COMMONWEALTH OF MASSACHUSETTS
DEPARTMENT OF ENVIRONMENTAL PROTECTION

THE CHEMICAL HEALTH EFFECTS ASSESSMENT METHODOLOGY
AND
THE METHOD TO DERIVE ALLOWABLE AMBIENT LIMITS

APPENDICES

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APPENDIX A

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APPENDIX C

GLOSSARY OF ACRONYMS

APPENDIX-C

Glossary of Acronyms

AAL	-Allowable Ambient Limit
A/C	-Acute and Chronic Toxicity (one of four health effects categories)
ACGIH	-American Conference of Governmental Industrial Hygienists
ADI	-Acceptable Daily Intake
ANSI	-American National Standards Institute
C	-Carcinogenicity (one of four health effects categories)
CalDHS	-California Department of Health Services
CAG	-Carcinogen Assessment Group (USEPA)
CAS	-Chemical Abstract Service registry number
CESARS	-Chemical Evaluation Search and Retrieval System (Michigan)
CHEM	-Chemical Health Effects Assessment Methodology (Massachusetts)
CIIT	-Chemical Industry Institute of Toxicology
CNS	-Central nervous system
DAQC	-Division of Air Quality Control (of the Massachusetts DEQE)
DEP	-Massachusetts Department of Environmental Protection
D/R	-Developmental/Reproductive Toxicity (one of four health effects categories)
EPA	-United States Environmental Protection Agency (USEPA)
FDA	-United States Food and Drug Administration (USFDA)
GENE-TOX	-Genetic Toxicology Program (USEPA)
HRG	-High Risk Group
IARC	-International Agency for Research on Cancer
ICPEMC	-International Commission for Protection Against Environmental Mutagens and Carcinogens
IRLG	-Interagency Regulatory Liaison Group
LAC	-lifetime average concentration (exposure concentration calculation in quantitative dose-response assessment)
LAD	-lifetime average daily dose (dose calculation for quantitative dose-response assessment)
LOAEL	-lowest observed adverse effect level
LOEL	-overall lowest observed effect level (from completed assessment of all developmental/reproductive toxicity studies used in developmental/reproduction toxicity category only)
LOEL*	-lowest observed effect level when only one dose used, or no dose-response observed (used only in developmental/reproductive toxicity category)
LOELs	-lowest observed effect level in a single given study

	(used only in developmental/reproductive toxicity category)
M	-Mutagenicity (one of four health effects categories in CHEM)
MAOL	-Most Appropriate Occupational Limit (in Chem)
MTD	-maximum tolerated dose (in carcinogenicity testing)
NAS	-National Academy of Sciences
NCAB	-National Cancer Advisory Board
NCI	-National Cancer Institute
ND	-No Data (in CHEM and AAL methodologies)
NESHAP	-National Emission Standard for Hazardous Air Pollutants
NIEHS	-National Institute of Environmental Health and Safety
NIOSH	-National Institute for Occupational Safety and Health
NLM	-National Library of Medicine
NRC	-National Research Council (of the NAS)
NTP	-National Toxicology Program (formerly NCI)
NTEUF	-non-threshold effects uncertainty factor (uncertainty factor applied in AAL derivation procedure)
NTEL	-nonthreshold effects exposure limit
OAQPS	-EPA Office of Air Quality Planning and Standards
ORS	-Office of Research and Standards (Massachusetts DEQE)
OSHA	-Occupational Safety and Health Administration
OSTP	-Office of Science and Technology Policy
OTA	-Office of Technology Assessment
PCB	-polychlorinated biphenyl
PEL	-Permissible Exposure Limit (OSHA occupational limit)
ppb	-parts per billion
ppm	-parts per million
RfD	-risk reference dose (formerly Acceptable Daily Intake - ADI)
RR	-risk ratio (used in developmental/reproductive toxicity category)
RTECS	-Registry of Toxic Effects of Chemical Substances (a NIOSH data base)
SAR	-structure-activity-relationship analysis
TEL	-threshold effects exposure limit
TEUF	-threshold effects uncertainty factor (applied in AAL derivation procedure)
TLV	-threshold limit value (ACGIH occupational limit)
TOX	-toxic effects uncertainty factor applied for inadequate toxicity data in AAL derivation procedure
TRL	-target risk level
TSCA	-Toxic Substances Control Act

APPENDIX D

PROCEDURES FOR CONDUCTING QUANTITATIVE DOSE-RESPONSE ASSESSMENT FOR CARCINOGENS

APPENDIX D
TABLE OF CONTENTS

I. Introduction

A. Background

The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL) was distributed as a draft for external review in June 1985. The document and methodology were developed by the Office of Research and Standards and the Division of Air Quality Control of the Department of Environmental Protection (The Department) as the health-based component of an Air Toxics Program.

In response to the comments received during the 1985 review, several important changes were made to CHEM/AAL. The principal change was to use quantitative dose-response assessment directly in the derivation of allowable ambient limits for carcinogens. The use of quantitative dose-response assessment for purposes of scoring is described in CHEM and the use of cancer unit risk in deriving the AAL is described in Part III, the Method to Derive Allowable Ambient Limits. The qualitative assessment of carcinogenicity is also described in CHEM (Part II, section D). The purpose of this Appendix is to describe in detail the procedures used for quantitative dose-response assessment for carcinogens.

B. Reasons for Changes in CHEM/AAL

In the draft version of CHEM/AAL (DEQE, 1985) an AAL for carcinogens and mutagens was determined on the basis of uncertainty factors applied to a selected occupational limit. The original toxic effects uncertainty factors were applied to chemicals with data indicating carcinogenic or mutagenic effects. The AAL resulting from this approach was criticized during the review process because: (1) the cancer risks

calculated at the AAL concentration (using unit risk values calculated by the Carcinogen Assessment Group [CAG] of the EPA Office of Health and Environmental Assessment) were high in some cases; and (2) there were examples of a lack of internal consistency such that one chemical would have an AAL which was lower than another chemical which is suspected to be a more potent carcinogen. Some examples of cancer risk calculations based on the 1985 draft AALs are shown in Table D-1. The estimated cancer risks are compared to the AALs (1×10^{-6} now adopted by the Department.

Two factors contributed to the variability in calculated risk. Of major importance in this regard was the way that the occupational limits addressed carcinogenicity. In some cases the threshold limit value (TLV) set by ACGIH is based on chronic toxicity only and does not account for carcinogenicity (e.g., carbon tetrachloride, chloroform). The stated reasons for making no adjustment in these two cases and several others suggest that ACGIH: (1) considers carcinogenesis to exhibit a threshold in some cases; (2) does not consider mouse liver tumors to be relevant in some cases; and, (3) does not consider gavage exposure in animal experimants to be relevant to occupational inhalation exposure in some cases. These conclusions are inferred from the statements made in the TLV documentation (ACGIH, 1986) but are not stated explicitly as a policy of ACGIH. In other cases the TLV is reduced by a factor of 100-1000 from the apparent no effect level for chronic effects to "account for" carcinogenicity. The recently published procedures for carcinogen identification (Spiritas et al., 1986) from the ACGIH TLV committee states that "Traditionally, the decision has been to take the lowest level known to induce cancer in experimental animals and divide by an arbitrary factor, such as 100 or 1000". An examination of the TLV documentation suggests that this approach has not been used consistently

Table D-1. Excess Lifetime Cancer Risk at Formerly Proposed AAL Concentrations (6-85).

Chemical	CAG Unit Risk[1] $(ug/m^3)^{-1}$	Former AAL[2] (ug/m^3)	Cancer Risk at former AAL (per million)
Benzene	$8.1x10^{-6}$	4.1	34
Beryllium	$2.4x10^{-3}$	0.007	16
1,3-Butadiene	$2.9x10^{-4}$	3.0	870
Cadmium	$1.8x10^{-3}$	0.005	9
Chromium VI	$1.2x10^{-2}$	0.001	12
Carbon Tetrachloride	$1.5x10^{-5}$	8.2	120
Chloroform	$2.3x10^{-5}$	13.6	320
1,2-dichloroethane	$2.6x10^{-5}$	0.54	14
PCB	$2.2x10^{-3}$	0.001	1.2
Vinyl chloride	$2.6x10^{-6}$	0.27	0.7
Vinylidene Chloride	$5.0x10^{-5}$	10.9	550

[1] Unit risk values developed by the EPA Carcinogen Assessment Group.

[2] AAL values released by the Department in 1985. THESE ARE NOT CURRENT VALUES.

and that other factors play a role in setting occupational limits for carcinogens. Even if this procedure were used consistently, the resulting risks would be high for continuous environmental exposure. In a typical animal carcinogenicity bioassay, the lowest detectable increase in tumor incidence is about 10%. Using linear extrapolation, the reduction of this dose by 1000 still results in an excess lifetime risk of 10^{-4} or one in ten thousand.

A second important cause of the variability in the cancer risk calculated at the previously proposed AAL is the quantity of data available and the application of uncertainty factors in CHEM/AAL. Total uncertainty factors applied to the adjusted MAOL ranged from 1 to 1000 for carcinogens. In some cases no uncertainty factor was applied because ACGIH or NIOSH apparently considered the carcinogenicity data in deriving the occupational limit. For example, no uncertainty factor was applied for carcinogenicity for chloroform. In other cases a total uncertainty factor of 1000 was applied to the adjusted MAOL because animal carcinogenicity was not considered in the occupational literature.

The application of uncertainty factors in CHEM/AAL and the treatment of chemicals by the groups setting occupational limits were not directly related to carcinogenic potency and did not result in a consistent level of risk at the AAL. It might be possible to achieve AALs which result in a consistent level of risk by applying a constant uncertainty factor to an occupational standard if a linear relationship exists between carcinogenic potency and chronic toxicity, and if the occupational limit is a consistent measure of chronic toxicity. A strong correlation has been shown between carcinogenic potency and acute toxicity as measured by LD_{50} (Zeise et al., 1985; Zeise et al., 1986). However, the uncertainty associated with this correlation was greater than

1 order of magnitude. A preliminary examination of the chemicals evaluated using CHEM for which CAG potency estimates were available suggests that a similar relationship may exist between the no-observed-effect-level (NOEL) for chronic effects derived from the occupational literature and carcinogenic potency. The uncertainty in this relationship is likely to exceed that for acute effects because of the few chemicals assessed and the difficulty in defining chronic endpoints.

