for the human and animal non-cancer endpoints and the animal cancer effect levels. Such a format would provide a more accurate representation of the levels of significant exposure and their relationship to one another.

V. CONTENT OF THE HEALTH EFFECTS REVIEW

A. In General, Toxicological Profiles Do Not Present a Critical Evaluation of the Literature

The second set of Toxicological Profiles do not, in general, appear to present a sufficiently critical evaluation of the toxicological literature. CMA raised this issue previously in Comments on Generic Issues Raised by the First 25 Toxicological Profiles (March 3, 1988). CMA recognizes that current ATSDR guidance in the preparation of the profiles dictates that the documents are not meant to provide all the information necessary to support judgments about the validity of particular studies. However, CMA strongly believes that the text should provide more critical comments on study quality.

B. A Section Should Be Added to the Health Effects Chapter Describing Toxicity Data by Other Exposure Routes

The Health Effects chapters of the Toxicological Profiles describe toxicity data by the three routes of exposure of concern to public health, specifically inhalation, oral, and dermal exposure. A forth section should be added, as necessary, to describe health effects data by routes other than these three, including intravenous, intraperitoneal, and subcutaneous injection. Quantitative dose-response relationships obtained by injection routes of exposure, while not directly relevant to the exposure routes of concern to public health, do provide useful information on the types of toxicity one would expect to see and relative sensitivity of different experimental animal species.

Currently, data for routes of exposure other than inhalation, oral, or dermal exposure are presented in the Relevance to Public Health section (e.g., Toxicological Profile for n-Nitrosodi-n-propylamine). CMA believes that toxicological data should not be introduced in this section, which should be reserved for interpretations of the available data based on review of the entire database. Furthermore, the availability of data for other routes of exposure should be

made clear to the users of the profiles by presenting these data in a separate section.

C. ATSDR Should Improve the Presentation of Genotoxicity Data

1. All Genotoxicity Data Should Be Presented in One Section Rather than in Sub-sections by Route of Exposure

In the second 25 Toxicological Profiles, ATSDR presents genotoxicity data in sub-sections by route of exposure (i.e., inhalation, oral, and dermal exposure). In vivo genotoxicity assays can serve as sensitive indicators of biological damage by reflecting the presence of deleterious metabolites at the target site. These assays are almost exclusively performed on hematopoietic tissue or actual blood cells, and therefore indicate the presence of the available metabolite in the bloodstream, independent of the route of exposure. In vitro genotoxicity assays are direct measures of genetic toxicity since the compound is generally added directly to the culture medium, either in the presence or absence of a metabolic activation system. In many cases the endpoints of the in vivo and in vitro studies are the same, e.g. chromosomal aberrations or mutational induction, requiring no translation between the in vivo or in vitro systems. The results of in vivo and in vitro genotoxicity assays must be reviewed as a battery of tests which are useful for reaching an understanding of an agent's genotoxic potential.

CMA believes that a more rational and useful approach would be for ATSDR to combine all of the genotoxicity data in one section, preferably immediately preceding the discussion of pharmacology/toxicokinetic data. This would assist the reader in making informed judgments regarding the mechanism of action of the compound and make it easier to assess the degree to which metabolism (i.e., by test organisms) alters the genetic toxicity of the compound.

2. Discussions of Genotoxicity Data Should Be More Scientifically Rigorous

As a general statement, the presentation of the genotoxicity studies is inadequate. The results are presented as narrative or qualitative statements (e.g. SCE levels increased) even though quantitative results are generally available for these studies. CMA is of the opinion that the data should at least be presented in summary tables that include more data (e.g., indications of dose-response) than the simple +/- that is currently used to indicate the presence or absence of a response. For example, the Toxicological Profile for Bis(2-chloromethyl)ether (BCME) has a narrative paragraph in the "Relevance to Public Health" section describing the effects of BCME in several in vitro systems. The results are not discussed in the context of dose-response or degree of positive or negative response. The results of the genotoxicity assays are surprising in view of the high reactivity of the compound with nucleic acids, predicted in a structure-function analysis despite the rapid hydrolysis of the compound in water, and should be discussed within that context.