In conclusion, the Department found that it is not possible to derive ambient limits on an uncertainty factor basis and expect them to be consistent when evaluated on a cancer potency basis. Therefore, more direct use of the carcinogenic potency will be made in setting allowable limits for air, when this information is available.

C. Cancer Potency Data

Quantitative dose-response assessment refers to the methods used to estimate the carcinogenic potency and unit risk using animal bioassays or human epidemiological studies. The carcinogenic potency is typically expressed as the risk for a given lifetime daily dose (usually expressed as mg/kg/d). This value is obtained by extrapolating the dose-response data in animals to low doses and making appropriate conversions to express human risk. The carcinogenic potency is then typically converted to a unit risk value. The unit risk is the risk associated with lifetime exposure to a given environmental level (usually expressed as ug/m^3 in air or ug/L in drinking water). The potency can be converted to the unit risk if information is available about the exposure and the absorption of the chemical. In the absence of this information a unit risk can be calculated from the potency by making assumptions about

the exposure and the absorption. For example, the unit risk for inhalation exposure is calculated by assuming that a 70 kg person inhales 20 m^3 of air/day and that the chemical is completely absorbed. An air concentration of 1 ug/m^3 results in a daily dose of 1ug/m^3 x 20m^3/70kg x 1 mg/1000 ug = 0.000286 mg/kg/d. This value is used to convert potency to unit risk.

A principal source of potency values is the Carcinogen Assessment Group (CAG) of the EPA Office of Health and Environmental Assessment. The CAG develops carcinogen assessments in response to the needs and priorities of various EPA offices. The CAG has published carcinogenic potency estimates for 55 chemicals (EPA, 1985a) and work on approximately 150 more is in progress (Personal communication - Charles Ris). The California Department of Health Services (CalDHS) has performed carcinogenicity dose-response assessments and calculated cancer potency for six chemicals for use in the state air toxics program and will be doing more in the future. Several other state agencies are currently performing or are planning to perform cancer risk assessments, as a part of their regulatory activities.

Because the carcinogenicity of chemicals of interest to the Department may not have been assessed by CAG or by any other qualified agency, the Department has developed the procedures described herein to perform these assessments. Of the 105 chemicals assessed in the development of CHEM/AAL, 43 have information available that could be used to estimate potency. Of these, potency values had been estimated by CAG for 27 chemicals. To insure the ability of the Department to assess chemicals as needed, it is necessary to perform quantitative dose-response assessment for carcinogens and to critically assess the data and calculations prepared by others. The procedures by which this will be accomplished

are contained in this Appendix. The application of current scientific understanding to dose-response assessment and the calculation of cancer potency is a technically complex process. In many cases choices must be made among several options that may not have solid theoretical or experimental foundations. These decisions have been referred to as science policy (Cal DHS, 1985), or as risk assessment policy (NRC, 1983), and require a combination of factual information and professional judgement. Many points in the risk assessment process generally and in quantitative dose-response assessment in particular, require science policy decisions, and the choices that are made have a large impact on the outcome of the analysis. For example, there is some evidence that a chemical causing cancer in one species will cause cancer in other species if adequately tested. However, since it is not known a priori that a particular chemical which causes cancer in animals is a human carcinogen, this is generally presumed to be the case as a matter of science policy so that animal experiments can be used in risk assessment for humans.

Science policy decisions range from those that have strong experimental support such as the presumption that a carcinogen in one species will be active in another, to those that have little experimental and theoretical support, such as the choice of mathematical model for low-dose extrapolation, or the method used to scale doses between species. Some of these decisions are made because there is a need for a consistent approach rather than because there is a clear scientific basis for the decision in a given case. In fact, each point at which a science policy decision must be made represents an issue which is the subject of ongoing scientific exploration. Not surprisingly, these are also areas of controversy and contention in the application of risk assessment to environmental regulation. The purpose of

this Appendix is to describe in detail the methods presently used by the Department to perform dose-response assessment including calculation of carcinogenic potency and unit risk values, and to specify to the extent possible the science policy options that will be used in that calculation.

D. Basis for the Procedures

The basis for much of the current discussion about risk assessment derives from the National Research Council report (NRC, 1983), which distinguishes risk assessment, "the use of the factual base to define the health effects of exposure", from risk management which is "the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data, and with social, economic, and political concerns to reach a decision." The NRC report defines risk assessment as consisting of four steps: hazard identification; dose-response assessment; exposure assessment; and, risk characterization. The discussion in this Appendix is concerned exclusively with dose-response assessment.

The scientific background of the process of carcinogenesis has been the subject of two recent reviews (OSTP, 1985; CalDHS, 1985). The Office of Science and Technology Policy report (OSTP, 1985) was written by senior scientists from several federal regulatory agencies together with a large group of experts in the disciplines reviewed. The California guidelines (CalDHS, 1985) were developed over several years by agency scientists with the participation of a group of experts in carcinogen risk assessment. These reviews provide a broad discussion of the current state of scientific understanding of many aspects of the carcinogenic process and the role of chemicals in that process.

On the basis of current understanding of chemical carcinogenesis and the factual information reviewed by OSTP, CalDHS, and others, and within the framework provided by the NRC report, several agencies have produced guidelines to be followed in performing risk assessment for chemical carcinogens (OSTP, 1985; CalDHS, 1985; EPA, 1986; Mass DPH, 1988). These guidelines are designed to promote consistency in the performance of risk assessment for chemical carcinogens, and to clarify for the interested public the procedures used in risk assessment. These guidelines constitute a statement of recommendations regarding the science policy choices which are to be made at various points in the process of risk assessment. They vary in their comprehensiveness and flexibility but are designed to retain flexibility with regard to procedures in order to accommodate special cases or specific applications and to allow incorporation of new data, new methodologies, or a new consensus of opinion. The guidelines reflect a consensus on the part of environmental scientists and regulators with regard to many of the policy decisions needed for carcinogen risk assessment. This consensus has resulted from an in-depth assessment of the available data by qualified scientists, current theories about chemical carcinogenesis, and the effect of the different options on the outcome. In general, such consensus represents the philosophy of regulatory agencies to act conservatively when there is a lack of scientific data or a strictly scientific basis to choose one option over another. The approaches recommended in these guidelines are considered by the Department to be the best approach given the currently available data, and are the basis for the procedures described herein.

In developing its procedure for dose-response assessment of chemical carcinogens, the Department has relied heavily on

the background provided by the OSTP (1985) and Cal DHS (1985) reports and on the guideline recommendations of the EPA (1986) and Cal DHS (1985). In particular the EPA guidelines have been followed closely.

E. Need for a Statement of Procedures

In the context of the Air Toxics Program the Department has elected to develop a standardized approach to the assessment of health effects of each chemical of interest. This procedure is intended to represent a specific approach to the assessment of carcinogens which is at once consistent with scientific fact and with generally accepted science policy, and also tailored to the specific needs of the Department. Using this approach, the Department can proceed expeditiously within the constraints of available resources, and at the same time, provide a consistent approach to the dose-response assessment of carcinogens. This will allow timely assessment of chemicals which are of interest to the Department while maintaining the scientific credibility of the procedure.

Like the approach to health effects assessment used in CHEM, the procedure for carcinogen dose-response assessment is designed to be a reasonable alternative to the extensive evaluations performed by some other agencies. One such approach, used by the EPA, CalDHS, and others, involves gathering and reviewing a broad range of background information as part of a cancer risk assessment. Information on chemical properties, sources, exposure, acute and chronic effects, metabolism and kinetics, short-term tests, and human and animal carcinogenicity data are reviewed. After consideration of all relevant data a dose-response assessment is performed.

An alternative approach to carcinogen dose-response assessment is the use of computerized data bases of carcinogenicity bioassay data, and application of a single uniform approach to dose-response calculation to all studies, with no critical evaluation of biological or technical factors (Gold et al., 1984; Peto et al. 1984; Crouch and Wilson, 1979). The procedures selected by the Department are considered to be a reasonable middle ground between the two approaches outlined above.

Because the procedures described herein were designed to fit the specific needs of the Department, this Appendix is necessary in order to define in detail the particular science policy and technical considerations which will be used. The procedures represent a standard approach applicable to all chemicals that have sufficient data to perform a quantitative dose-response assessment. The limits of the analyses to be performed and the extent of the data review that will be routinely undertaken by the Department are discussed, as well as the circumstances under which the standard approach may be augmented by additional data and analysis when available. This Appendix provides the details of the technical approach and policy decisions to be used by the Department.

II. Quantitative Dose-Response Assessment Procedures

A. Qualitative Assessment

The qualitative assessment of carcinogens consists of a consideration of the overall weight-of-evidence, and an evaluation of the likelihood that the chemical is a human carcinogen, based on all relevant data. This assessment is termed hazard identification in the NRC terminology. The procedure used by the Department is explained in CHEM, Part II, Section D (3a), Qualitative Evidence. The classification

scheme for the weight-of-evidence is adapted from the EPA Guidelines (EPA, 1986). The evidence from human epidemiological studies and from experimental animal studies is reviewed, evaluated separately, and classified as sufficient, limited, or inadequate. The combination of animal and human evidence is used to classify chemicals into Group A-Human Carcinogen, Group B-Probable Human Carcinogen, Group C-Possible Human Carcinogen, Group D-Not Classifiable as to Human Carcinogenicity, Group E-Inconclusive Evidence, Group F-Nonpositive Evidence of Carcinogenicity, or No Data (chemical not tested). Although the weight-of-evidence classification does not play a direct role in the quantitative dose-response assessment, it is indirectly involved in determining the use of carcinogenic potency data. For example, the EPA guidelines state that chemicals in "Groups A and B would be regarded as suitable for quantitative risk assessment", while agents "in Group C will generally be regarded as suitable for quantitative risk assessment", but this should be decided "on a case-by-case basis" (EPA, 1986).

Some EPA offices and State agencies have elected to calculate carcinogenic potency for chemicals in group A and B, but not for Group C. Other agencies have elected to use the weight-of-evidence classification to determine the acceptable risk level, with Group A being regulated at a lower risk level than Group B. After considering these approaches, the Department elected not to use either method because the validity and accuracy of a calculated carcinogenic potency value do not depend directly on the weight-of-evidence. Rather, the validity of a potency value depends on the biological relevance and technical adequacy of the data used to calculate the potency. The factors to be considered in determining whether a unit risk value will be used are described in section II.C. The Department will

generally follow the EPA guidelines as cited above and perform dose-response assessment for chemicals in Groups A, B, and C. However, for all chemicals and data sets, the adequacy of the data for dose-response assessment will be evaluated on a case-by-case basis using criteria discussed in section II.C. of this Appendix.

B. Sources of Data

The principal source of information for quantitative dose-response assessment is the Carcinogen Assessment Group (CAG) of the EPA Office of Health and Environmental Assessment. The EPA performs exhaustive assessments of all relevant data including acute/chronic toxicity, mutagenicity, pharmacokinetics, metabolism, animal carcinogenicity and human epidemiology, and the CAG uses these data to estimate carcinogenic potency. The carcinogenic potency is typically converted to a unit risk, which is the risk at a defined unit level of exposure. For air exposure, the unit risk is expressed as the estimated excess lifetime cancer risk from lifetime exposure to one microgram of the chemical per cubic meter of air. The CAG has estimated unit risk values for approximately 55 chemicals to date (EPA, 1985a) and there are 150 more evaluations in progress (Charles Ris-Personal Communication, 5/87). The CAG will continue to be the primary source of unit risk values for the Department. CAG unit risk values are reviewed by the Department and will be used as recommended by CAG with few exceptions.

Exceptions to the use of CAG unit risk values occur for three possible reasons. First, the CAG value may have been calculated and published as part of the 1980 Ambient Water Quality Criteria Documents. The procedure used in these assessments may not be relevant for air toxics, may be inconsistent with current EPA guidelines, or with the

criteria adopted by the Department as described in this document, and may therefore not be appropriate for use (e.g., ethyl acrylate). Second, the Department may disagree with a CAG evaluation and decline to use the CAG unit risk value. For example, the Department does not agree with the CAG use of human retention data in the unit risk calculations for trichloroethylene (EPA, 1985c) and tetrachloroethylene (EPA, 1985b, 1986), and has revised the unit risk values accordingly. Third, in some cases, the unit risk values being developed by CAG are preliminary and not yet final or peer-reviewed. The Department will not usually use CAG unit risk values that have not been formally released by the EPA. For example, unit risk values for acetaldehyde and 1,2-dichloropropane were obtained in a telephone conversation with CAG staff. Neither was adopted for use by the Department because it is not clear whether the assessments are consistent with the criteria used by the Department. Appendix E contains the dose-response calculations and documentation for each chemical evaluated.

When CAG has not assessed a chemical which is of interest to the Department, assessments from other sources are reviewed. Various public agencies have performed, or plan to perform detailed risk assessments as a part of regulatory programs. These include the California Department of Health Services, Northeast States for Coordinated Air Use Management, and agencies in the States of New Jersey, Connecticut, and Michigan, among others. It is also likely that participation by private agencies and individuals in the performance of risk assessment will increase. For example, scientists at the Chemical Industry Institute for Toxicology have published a quantitative risk assessment for formaldehyde (Starr and Buck, 1984). As a matter of standard procedure, the Department will obtain and review CAG unit risk calculations when available. The Department does not

intend to routinely review all unit risks from all sources that are available for a given chemical. However, while a thorough risk assessment for a single chemical represents a great deal of effort, it would be a significant benefit to the Department to make use of the work of other qualified agencies and individuals. Therefore the Department will review available risk assessments and will be responsive to information submitted by interested parties, within the constraints of available resources.

When the CAG has not evaluated a chemical which is of interest to the Department, and when an acceptable dose-response assessment is not available from any other source, a unit risk value will be calculated by the Department. The remainder of this Appendix is concerned primarily with the technical details of this calculation. As a standard procedure the Department will use data from the National Toxicology Program (NTP)/National Cancer Institute (NCI) Carcinogenesis Bioassay Testing Program (hereafter NTP) when available and appropriate. The NTP studies are a preferred source of data because they conform to strict criteria with regard to technical adequacy of experimental design and performance, and data collection and analysis. The NTP studies are designed and carried out in a relatively consistent manner, they are well-documented, and they undergo a detailed technical audit and expert scientific review before being released. For the chemicals assessed to date, all unit risk values calculated by the Department have been based on NTP studies, with the exception of the unit risk for acetaldehyde which was based on a study by Woutersen et al. (1986), and formaldehyde (CIIT rat study, 1983).

The Department will retain the option to use other sources of data for quantitative dose-response assessment. Studies which have undergone scientific peer review are

preferred and the technical adequacy of a given study will be judged based on previously published criteria (Sontag et al., 1976; IARC, 1980; NTP, 1984; OSTP, 1985). It is not the intent of the Department to comprehensively evaluate all data for each chemical with regard to relevance to quantitative dose-response assessment. However, the Department will obtain and analyze data from available sources as warranted, and will be responsive to information submitted by interested parties, within the constraints of available resources.

In general the Department will consider quantitative dose-response assessments based on human studies to be preferred to those based on animal studies, and will use unit risk values based on human data when they are available and are well-documented. For example, the CAG dose-response assessment for benzene uses data from occupational exposure (EPA, 1979), while the CalDHS elected to base its dose-response assessment on a draft of the NTP gavage study (NTP, 1986) because of certain questions about the human studies (CalDHS, 1984). The Department elected to adopt the CAG assessment because it is based on information from human exposures.

C. Selection of Data for Quantitative Dose-Response Assessment

The adequacy of the data for a given chemical for use in quantitative risk assessment must be judged on the basis of both the overall weight-of-evidence and the technical adequacy of the particular study. The EPA guidelines state that chemicals in Groups A-Human Carcinogen and B-Probable Human Carcinogen would be regarded as suitable for quantitative risk assessment and that chemicals in Group C-Possible Human Carcinogen will generally be regarded as suitable for quantitative risk assessment, but judgements in

this regard may be made on a case-by-case basis. The EPA does not elaborate except to say that adequacy is "determined by the quality of the data, its relevance to human models of exposure, and other technical details" (EPA, 1986). The Department will take a position similar to EPA with regard to the adequacy of a data set for quantitative assessment. A chemical which falls in Group C has, by definition, produced a statisitically significant increase in tumors in only one species, strain, or published experiment. In this case, the decision to use quantitative dose-response assessment must be based on criteria other than the weight-of-evidence. Also, for chemicals producing a carcinogenic response at multiple sites and/or in multiple species, a decision must be made regarding the site and species which will be used for quantitative dose-response assessment. These decisions must also be based on consistent criteria.

The criteria on which these decisions are based are related to biological factors which are important to the interpretation of the carcinogenic response, and to the technical consistency and quality of the study. The criteria used for these purposes are similar to the considerations used in performing the qualitative assessment of carcinogens. The EPA guidelines outline several factors which can increase the weight-of-evidence, including "increase in number of tissue sites affected...number of animal species, strains, sexes, and number of experiments and doses...occurrence of a clearcut dose-response ...high level of significance ...dose-related shortening of time-to-tumor...and dose-related increase in the proportion of tumors that are malignant" (EPA, 1986). The EPA guidelines reiterate OSTP principle 4 which states that agents causing extensive organ damage, hormonal disruption or other "non-physiological responses...must be carefully reviewed" (OSTP 1985). The EPA guidelines also state that carcinogenic responses in

animals "should be reviewed carefully as they relate to the relevance of the evidence to human carcinogenic risks" (EPA, 1986). Squire (1981) discussed several criteria for evaluation of animal cancer bioassays in order to construct a weighting system for carcinogens. The factors considered by Squire, listed in order of decreasing weight, include: number of species and sites, spontaneous incidence, potency, malignancy, and results from short-term tests (Squire, 1981). A weighting system constructed by Crump and Co. (1986) for the purpose of generating a confidence index for a quantitative dose-response assessment incorporated the following factors: temporal exposure pattern, length of treatment, identity of test material, number of treatment groups, numbers of animals used, and other factors.

Several of the factors mentioned above are relevant to the choice of study and tumor site that will be used for dose-response assessment. Because of the number of different factors involved and the varying weight ascribed to them, the decisions made using these factors are not reducible to a simple set of logical conditions. Instead, the decisions must be made on a case-by-case basis on the overall balance of the evidence. The factors to be considered in the decision about which study and site to use for quantitative dose-response assessment are discussed in following sections. For a chemical in weight-of-evidence Group C, this is equivalent to a decision about whether to use quantitative risk assessment at all, since there is only a single tumor site for chemicals in this category. For chemicals in weight-of-evidence Group A or B, the choice of the most appropriate study and tumor site rests on these criteria.

1. Statistical Significance

Only tumor sites showing a significant increase in

the incidence of malignant tumors, or a statistically significant decrease in time to tumor, will be used. In the case of NTP reports, only those sites which the NTP considers to be significant will be used. The Department will rely on the statistical analysis of the study authors to determine statistical significance of increases in tumor incidences. Statistical tests for differences based on pairwise comparisons or on trends will be considered to be appropriate analyses for bioassay data. After careful review the Department will generally adopt the same criteria for significance as the original authors. (Note: there may be cases where a tumor site is considered "significant", even though not meeting the formal statistical tests applied in these examinations. This does not mean that the results are not statistically significant, but simply that the formal statistical tests may not be adequate for the application. For example, for a site with historically very low tumor rates, two or three tumors in a group of 50 animals does not meet the usually applied criteria for statistical significance, but this may be overruled by the application of knowledge about historical data formalized by using a statistical test which incorporates historical data).