Another example of the inconclusive and often confusing presentation of genotoxicity material occurs in the Toxicological Profile for N-nitrosodimethylamine (NDMA), where in Section 2.7 "Interactions With Other Chemicals," the statement is made that "...4 weeks of ethanol pretreatment in rats worsened the effects on DNA repair that occurred following DNA alkylation induced by NDMA..." It is not clear which assay is being used, which kind of DNA repair is being monitored, what the dose range is, and what "worsening" the effect means (more repair, less repair, error-prone repair?)

Table 2-4 of the same profile (Genotoxicity of N-Nitrosodimethylamine In Vivo) lists two sister chromatid exchange experiments, one of which is positive, the other

equivocal. Some indication of the extent of the response or the presence of a dose-response relationship would increase the utility of the data and provide a strong basis upon which to draw conclusions from the data.

VI. ATSDR SHOULD PROVIDE A MORE THOROUGH DISCUSSION OF THE ADEQUACY OF THE DATABASE AND THE IDENTIFICATION OF DATA NEEDS

ATSDR has substantially revised the section on Adequacy of the Database in the second set of Toxicological Profiles, which we believe has resulted, in many respects, in a substantially improved section over the first set of Toxicological Profiles. In the second set of profiles, the discussions of adequacy of the data base are more specific and they provide some necessary interpretation of the data. However, for the profiles to be useful to ATSDR, in collaboration with NTP and EPA, in setting priorities for data needs across chemicals that have been profiled, more consistent and explicit consideration of all relevant information will be needed.

CMA has submitted comments previously on the issue of data needs in Comments on Approaches to Identifying Critical Data Needs for Establishing Significant Human Exposure Levels, December 4, 1987 and Comments on Generic Issues Raised by the First 25 Toxicological Profiles, March 3, 1988. Because of the importance of this issue, we have reiterated some of the comments still relevant to data needs below:

- Potential exposures likely to be experienced by individuals in the vicinity of a hazardous waste site, as indicated by monitoring data and information on physical-chemical properties and environmental fate, are a crucial part of the assessment of critical data elements needed to establish levels of significant human exposure. For example, one could speculate that a highly water-soluble chemical detected only in ground water and not expected to volatilize based on physical-chemical data would present the greatest risk to health, if inherently toxic, as a result of chronic ingestion. For such a chemical, absence of inhalation or dermal toxicity

data or other short-term data would not necessarily represent a significant data need.

- CMA recommends that an approach involving the weight of the evidence of the entire data base for relevance to human exposure be used for determining the adequacy of the data base for each route/effect/duration combination. Such an approach would better permit appropriate consideration of data that does not meet scientifically acceptable standards and allow inferences from other route/effect/duration data.

- Lack of route-specific data does not necessarily equate to significant data needs for the route of exposure. Data on systemic toxicity occurring from exposure via one route can be used to predict the toxic effects of exposure via another route, provid d that consideration is given to such factors as available data on target-site concentrations and information on metabolism and the relative degree of absorption. When these data are not available, however, extrapolations of predicted toxicity across routes of exposure are more difficult. Although there is a scientific basis for inferring toxic responses across routes for systemic effects, particularly between oral and inhalation toxicity, there is a greater uncertainty in drawing inferences about toxic responses involving dermal exposure, largely because of limited knowledge about dermal absorption. Comparable exposures via the dermal route do not necessarily change the systemic effects from exposure to a chemical via inhalation or ingestion, but rather may change the magnitude of the toxic response due to differential absorption. It is clear, then, that a case-by-case analysis of

chemical-specific data must be performed if a true weight of the evidence evaluation is to be made. There are cases where it is not appropriate to use data from one route of exposure to predict toxicity resulting from exposure via another route, particularly where the toxic effects occur at the site of administration (e.g., inflammation of the nasal mucosa observed upon inhalation exposure could not have been predicted from oral or dermal administration).

- Absence of endpoint or duration-specific studies does not always equate to a significant data n for establishment of a significant level of h n exposure. The application of some types o uncertainty factors, identified by the term "extrapolation factors," are scientifically supported and permit the inference of levels of significant human exposure from NOAELs or LOAELs for other endpoints or durations of exposure. For example, retrospective examination of toxicity data has shown that for the majority of chemicals, the subchronic NOAEL will be no more than 10 times larger than the chronic NOAEL, supporting an extrapolation factor of 10 when inferring chronic SHELs from subchronic data. Thus, certain data gaps identified by a check list approach are not necessarily significant data needs if scientifically supported inferences can be made from available toxicity data. Currently, it is possible to predict lower bound estimates of chronic NOAELs from subchronic NOAELs, subchronic/chronic NOAELs from acute LD_{50} values, and NOAELs from LOAELs.