2. Combining Neoplasms for Evaluation of Carcinogenicity

NTP policy states that benign and malignant neoplasms of the same cell origin should be analyzed both separately and in combination. The same applies to neoplasms having the same histogenesis but showing different morphologic or cellular features (McConnell et al., 1986). Since the carcinogenic evaluation of any given chemical may differ depending on whether and how neoplasms are combined, and since tumor formation is

only one of many responses caused by chemicals in mammals, it is important to look at tumor formation in the context of the study results as a whole. For example, in a given study, tumors originating from the same cell type in treated animals may be statistically significantly increased when combined, but may not show a statistically significant increase when analyzed separately. In evaluating such a study, the same results might be considered positive in the first case, and non-positive in the latter case. Conversely, combining tumors may mask a possible carcinogenic effect which would be apparent if benign and malignant tumors are evaluated separately. Combining neoplasms in such cases could result in a false-negative evaluation. Since regulatory action is often based on the results of carcinogenic evaluation, it is important to carefully consider each case, and to use all of the data presented in making decisions about whether and when it is appropriate to combine neoplasms.

The NTP has published criteria for combining neoplasms based on the following:

> "(a) Substantial evidence exists for progression of benign to malignant neoplasms of the same histomorphogenic type. Progression is considered more important if demonstrated within the study in question than if comparisons must be made with past experience (although this knowledge is valuable).
>
> (b) The occurrence of hyperplasia may be used as supporting evidence alone, but more so when the criteria for differentiating hyperplasia from benign neoplasia are not clear (i.e., borderline lesions) or when they are arbitrary and do not reflect the biologic potential of a given lesion.
>
> (c) Most neoplasms of the same histomorphogenic type are combined even if they occur in different anatomic sites.

(d) Neoplasms of different morphologic classification may be combined when their histomorphogensis is comparable.
These criteria are used as a first step in combining neoplasms. Other combinations are possible and are used at times, but these have ordinarily been given less scientific weight in the interpretation of carcinogenic potential."

Source: McConnell et al; 1986, p. 285

In addition, McConnell et al. have provided a list of organs and tissues indicating where combining neoplasms is or is not appropriate, based on those organs and tissues in which neoplasia are most often observed in F344 rats and B6C3F mice. They note that organs and tissues not currently on the list are evaluated on a case-by-case basis, and that there may be occasions where lesions not normally combined would be examined in combination if appropriate (e.g., neoplasms of different morphologic types in the same organ to establish a target organ effect)(McConnell et al., 1986, page 285).

The Department will use the recommendations cited above to determine appropriate combinations of tumors, based on the bioassay data and statistical analyses provided by study authors. Where EPA and NTP have not followed these recently published guidelines, the Department will use the NTP criteria if adequate information is provided in the bioassay report.

3. Combination of Sexes

Tumor incidences from male and female animals of the same species will generally not be combined for dose-response assessment, unless they are similar, in

order to identify and use the most sensitive site and species for the assessment.

4. Adjustment of Incidence Data

Tumor incidences are usually reported as the total incidence found at the end of the study. In general, the total incidence as reported in the bioassay report will be used for dose-response modeling. An adjusted incidence should be used if significant dose-related mortality occurs in a long-term study. This adjustment is made because animals dying early due to (non-cancer) toxicity are no longer at risk of developing tumors, and groups with increased mortality will underestimate the incidence of tumors that would have appeared if the animals had survived.

In the older reports in the NCI/NTP testing program, and in data from other sources, there is often no adjusted incidence reported. In this case, the final incidence data will be used and the Department will not calculate adjusted incidences. Adjusted incidences will only be used when there is a significant dose-related decrease in survival and the adjustment is reported by the authors. As discussed in section II.C.10, preference will be given to data sets which show no effect on survival, and only in cases in which all data sets show a significant increase in mortality will adjusted incidences be used. This approach is adopted in order to reduce the time involved in making dose-response assessments and will be followed except in special cases. In recent NTP reports the adjusted incidences are given as percent incidence. When adjusted incidences are used for dose-response modeling the incidence will be calculated as (adjusted incidence,

%) x (number of animals examined)/100, and will be rounded to the nearest integer.

5. Tissue Damage

In many cases the high doses used in animal bioassays cause serious tissue damage, resulting in inflammation, regeneration, or repair, at the site where tumors develop. This raises the possibility that the appearance of tissue damage may be causally related to the formation of tumors (Clayson, 1987). This theory suggests that tissue damage could lead to tumor formation by causing cell proliferation. Increased cell proliferation could then be an initiating factor by leading to more error-prone DNA synthesis or repair (Shank and Barrows, 1985), or it could be a promoting factor to unrelated initiating events by causing fixation of DNA damage during cell replication. This concept is supported experimentally by (1) the phenomenon of solid state carcinogenesis, (2) the increased incidence of tumors in animals with urinary tract stones, and (3) the lack of tumors at noncytotoxic doses of BHT A-treated forestomach of rat (Clayson, 1986). However, while chronic toxicity may play a role in carcinogenesis, chronic toxicity itself does not lead to cancer. In experiments with chemicals causing chronic liver damage in regenerative nodules, none metasticize or appear to be malignant. When exposed to genotoxic chemicals at doses causing maximum tumor response, chronic toxicity often follows, but there are also chemicals causing chronic toxicity without causing tumors (Cothern, 1987).

The existence of a threshold mechanism does not rule out the possibility that an agent also produces

initiating events. In this case the agent could promote its own initiating effect and a threshold model would not be appropriate because there would be some initiating activity at low doses. In this scenario it could be inferred that the dose-response curve would rise more steeply at the high (promoting) dose, as pointed out by the CalDHS (1985). If the doses used in the bioassay were above the threshold for promotion, the potency at low doses could then be overestimated because a linear extrapolation model would not model the low-dose slope. On the other hand, it is also possible that doses high enough to cause tissue damage may result in an underestimate of potency (e.g., as in radiation carcinogenesis) because precisely those cells most likely to transform may be those most likely to be killed off. At the least, it can be said that this situation complicates decision-making in quantitative dose-response assessment. Although the possibility of a threshold-type of effect is acknowledged in the EPA guidelines in the statement "Evidence indicating that high exposures alter tumor response by indirect mechanisms that may be unrelated to effects at lower exposures should be dealt with on an individual basis" (EPA, 1986), there is no consensus about how it should be "dealt with". The California DHS concludes that there are not "convincing scientific or public health grounds to justify incorporating the cytotoxic theory into the risk assessment process" (CalDHS, 1985).

The Department believes that insufficient grounds exist to conclusively distinguish between cytotoxic promoting effects and initiating effects in a standard regulatory context. An increase in tumors at a site which is also a target for acute and chronic toxicity is therefore considered to be qualitative evidence that an

agent is carcinogenic. However, decisions regarding the relevance and use of quantitative dose-response assessment are made on a case-by-case basis for each chemical. Information considered in the decision-making include degree and type of tissue damage, spontaneous (background) tumor incidence at the site and in the species/strain/sex of animal, data from short-term tests, and tumor site and type.

In regard to the difficult issue of mouse liver tumors, the Department currently follows the guidance recently provided by the EPA Science Advisory Board, recommending that". . .for the most part, mouse liver tumors are indicative of human carcinogenicity" (Cothern, 1987). The Board also concluded that male rat kidney tumors alone ". . .may not be indicative of human carcinogenicity. . ." (Cothern, 1987). The Department will continue to monitor new developments in this area of risk assessment, and will modify the procedures presented here on a periodic basis, as warranted.

It should be noted again that these considerations apply only to the decision to use quantitative dose-response assessment and not to the qualitative assessment. The occurrence of clear increases in tumor incidence, even at sites with significant tissue damage, is considered to be evidence of carcinogenicity in the context of the qualitative assessment of carcinogenicity. In the context of quantitative dose-response assessment some sites or tumors types may not be considered to provide a reasonable quantitative estimate of carcinogenic potency for humans. This will be decided on a case-by-case basis as described above.

6. Spontaneous Tumor Incidence

Spontaneous (background) tumor incidence will be used in conjunction with consideration of tissue damage as described above. In general it is preferable to use a site with lower spontaneous incidence for dose-response assessment. However, it should be noted that in the three largest animal experiments which have ever been performed, the megamouse experiment on 2-AAF and British MAFF experiments in rats on dimethyl and diethyl nitrosamine, it was the liver - the site with a high background incidence - which showed the most linear dose-response relationship down to the lowest doses. Furthermore, the doses were well below those at which overt tissue damage was being caused. Thus, information on spontaneous tumor incidence should be weighed in the context of overall site selection for dose-response assessment, but cannot alone rule out the use of quantitatve assessment.

7. Evidence from Short-Term Tests for Genetic Toxicity

Consideration of results from short-term tests can be useful for distinguishing initiating from non-initiating carcinogens. Such information is applicable only to the choice of whether to perform quantitative dose-response assessment, and not to the selection of the appropriate site. As such, it will generally be used in conjunction with information about tissue damage as described above. Positive evidence from short-term tests provides a stronger basis for use of a unit risk calculation while substantial nonpositive mutagenicity data indicate that unit risk calculation may not be appropriate when tissue damage is present.

When tissue damage is absent, a lack of evidence or nonpositive evidence from short-term tests is not sufficient grounds to choose not to do quantitative assessment.

8. Dose-Response Characteristics of Tumor Response

Evidence of tumors is considered to be less desirable for quantitative dose-response assessment if the increase occurs only at the low dose, only at the high dose, or only at the end of the study. In general, it is preferable to use a site with more than one significantly increased dosed group and a dose-related response. These considerations will be used to select the most appropriate tumor site for dose-response assessment when there is more than one site, but are not considered to be sufficient reason to choose not to use a study for dose-response assessment when no other adequate study is available.

9. Study Compromised by Exceedance of the MTD

The Maximum Tolerated Dose (MTD) is used to ensure that a carcinogen bioassay will not miss labelling a chemical as a carcinogen because too low a dose of the carcinogen has been used (Clayson, 1986). Thus it is preferable to use an animal bioassay which did not show an increase in non tumor-related mortality or a substantial decrease in weight gain in treated animals as compared to controls. In general the effect on non-tumor mortality is considered to be more important and will be considered first. These factors are not sufficient to indicate that quantitative dose-response assessment should not be conducted, but are used to select appropriate sites when there is more than one

positive data set. When there is a significant dose-related increase in non-tumor mortality in any positive data set, an alternative data set which shows no such effect on mortality will be used when available. If all available data sets show significant non-tumor mortality effects, the least affected data set will be preferred. A gross dose-related increase in non-tumor mortality would be sufficient reason to decide that a study is not adequate for dose-response assessment if the results are seriously compromised as a result (e.g., 1,1,1-trichloroethane).