- CMA believes that it is preferable to use human data to establish a significant level of human exposure for a chemical when human data of sufficient quality and relevance are available. Where such human data are not available, the adquacy of animal data for establishing significant human exposure levels must be critically evaluated. In many cases, the combination of human plus animal data will require expert scientific evaluation.

- Consideration should be given to judgments made about the adequacy of toxicity data by regulatory and public health agencies and other expert bodies. CMA emphasizes, however, that in reviewing the decision-making processes of other agencies and expert groups, ATSDR should not adopt actual numerical standards or guidelines set by the groups without a full review of the background information used to establish these standards. Such decisions involve risk management decisions and may incorporate considerations other than health-based concerns. Rather, ATSDR's responsbility should be to examine, on a case-by-case basis, the interpretation of the toxicity data which form the basis of a given standard or guideline in the process of establishing a significant human exposure level.

- CMA believes it is unlikely that, for a carcinogenic substance with adequate cancer bioassay data, additional subchronic/chronic toxicity data will change conclusions regarding acceptable levels of human exposure.

- CMA recommends that research programs designed to address signficant data needs involve a hierarchical sequence of tests (i.e., tier testing). Longer-term

studies (e.g., chronic toxicity tests or multigeneration reproduction tests) would be conducted only if shorter-term studies and real-world human exposure situations indicated a need for more extensive testing.

Additional comment based on a review of the second set of Toxicological Profiles are presented below.

A. The Adequacy of the Database Should Be Discussed with regard to its Use in Estimating Significant Human Exposure Levels

In "Guidelines for Development of Toxicological Profiles" (52 Fed. Reg. 12870), the Department of Health and Human Services (DHHS) and the Environmental Protection Agency (EPA) state the following: "The toxicological profiles also must focus on important data needs that preclude the determination of significant levels of human exposure or contribute substantially to the uncertainty of such levels. With regard to the identification of these data needs, the agencies will assess the quality of the data which support the determination of significant human exposure levels and where major gaps in the supporting data exist, identify those data needs in the toxicological profiles."

This statement indicates that ATSDR should discuss the database for a substance in the context of its adequacy for determining significant human exposure levels. There appears to be little attempt to do this in the second set of 25 Toxicological Profiles. Absence of such a discussion may be a function of the lack of a clear definition of "significant levels of human exposure." Significant levels of human exposure are introduced by ATSDR in the Foreword to the profiles, but are never explicitly defined. ATSDR subsequently refers to "levels of significant exposure," and based on statements made in Section 2.2 of the profiles, considers this term to include LOAELs, NOAELs, and MRLs. ATSDR leaves to the

users of the profiles the determination of the significance of exposure levels with respect to humans.

Despite ATSDR's apparent interpretation of levels of significant human exposure as LOAELs, NOAELs, and MRLs, CMA believes that many users of the profiles will equate levels of significant human exposure with MRLs for noncarcinogens and CECs ~~CPFs~~ for carcinogens. Such an interpretation could result in an inappropriate perception about data gaps and data needs. This misperception would arise from the fact that although data for a given duration/route/endpoint category may be sufficient to define NOAELs and LOAELs, data might not be adequate to derive an MRL.

Where MRLs and ~~CPFs~~ CECs are developed, ATSDR should discuss the level of confidence in these values and identify data that would reduce the level of uncertainty associated with these values. One might expect that where MRLs and CPFs are developed for a duration/route/endpoint category, the database can be considered adequate, and for such categories further toxicity testing would not be required. In this context, the criteria for deriving MRLs, and the relationship between MRLs, CECs ~~CPFs~~ and levels of significant (human) exposure should be clarified.