A severe dose-related effect on body weight (greater than expected at the MTD) will be used as supportive evidence that a data set is inadequate for dose-response assessment but will not by itself indicate that a study is inadequate for dose-response assessment, unless there is a greater than 20% body weight deficit over the majority of the animal lifespan. In the case of the NTP studies, considerations of body weight and survival are used by the NTP to decide whether the study is adequate for interpretation, and studies which are severely compromised by exceedance of the MTD are considered to be inadequate for interpretation since such an exceedance may alter or mask a carcinogenic effect. A study which is interpreted as adequate by the NTP is therefore unlikely to be found to be inadequate by the Department. In most cases these criteria will only be used in selection of the most appropriate tumor site for dose-response assessment.

10. Study Compromised by Inadequate Dosing Pattern

If the dosing pattern is substantially different from a daily dose or substantially less than lifetime

then the study will not be used for quantitative dose-response assessment. If doses are administered less frequently than once per week or are administered for less than 60 weeks or if the experiment is terminated before 80 weeks, the data will be considered to be inadequate for dose-response assessment (unless statistically significant increases in tumors are induced prior to this time).

11. Pharmacokinetic or Metabolism Differences

If there is sufficient evidence of differences in pharmacokinetics or metabolism to make extrapolation between routes, species or doses unreliable, the study will not be used for quantitative dose-response assessment. This criterion is discussed further in section II. D under dose calculation.

The criteria discussed above will be used to select the most appropriate site and study for dose-response assessment. These criteria are for this purpose only and do not apply to the qualitative assessment. As a result, it is possible for a chemical to be placed in weight-of-evidence Group B and have no unit risk value because the data did not fit these quantitative criteria (e.g., ethyl acrylate). In principle, this could also be true for a chemical in Group A, although this did not occur with the 105 chemicals evaluated.

D. Dose Calculation for Dose-Response Modeling

The calculation of unit risk involves the mathematical modeling of the relationship between the dose of the carcinogen and the response measured as tumor incidence or time-to-tumor. To do this it is necessary to choose a

mathematical model, and also an appropriate expression of the dose. The mathematical modeling is discussed in section II.F. The following discussion will describe the procedures used by the DEQE for dose calculation.

The dose calculation is the conversion of the administered dose or the exposure concentration to a dose metameter, or surrogate dose expression, which is suitable for use in dose-response modeling. In carcinogenicity bioassays the administration of the chemical is reported in terms of gavage dose (mg/kg/d), air concentration (ppm), or food or drinking water concentration (ppm). These expressions of dose or exposure will be referred to as the administered dose or administered exposure. For dose-response assessment a variety of different dose metameters could be used. It is standard practice to convert the administered exposure concentration (ppm in air, food, or water) to a measure of daily dose in mg/kg/d, and to calculate the average daily dose (also in mg/kg/d) over the lifetime of the animal studied. The dose metameter recommended for use in dose-response modeling is the surface area scaled lifetime average daily dose (EPA, 1986; CalDHS, 1985). The calculation of the average daily dose for dose-response modeling is discussed in this section for each route of exposure. Further adjustments to this dose can be made based on information about absorption, metabolism, or pharmacokinetics, and these are discussed in section II.E. The calculation of surface area scaled dose is discussed in section II.D.7.

1. Administered Dose and Administered Exposure Concentration

Although the specific details of the dose calculation will depend on the route of administration,

some general aspects are common to the different routes. As a standard procedure it is assumed that the administered dose as (mg/kg/d) is an appropriate measure of the dose for dose-response assessment for gavage, feed, or drinking water exposure. It is assumed that exposure concentration for inhalation studies (mg/m^3) can be used for dose-response assessment. It is generally assumed that it is valid to extrapolate across species, routes of exposure, and from high to low doses, as described below. These assumptions may be modified when appropriate data are available as described in later sections.

2. Lifetime Average Dose

The dose expression used for dose-response assessment is calculated as the lifetime average daily dose, or lifetime average daily exposure concentration for inhalation studies. For this purpose the lifetime of both rats and mice is assumed to be 104 weeks from birth. Although this value may underestimate the lifetime of rodent species, especially the rat, a study length of 104 weeks has commonly been used for carcinogenicity bioassays apparently for reasons of convenience and because the spontaneous tumor rate increases with study duration, reducing the sensitivity of the experiment for detecting treatment-related tumor formation. Although longer nominal lifespans can be justified, such as 130 weeks for rats (used by Crump and Co., 1986), CAG has used 104 weeks as a standard and the Department will do likewise.

Because experimental design of carcinogenicity bioassays varies, several different contingencies must be accounted for when calculating the lifetime average

dose. When the experimental design employs dosing for more than 104 weeks, the lifetime average dose will be calculated for the entire time of dosing. If dosing is ended earlier than 104 weeks of age and the animals live for 104 weeks or longer, the dose will be averaged over 104 weeks. If both dosing and study time are terminated prior to 104 weeks, the lifetime average dose is averaged over the total study time and a further adjustment will be made for less than lifetime exposure as discussed later.

3. Dose Calculation for Gavage Studies

For gavage studies the lifetime average dose (LAD) will be calculated as follows:

$$\text{LAD} = \underset{\text{(mg/kg/d)}}{\text{daily dose}} \times \underbrace{\frac{\text{days dosed per week}}{7}}_{\text{(mg/kg/d)}} \times \frac{\text{weeks dosed}}{104}$$

The last term would be replaced by (weeks dosed/study time) for studies that were terminated prior to the 104 week lifespan and it would be replaced by 1 for studies in which the animals were dosed for 104 weeks or longer. The study time is the age of the animals at the termination of the experiment.

4. Dose Calculation for Feeding Studies

For studies in which the chemical is incorporated into animal feed the dose (in mg/kg/d) can be calculated either on the basis of actual measurements of food consumption or on the basis of assumptions about food consumption in the absence of data. It is preferable to use estimates of dose based on measurements of food consumption made during the bioassay and this information will be used whenever it is available. This

information is usually presented as an estimate of average daily dose in mg/kg/day and this administered dose will be converted to lifetime average dose as described for gavage studies. If the concentration of the chemical in the diet is presented and no information is available on food consumption an estimate of dose will be calculated based on the equations derived by Crouch (1983). These equations are scaled to calculate the average dose in mg/kg/day and were derived using food consumption data from an early NCI bioassay. For this calculation the body weight at approximately 60 weeks is used. The equations for mouse dose are scaled to a nominal lifespan of 91 weeks and the results must be adjusted to reflect the 104 week nominal lifespan used by DEQE. This approach is preferred to that presented by the EPA which uses empirically derived factors for the fraction of the body weight consumed as food per day. The EPA approach assumes that the daily dose measured in adult animals gives an equivalent dose for all ages. The equations presented by Crouch (1983) are preferred because these equations integrate the food consumption over the entire animal lifespan and therefore account for the changes in food consumption patterns with age.

5. Dose Calculation for Drinking Water Studies

For studies in which the chemical is administered via the drinking water the administered dose (in mg/kg/d) can be calculated based on water consumption measurements made during the study or on the basis of assumptions about the water consumption if measured water consumption is not reported. Estimates of dose based on measurements of water consumption made during the bioassay are preferable and are used whenever

available. This administered dose estimate will be converted to a lifetime average dose as described for gavage studies. When only the concentration of the chemical in the drinking water is given the dose will be estimated using the equations used by EPA (1984).

For this calculation the CAG uses empirically derived factors as follows:

Species	Weight(kg)	f
man	70	0.029
rat	0.35	0.078
mouse	0.03	0.17

The value f is the fraction of the body weight consumed as water per day and the dose in mg/kg/day is then (f x ppm in the drinking water). This approach assumes that the daily dose calculated at a single body weight is equivalent to the dose at all ages. This is similar to the approach presented by the CAG for dietary administration as mentioned above. Although the approach developed by Crouch (1983) using empirically derived equations integrating consumption over the animal lifetime is preferred for feeding studies, analogous equations for drinking water consumption are not available to the Department at this time.

6. Dose Calculation for Inhalation Studies

For inhalation studies the standard procedure will be to assume that the lifetime average exposure concentration (mg/m^3) is an equivalent exposure across species. The lifetime average exposure concentration will be calculated as follows:

$$LAC = \text{experimental exposure concentration (ppm)} \times \frac{\text{hours exposed/day}}{24} \times \frac{\text{days exposed/wk}}{7} \times \frac{\text{wks exposed}}{104}.$$

The last term will be replaced by 1 if the exposure period is more than 104 weeks and will be replaced by weeks dosed/study length for studies that are terminated prior to the 104 week nominal lifespan.

As discussed in section II.D.7, equivalent doses across species are assumed to be related to the surface area, or to the body weight raised to the 0.67 power. This approach for inhalation studies assumes that the dose scaling between species is accounted for because the volume of air breathed (ventilation rate) is proportional to the body weight to the 0.74 power in different species (Davidson et al., 1986). Because the ventilation rate is nearly proportional to the surface area across species, the amount of chemical inhaled (the administered dose) is proportional to surface area, and it is not necessary to adjust the exposure concentration to account for interspecies scaling. It is also generally assumed that there are no dose-dependent metabolism or dose-dependent pharmacokinetic effects which affect the high to low dose extrapolation. Although these assumptions are clearly not accurate in all situations, they will be used in the absence of additional information. The use of pharmacokinetic data in the quantitative dose-response assessment will be discussed in more detail in the next section II.E. In the remainder of this section the possible effects of these assumptions will be outlined.

The assumptions for dose adjustment for inhalation studies should be accurate when the chemical of concern

is very reactive or very water soluble. In the case of water soluble or reactive chemicals, the chemical is likely to be completely absorbed at all concentrations in all species.

It is therefore appropriate to assume that the dose is implicitly scaled to surface area if the lifetime average exposure concentration is used in the dose-response assessment, because the inhaled volume scales between species with the surface area. Anderson (1983) suggests that reactive or soluble chemicals should be treated by calculating the dose on a mg/kg/d basis using a standard value for daily volume breathed and then scaling to surface area. The resulting carcinogenic potency then must be converted to an inhalation unit risk, again using standard biological values. This appears to be an unnecessary step, since ventilation rate automatically scales the inhaled dose to surface area, and one that adds an additional error since the breathing rates are based on standard values and do not account for differences in animal weight or for differences in respiratory rate with age. The use of this approach in calculating inhalation unit risk can result in a two-fold difference in unit risk compared with the results obtained by fitting the extrapolation model to the LAC.

Anderson (1983) recommends a similar approach for particles including the assumption of 100% uptake of the total ventilation. The accuracy of this assumption will depend on the size and solubility of the particle. For particles in the size range of 0.5-10 microns, 50-70% will deposit (Task Group on Lung Dynamics, 1966). Larger and smaller particles will be more completely absorbed. For soluble particles the deposited fraction

can be assumed to be completely absorbed. For insoluble particles the dose depends on other factors. Larger insoluble particles that deposit in the airways will be cleared by mucociliary transport and swallowed, and the absorbed dose will depend on gastrointestinal solubility and absorption. Smaller particles will deposit in the alveolar space and the systemic dose will depend on the clearance rate and dissolution rate. In the cases of particulate exposure and gases which have low solubility and are rapidly metabolized, the assumption of 100% absorption or deposition will result in an overestimate of the dose in an animal bioassay which can lead to an underestimate of potency for the animal. For this reason the Department prefers to assume the the deposition and absorption of these substance are the same between species, and to use the LAC as the dose metameter for dose-response assessment.

For partially soluble vapors which reach equilibrium, Anderson (1983) recommends the use of equivalent exposure concentrations between species for dose-response modeling. In this situation the exposure concentration reaches equilibrium with the body burden at high doses and the amount of the inhaled dose absorbed is limited to the amount metabolized or eliminated by other routes. This approach assumes that the pharmacokinetics are the same in different species and at high and low doses and that metabolism is related to the surface area between species. However, the assumption that exposure concentration can be used to extrapolate from high to low doses may be invalid because any saturation of metabolism will be dose-dependent and so a lower proportion of the inhaled dose may be absorbed at higher exposures. This can result in a large overestimate of the dose because the

amount of the inhaled dose which is absorbed at high exposures can vary between a large fraction for chemicals which are metabolized rapidly to a very small amount for chemicals which are metabolized slowly. Many chemicals that are partially soluble vapors have been studied sufficiently that data are available to relate the exposure concentration to the absorbed or metabolized dose. The recent advances in the development and validation of physiologically-based pharmacokinetic modeling also hold promise for defining the relationship between the exposure concentration and the effective dose. In the absence of information defining this relationship, the Department will consider the exposure concentration to be a valid dose metameter for dose-response modeling, although this could lead to an underestimate of risk at low doses.

7. Scaling of Dose

Dose scaling between species will be done using the surface area approach as recommended by EPA (1986) and the CalDHS (1985). The animal lifetime average daily dose expressed as mg/kg/d is multiplied by a factor of $(b.w./70)^{1/3}$ with b.w. equal to the animal body weight in kilograms. This calculation gives the equivalent human dose expressed as mg/kg/day. For this calculation the animal weight is the average weight for the group of animals as reported in the study and is obtained as the average weight over the last 30 weeks of the study. The actual measured weights are preferred. When they are not available, standard weights will be used. The standard weights used in this case will be 0.030 and 0.035 kg for female and male mice respectively and 0.35 and 0.40 kg for female and male rats respectively. The value of 70 kg is used as a standard adult (male) human

body weight. This scaling factor is not used in inhalation studies in which the dose metameter used in dose-response assessment is the lifetime average exposure concentration.

E. Use of Pharmacokinetic Data

The use of lifetime average daily dose for quantitative dose-response assessment assumes that there are no interspecies, interroute, or dose-dependent differences in the shape of the dose-response relationship. In the absence of other information the position of the Department is that the use of surface area adjusted lifetime average daily dose is a reasonable approach to dose-response modeling. Pharmacokinetic and metabolism data can provide information about the relationship between dose and response by providing a refined estimate of the effective dose. The Department will consider the use of additional data regarding pharmacokinetics and metabolism as an optional additional step to the procedure outlined above for dose calculation. This allows the use of new data and approaches with regard to the inclusion of pharmacokinetic data in dose-response assessment. The Department does not intend to undertake a detailed review of all the available data for every chemical assessed in all cases. However, it is the position of the Department that the inclusion of valid and applicable pharmacokinetic data in the risk assessment process constitutes an improvement in the procedure and the Department will therefore attempt to consider any available data or any information submitted by interested parties, within the constraints of available resources. Because the use of pharmacokinetic data in risk assessment is a rapidly developing and complex field, there are currently no agreed upon guidelines or recommendations for their use. In the

context of these procedures, the following general comments will outline the position of the Department with regard to the use of pharmacokinetic data.

1. Pharmacokinetic data refer to any information which quantitatively describes the relationship between the administered dose and the dose at the ultimate site of the toxic response and could include information regarding retention, absorption, disposition, distribution, metabolism, reaction, binding, and elimination. Also included is information describing or comparing these parameters in different species, for different routes of exposure, or at different doses.

2. The process relating administered dose to target site dose can be thought of, in general, as a sequential multistep process and each successive step is considered to be more proximate to the target dose. Estimates of doses at steps more proximate to the target dose are considered to be a more appropriate dose metameter for dose-response modeling than any preceding step. The steps that are postulated to occur between administered dose and the expression of the effective dose must be justifiable based on the available data, and on theoretical concepts about mechanisms of carcinogenesis for a particular chemical. For example, the following scheme could represent the process for an inhaled liver carcinogen:

inhaled dose ----> absorbed dose ----> dose to liver

---->metabolized dose --> reactive metabolite dose

to liver -->reactive metabolite dose to liver nucleus

---->DNA binding ....

3. Any pharmacokinetic data which are scientifically validated (peer reviewed and replicated) and which describe the relationship between administered dose and some other dose metameter along a biologically reasonable and clearly described pathway will be considered to be an improvement over the use of administered dose for dose-response modeling.

4. Lack of data describing species-, route-, or dose-dependent pharmacokinetics will not be considered sufficient reason to invalidate a data set for dose-response assessment and in this case the administered dose will be considered a valid dose expression. This will be the case even in cases for which a reasonable argument could be made that a dose-, species, or route-specific difference may occur. Pharmacokinetic data will be used to refine the quantitative dose-response assessment whenever possible. It is recognized that under various plausible scenarios the use of administered dose for dose-response assessment could either underestimate or overestimate the risk. However, in the absence of suitable pharmacokinetic data it may not be possible to account for these effects, even though these may be plausible or likely. In general in these cases it will be assumed that the administered dose represents a reasonable dose metameter for dose-response modeling and will be used.

F. Dose-Response Modeling

1. Choice of Model

The multistage model will be used to extrapolate from high dose to low dose in most cases. The multistage model has been used widely and is considered

to be an appropriate model under most circumstances (EPA, 1985, California DHS, 1985). It is consistent with some theoretical mechanisms of carcinogenicity and it incorporates the assumption of low dose linearity and lack of a threshold in low dose extrapolation. It is understood that choice of the model is critical with regard to the outcome of the quantitative dose-response assessment and can be the largest contributor to the uncertainty in the process (Anderson, 1987). The Department takes the position that the multistage model is appropriate and it will be used. When time-to-response data are available a multistage model with a time-dependent term may be used.

2. Calculation of Unit Risk

Potency estimates will be obtained from the multistage model for each data set considered adequate for dose-response assessment based on the criteria described in section II.C. The potency estimate used will be the 95% upper confidence limit on the linear term. For these calculations the Department uses the MSTAGE computer program developed by Crouch (1985).

3. Adjustment for Nonmonotonic Data

When the experimental tumor incidences do not increase in a dose dependent manner at high experimental doses the highest dose may be eliminated to improve the model fit. The procedure described by Anderson (1983) will be followed. If the predicted value from the multistage model when all data are used is significantly different ($p<.05$) than the observed incidence at the highest dose by the chi-square test, the upper dose group will be dropped and the model will be fit to the

remaining data points. This procedure will not be applied to data sets with only two dosed groups.

4. Adjustment For Less Than Lifetime Exposure

If an animal bioassay was terminated at a time prior to the end of the lifespan of the animal (104 wk), the potency estimates will be adjusted to account for the development of tumors that would have appeared had the animals lived their full lifetime. The potency (q_1*) will be multiplied by a factor of $(104/LE)^3$ (Anderson, 1983) where LE is the length of the experiment in weeks. This is based on the observation that human tumor incidences at a variety of sites increase in proportion to age raised to a factor of 3 to 6, with some sites being much higher.

5. Choice of Potency Value

The carcinogenic potency values calculated as described will be used to select the final potency value. The highest potency estimate determined at any of the sites considered to be adequate based on the criteria discussed in section II.C. will be selected. In particular, the selection of the final potency value will depend on the criteria described in subsections 6, 7, 9, 10, and 11 of section II.C.