B. ATSDR Should Identify True Data Needs based on a Consideration of All Relevant Information

As ATSDR is well aware, data needs are not equivalent to data gaps (the simple absence of experimental data for particular toxicological endpoints). Identification of true data needs requires consideration of all relevant information, including physical/chemical properties, environmental fate and transport, potential for human exposure, pharmacokinetics and mechanism of action, and inferences about toxicity from health effects data for other durations and routes of exposure. For example, information on physical-chemical properties and human exposure potential would identify those media (e.g., drinking water) and pathways of exposure (e.g., oral) by which exposure

to populations near a hazardous waste site would occur. This information is reflected in some profiles; for example, in the Toxicological Profile for Bromodichloromethane under single dose exposure, the comment is made that "Studies by the oral route are likely to be most relevant, but studies of acute inhalation and dermal toxicity would also be useful, since humans may be exposed by these pathways while bathing or swimming." We would encourage ATSDR to generalize this statement to all durations of exposure and endpoints of toxicity and perhaps present this information in the introductory statements under Existing Information on Health Effects of BDCM. Furthermore, information on potential for human exposure should be explicitly considered for all profiled chemicals in the Adequacy of the Database sections.

The Adequacy of the Database sections should not overlook regulatory precedents for inferring toxicity, where a data gap exists, from data for other durations of exposure and other routes of exposure, provided that consideration is given to such factors as target-site concentrations, relative absorption, metabolism, and excretion, and cumulative toxicity. CMA discussed this point in both sets of comments previously submitted to ATSDR. The current Toxicological Profiles, and in particular the figures of Existing Information on the Health Effects of [X], leave the impression that it is impossible to draw any conclusions about health effects from data for other durations of exposure or other routes of exposure. This impression is inconsistent with well established precedents for extrapolating from available data to infer no-observed-effect levels (NOELs) where data for a given duration or route of exposure are not available (e.g., EPA's reference dose methodology).

CMA does not necessarily suggest that such extrapolations be performed in the Toxicological Profiles, but strongly believes that ATSDR should provide, at a minimum, a statement in the profiles indicating that information for a given endpoint and exposure route may exist by way of inference.

Extrapolating from data for other durations of exposure or routes of exposure is important for assessing true data gaps (and thus in prioritizing data needs) and for public health professionals in evaluating risks to public health based on currently available (and generally limited) data.

C. The Discussion of Specific Data Needs Must Acknowledge Useful Data that Currently Exist

CMA encourages ATSDR to more consistently provide a comprehensive review of all available data with respect to data adequacy. For certain endpoints, notably immunological, neurobehavioral, and reproductive/developmental effects, little routine toxicity testing is conducted. Information on these endpoints, however, can be gleaned from chronic or subchronic studies in which the relevant parameters were evaluated. Clinical tests (e.g., hematology) conducted as part of a chronic study provides information on a compound's potential to cause immunological effects. Histologic examinations provide one of the most sensitive measures of toxicity. For example, chronic and subchronic studies that include examination of reproductive organs can flag a chemical's potential for inducing reproductive effects. In fact, the U.S. Food and Drug Administration requires reproduction studies for certain categories of food additives only when results of other studies indicate reproductive organ toxicity.

The Toxicological Profile for Bromodichloromethane illustrates CMA's concern. The Toxicological Profile states that "no studies were located regarding effects of BDCM on reproduction." The National Toxicology Program conducted a two-year gavage study of bromodichloromethane, however, which included histologic examination of the reproductive organs in male and female rats and mice (NTP. 1987. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Bromodichloromethane (CAS No. 75-27-4) in F344/N Rats and B6C3F1 Mice (Gavage Study), NTP TR 321). No effects were seen in any of the reproductive organs. Similarly, in the

Toxicological Profile for DDT, DDE and DDD, the statement was made that "little or no information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in animals exists," although a number of these endpoints were examined in NCI bioassays and in a study with human volunteers. Of the Toxicological Profiles reviewed by CMA, the general utility of data from histological examinations was recognized in only one profile, the Toxicological Profile for n-Nitrosodi-n-propylamine. In the Adequacy of the Database section, it is stated that "Histological examinations of reproductive organs of animals exposed in subchronic and chronic studies would provide relevant data," and "Histological examination of organs and tissues of the immunological system from animals exposed in subchronic and chronic studies would provide relevant information as immunotoxicity data for N-nitrosodi-ni-propylamine are not available." This interpretation of available study data should be performed consistently for all profiled chemicals.

CMA strongly believes that negative as well as positive study findings should be considered in the adequacy of the database section. Although negative study results such as those illustrated above may not prove that the compound does not cause adverse reproductive effects, the information is important in setting priorities for toxicity testing among all profiled chemicals.

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