6. Unit Risk Calculation For Air

The unit risk for air exposure will be based on a lifetime continuous exposure to 1 ug/m^3 air concentration. For most chemicals the calculated potency will be expressed in units of $(mg/kg/d)^{-1}$. To convert this value to a unit risk expressed as $(ug/m^3)^{-1}$,

the potency is multiplied by a factor of 0.000286. This value is derived as follows:

$$0.000286 \frac{mg/kg/d}{ug/m^3} = \frac{20\ m^3}{day} \times \frac{1}{70\ kg} \times \frac{1\ mg}{1000\ ug}$$

This conversion assumes a 70 kg person inhales 20 m^3 of air per day and that the human dose is equivalent to the total inspired dose (i.e. 100% absorption). Based on considerations similar to those discussed in section II.D.7, this is likely to be a reasonable assumption in some cases, but to overestimate the dose in other cases. At concentrations of interest for ambient exposures it is unlikely that significant accumulation of the chemical in blood or saturation of metabolism will occur for most chemicals. Therefore, for large particles and soluble chemicals the assumption of 100% absorption is reasonable. For small particles and partially soluble chemicals, some of the inhaled chemical is likely to be exhaled and the assumption of 100% absorption will overestimate the actual dose. Andersen (1981) used a physiologically-based pharmacokinetic model to predict absorption under various conditions. This model predicts that the actual absorption of inhaled partially soluble gases will decrease as the blood-air partition coefficient decreases below a value of approximately 10. The models predict that the absorption of partially soluble gases will increase to a maximum value of 70% at blood-air partition coefficients above 10. This prediction results from the fact that the absorption of these gases occurs in the alveolar region of the lung and the alveolar ventilation is approximately 70% of the total ventilation. This prediction also assumes that 100% of the absorbed dose is metabolized. This is a reasonable assumption for most chemicals at environmental concentrations. However, the risk may

actually be over- or underestimated. It depends on the difference between absorption in the animals under the experimental conditions, and absorption by humans under environmental conditions. When the dose-response modeling for an inhalation study uses the lifetime average concentration (see section II.D.7), the unit risk will be obtained directly from the model and will be expressed in units of (ug/m^3). In this case the unit risk value for humans for air is equal to the unit risk value derived from the animal study. Thus, it is assumed that the absorption of the inhaled dose is the same in different species and that there are no dose-dependent effects on carcinogenic potency. The validity of these assumptions is discussed in section II.D.7 and the Department's position with regard to the modification of these assumptions in special cases is discussed in section II.E.

G. Interpretation of Unit Risk Value

In the quantitative dose-response assessment process there are many factors which lead to uncertainty in the final unit risk value. Some of these uncertainties would be expected to lead to an overestimate of risk, and others to an underestimate of risk. In general the procedures used are designed to be conservative from the point of view of protection of the public health and as such they may tend to overestimate the risk. For this reason the unit risks are considered to be "a plausible upper limit to the risk. . . .The true value of the risk is unknown and may be as low as zero" (EPA 1985). The EPA Health Assessment Document for Epichlorohydrin states that "the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could

be much lower" (EPA, 1984). It is the position of the Department that the unit risk values calculated as described herein, or calculated by others and adopted for use by the Department represent the best available estimates of the human risks due to exposure to given chemicals, and will be used in regulatory decisions-making.

H. Reports of Dose-Response Assessments

A brief report has been prepared by the Department for each chemical assessed and will be available to interested parties. Each report describes the qualitative assessment of the data on carcinogenicity and the dose-response assessment. The study used for dose-response calculation and the rationale for selection of the study and tumor site will be described in detail, as well as the tumor incidence data, the dose calculation, and the use, if any, of pharmacokinetic data. Each report describes any assumptions made in the unit risk calculation and presents the unit risk values obtained along with a brief discussion of other risk assessments that have been performed. Reports prepared to date are presented in Appendix E of this document.

I. Results

During the development of CHEM, 105 chemicals were evaluated. Of these 105 chemicals, 46 had some evidence of carcinogenicity and had a CHEM carcinogenicity score of A,B,C, or D. Unit risk values were calculated and used for 38 of these. Unit risk values were not used for the other 8 chemicals for the following reasons: Two chemicals have qualitative evidence of carcinogenicity but quantitative data were unavailable to the Department (benzyl chloride and hydrazine). The data for hydrazine and benzyl chloride may be adequate for dose-response assessment but are not from the

NCI/NTP program and have not yet been obtained and reviewed by the Department. Nickel, nickel oxide, and lead subacetate have no unit risk value because the positive animal studies used subcutaneous or intramuscular injection and could not be used for dose-response assessment. The human studies for nickel oxide were not considered to be adequate for dose-response assessment by the EPA. The studies showing carcinogenicity due to mirex exposure are not considered to be adequate for dose-response assessment due to limitations in study design. The data for ethyl acrylate were not considered to be adequate for dose-response assessment because gavage treatment produced only local tumors of the forestomach in rats and mice. Tumor production due to ethyl acrylate exposure is likely to be by a direct mechanism (toxic insult leading to cell proliferation) and extrapolation between routes is not reliable. The unit risk value for chlorobenzene was not used because only benign tumors were found in the carcinogenicity bioassay. The data for the remaining 38 chemicals were considered adequate for dose-response assessment, and unit risk values have been calculated for each. The unit risk values adopted by the Department are listed in Table D-2 with the source of the unit risk value. The details of the calculations of the unit risk values, the rationale for selection of site and study used, and the rationale for use of dose-response assessment, are described in a Carcinogenicity Dose-Response Assessment report for each chemical, included in Appendix E to this document.

Table D-2. Unit Risk Values Adopted for Use by the Department as of 3-87.

Chemical	$(ug/m^3)^{-1}$	Source
Acetaldehyde	2.3×10^{-6}	DEP
Acrylonitrile	6.8×10^{-5}	EPA/CAG
Aniline	7.1×10^{-6}	DEP
Asbestos	7.6×10^{-3}	CAG/OAQPS
Benzene	8.1×10^{-6}	EPA/CAG
Beryllium	2.4×10^{-3}	EPA/CAG
1,3-butadiene	2.9×10^{-4}	EPA/CAG
Cadmium	1.8×10^{-3}	EPA/CAG
Carbon tetrachloride	1.5×10^{-5}	EPA/CAG
Chromium VI cmpds	1.2×10^{-2}	EPA/CAG
Chlordane	3.7×10^{-5}	EPA/CAG
Chloroform	2.4×10^{-5}	EPA/CAG
p-dichlorobenzene	2.4×10^{-6}	DEP
1,2-dichloroethane	2.6×10^{-5}	EPA/CAG
dichloromethane	4.1×10^{-6}	EPA/CAG
1,2-dichloropropane	1.8×10^{-5}	DEP
di(ethylhexyl)phthalate	1.3×10^{-6}	DEP
1,4-dioxane	4.1×10^{-6}	DEP
Epichlorohydrin	1.2×10^{-6}	EPA/CAG
Formaldehyde	1.3×10^{-5}	EPA/OTS
Heptachlor	1.3×10^{-3}	EPA/CAG
Hexachloroethane	4.0×10^{-6}	EPA/CAG
Lindane	3.8×10^{-4}	EPA/CAG
PCB	1.2×10^{-3}	EPA/CAG
Propylene oxide	6.6×10^{-7}	DEP
Selenium sulfide	2.0×10^{-5}	DEP
Styrene	5.7×10^{-7}	EPA/CAG
1,1,2,2-Tetrachloroethane	5.8×10^{-5}	EPA/CAG
Tetrachloroethylene	5.5×10^{-5}	DEP
Toluene diisocyanate	6.8×10^{-6}	DEP
o-toluidine	5.7×10^{-6}	DEP
1,1,2-Trichloroethane	1.6×10^{-5}	EPA/CAG
Trichloroethylene	1.6×10^{-6}	DEP
2,4,6-Trichlorophenol	6.2×10^{-6}	DEP
Vinyl chloride	2.6×10^{-6}	EPA/CAG
Vinylidene chloride	5.0×10^{-5}	EPA/CAG

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APPENDIX E

CARCINOGENICITY DOSE-RESPONSE ASSESSMENTS

TABLE OF CONTENTS

Introduction

This document is an Appendix to the Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL). These procedures have been developed for use in the Massachusetts Air Toxics Program.

This Appendix contains summary reports describing the quanitiative risk assessments performed by CAG and/or DEP. The reports include information about the basis for the qualitative assessment and the details of the unit risk calculation (when performed by DEP). Chemicals are aasigned to a weight-of-evidence category based on the EPA guidelines. The weight-of evidence classification may be obtained from the EPA, or determined by DEP if not available from EPA. The source and basis for the weight-of-evidence classification are described.

The derivation of the unit risk value is described in these reports. When there is a unit risk value recommended by the Carcinogen Assessment Group (CAG), the value will be reviewed by DEP and compared to DEP - calculated unit risks. If DEP and CAG values do not differ significantly, the CAG value will be adopted in the interest of consistency with EPA. When DEP does not adopt a CAG unit risk value, or when there is not CAG unit risk value, the details of the DEP calculation are presented. This includes the rationale for selection of study and tumor site used to calculate carcinogenic potency, the calculation of human equivalent dose, and the calculation of inhalation unit risk. When quantitative dose-response assessments are available from other sources, they will be reviewed and compared with the DEP value. The unit risk value adopted by DEP will be given and the basis for that selection will be explained.

These assessments have been performed as discussed in Appendix D of this document. In many case, reference is made to Appendix D for the details of the assessments. The reader is directed to Appendix D for discussion of the procedures used and the criteria used to make various decisions required in the analysis.

Also included in these reports are the mutagenicity weight-of-evidence as derived in CHEM, and any information that is available about the current status of the chemical in the NTP carcinogenesis bioassay program. All references are included in a section at the end of the Appendix. The tables are presented and numbered separately for each report.

Carcinogenicity Dose-Response Assessment for Acetaldehyde

Summary

The weight-of-evidence classifications for acetaldehyde are Group B2-Probable Human Carcinogen and Substantial for mutagenicity. CAG has derived a unit risk value of $2.2x10^{-6}$ $(ug/m^3)^{-1}$. The value was obtained in a telephone conversation with Charles Ris of the CAG (12-9-86). The DEP unit risk was calculated using the Woutersen et al. (1986) inhalation study. The unit risk value calculated by DEP is based on the incidence of nasal adenocarcinoma in the male rat. The DEP unit risk value is $2.26x10^{-6}$ $(ug/m^3)^{-1}$. The DEP unit risk value of $2.26x10^{-6}$ $(ug/m^3)^{-1}$ is adopted by the DEP for use in risk assessment of inhalation exposure.

Background

The designation of weight-of-evidence as Group B2-Probable Human Carcinogen for carcinogenicity is based on nasal tumors in rats (Woutersen et al., 1986) and in hamsters (Kruysse et al., 1975) after inhalation exposure, and injection site sarcomas after subcutaneous injection. The weight-of-evidence is classified by DEP based on EPA guidelines. IARC reviewed the evidence for carcinogenicity for acetaldehyde and concluded that there was sufficient animal evidence (IARC, 1985). The inhalation study by Woutersen et al. (1986) is the only study known to the DEP that can be used for quantitative dose-response assessment. A preliminary report of the interim sacrifices in this study was reported (Woutersen et al., 1984). The documentation for the CAG dose-response assessment was not available at the time of this writing and it is presumed to be based on this study. Because this documentation was not available, the DEP performed this dose-response assessment using the Woutersen et al. study. Acetaldehyde was listed as approved for toxicology studies in the National Toxicology Program on the 9-86 management status report but was not listed on the 1-87 status report (NTP, 1986a, 1987).

DEP Unit Risk Calculation Using the Woutersen et al. (1986) Study

Male and female rats were exposed to 0, 735, 1410, and 1521 ppm acetaldehyde for 6 hr/day, 5 days/week, for up to 28 months. The high dose group was initially exposed to 3000 ppm but was reduced gradually to a concentration of 1000 ppm during the first year of the study due to toxicity. The time-weighted average for the entire study was 1521 ppm for the high dose animals exposed for 28 months. There were 55 animals per exposure level exposed for 28 months. Rats of each sex were sacrificed at 13 weeks (5

animals), 26 weeks (5 animals), 12 months (10 animals), and 12 months with a 12 month recovery period (30 animals). The results for the 28 month exposure are used for dose-response assessment.

Mortality was significantly increased in the high-dose group, and body weight was significantly decreased in the two highest dose groups, in both males and females. Nasal squamous cell carcinoma and nasal adenocarcinoma increased significantly in both male and female rats. These tumor types (shown in Table 1) are used for dose-response modeling. These tumor types should not be pooled for assessment according to NTP guidelines (NTP, 1984; McConnell et al. 1986) and therefore were not pooled for dose-response assessment. The reported incidences were not adjusted by the authors to account for early mortality in the dosed groups.

Nonneoplastic pathology was also reported including degeneration and hyperplasia of the olfactory epithelium at all exposure levels, and squamous metaplasia, keratinization, and rhinitis at the two higher exposure levels. Laryngeal hyperplasia was also reported in the highest exposure level.

The lifetime average exposure concentration (LAC) was calculated using the following equation:

$$\text{LAC (ppm)} = \text{exposure concentration (ppm)} \times \frac{6}{24} \times \frac{5}{7} \times 1.$$

The time-weighted average exposure concentration for the high dose group was calculated using the concentrations and durations reported and a total exposure of 850 days (28 mos.). The lifetime average concentration is listed in Table 1 expressed as ppm and as mg/m^3. The dose-response model was fit to the lifetime average concentration in mg/m^3.

The dose-response model was fit to the tumor incidence data as shown in Table 1. For nasal adenocarcinoma the incidence in the high dose group did not increase in a dose-related pattern resulting in a poor fit using the multistage model. This may be due to the high mortality in this group. For this site the high-dose group was eliminated and the model was fit to the data from the control and two dosed groups. The 95% upper confidence limit on the linear term of the multistage model is used as the potency estimate and is listed in Table 2 for each site. Because the multistage model was fit to the lifetime average concentration, the upper confidence limit (q_1^*) is expressed in units of $(mg/m^3)^{-1}$. The site selected as the most appropriate site for dose-response assessment is the male rat nasal adenocarcinoma because it is the most sensitive of the sites analyzed. The unit risk based on this site is $2.26 \times 10^{-6} (\mu g/m^3)^{-1}$. There is no need to adjust this value for less than lifetime

exposure because the exposure was longer than the nominal lifetime of the animals.

A unit risk value can also be calculated using the groups exposed for 12 months followed by a 12 month recovery period. This was done for purposes of comparison only. The data from these groups would generally be considered inadequate for dose-response assessment by the DEP because the exposure was only half of the animals' nominal lifetime and because there were only 30 animals per group. When the exposure is expressed as the lifetime average concentration, the unit risk value for nasal adenocarcinoma is 3.0×10^{-6} $(ug/m^3)^{-1}$ for both males and females. If the exposure is expressed as the average during the year the animals were exposed, the unit risk values would be approximately one half of this value.

Discussion

This dose-response assessment was performed according to the methods described in Appendix D. This assessment does not use additional data to account for dose or species dependent effects on carcinogenic potency. It is therefore assumed that high-dose to low-dose and species-to-species extrapolation is valid, consistent with the DEP position that these extrapolations are a reasonable approach to dose-response assessment. Because of the solubility and reactivity of acetaldehyde and the fact that the toxicity occurs at the site of contact with the body, the unit risk calculated for inhalation exposure should not be used to derive unit risk for other routes of exposure.

Table 1 Tumor Incidence and Dose Calculation for Dose-Response Assessment of Acetaldehyde Using Woutersen et al. Study.

Exposure Concentration ppm	Nasal Tumor Incidences: Squamous Cell Carcinoma	Nasal Tumor Incidences: Adeno-carcinoma	Lifetime Average Exposure Concentration ppm	Lifetime Average Exposure Concentration mg/m^3
Rat- male				
0	1/49	0/49	0	0
735	1/52	16/52	125	225
1412	10/53	32/53	268	482
1521	15/49	21/49	272	490
Rat-female				
0	0/50	0/50	0	0
735	0/48	6/48	125	225
1412	5/53	26/53	268	482
1521	17/53	21/53	272	490

Table 2. Carcinogenic Potency for Acetaldehyde using Woutersen et al. Study

Tumor Site	q_1^* $(mg/m^3)^{-1}$
Rat-male	
Squamous cell carcinoma	3.43×10^{-4}
Adenocarcinoma	2.26×10^{-3}
Rat-female	
Squamous cell carcinoma	1.51×10^{-4}
Adenocarcinoma	8.89×10^{-4}

Carcinogenicity Dose-Response Assessment for Acrylonitrile

Summary

The weight-of-evidence classifications for acrylonitrile are Group A Human Carcinogen and Sufficient for mutagenicity. The EPA has reviewed the available toxicological data in the Health Assessment Document for Acrylonitrile (EPA, 1983). The weight-of-evidence classification is based on the EPA analysis of the animal data and of four epidemiological studies showing evidence of lung cancer in humans exposed to acrylonitrile (EPA, 1983). The EPA considers three of these studies to be suggestive and one to be adequate and the adequate study is used by the EPA for quantitative dose-response assessment. The IARC evaluation of the data on carcinogenicity of acrylonitrile concluded that there was limited human evidence and sufficient animal evidence (IARC, 1979a, 1982c). The animal evidence cited by IARC includes positive responses in rats at multiple sites, and in studies using inhalation, gavage, and drinking water. There is no current activity in the NTP program on acrylonitrile. The CAG unit risk value is 6.8×10^{-5} $(ug/m^3)^{-1}$ and is based on data from human inhalation exposure. The CAG unit risk value is adopted by the DEP for use in risk assessment of inhalation exposure

CAG has also derived potency estimates for ingestion exposures based on animal drinking water studies (EPA, 1983). The inhalation and ingestion carcinogenic potencies are different and the unit risk for one route should not be used to derive a unit risk for the other route.

Carcinogenicity Dose-Response Assessment for Aniline

Summary

The weight-of-evidence classifications for aniline are Group C-Possible Human Carcinogen and Limited evidence for mutagenicity. The CAG unit risk value is 7.4×10^{-6} $(ug/m^3)^{-1}$. The CAG value was obtained in a phone conversation with Charles Ris (9-17-86). The DEP unit risk value, calculated based on the incidence of spleen hemangiosarcoma in male rats in the National Cancer Institute feeding study (NCI, 1978g), is 7.09×10^{-6} $(ug/m^3)^{-1}$. This unit risk value is adopted by the DEP for use in risk assessment of inhalation exposure.

Introduction

The weight-of-evidence designation of aniline as Group C-Possible Human Carcinogen derives from the NCI study (NCI, 1978g) which shows malignant tumors at multiple sites in a single species. Other studies were cited by IARC as inadequate for evaluation (IARC, 1982a), and the IARC concluded that there was limited animal evidence and inadequate human evidence. The NTP report is the only study used by the DEP for quantitative dose-response assessment. The documentation for the CAG unit risk value was not available at the time of this writing, but is probably based on the NTP study. Because the EPA documentation was not available, the DEP performed this dose-response assessment using the NCI study. This study used aniline hydrochloride mixed into the animal feed. It is assumed that the carcinogenic activity of aniline hydrochloride is due to aniline. A new study of aniline was listed as approved for toxicology study in the 9-86 NTP Management Status Report but was not listed in the 1-87 status report (NTP, 1986a, 1987).

DEP Unit Risk Calculation Using the NCI Study (NCI, 1978g)

In the NCI study, F344 rats were fed diets containing 0.3 or 0.6 percent aniline hydrochloride and B6C3F1 mice were fed diets containing 0.6 or 1.2 percent aniline hydrochloride. These diets were fed to the animals from 6 weeks of age till 109 weeks of age, when all surviving animals were sacrificed.

No statistically significant effect of treatment on survival occurred in any group. Body weight gain was significantly reduced in the male mice but not in any other group.

Increases in the tumor incidence at several sites were considered to be significant by the NCI. In male rats increases in spleen hemangiosarcoma, spleen fibroma or sarcoma NOS, and

fibroma or sarcoma NOS of multiple organs were observed. Increased fibrosarcoma or sarcoma NOS at multiple organ sites occurred in female rats. There were no statistically significantly increased tumors in the dosed mice. The statistically significant increase in adrenal neoplasms in male rats was not considered by the NCI to be biologically significant due to the variable spontaneous occurrence of these tumors.

Nonneoplastic pathology was also observed in treated rats including papillary hyperplasia and fibrosis of the splenic capsule.

A lifetime average daily dose (LAD) was calculated using the equations reported by Crouch (1983), and is listed in Table 1. The equations of Crouch are used by DEP to calculate dose for feeding studies when there is no reported estimate of dose based on measurement of food consumption. The lifetime average daily dose was expressed as aniline rather than aniline hydrochloride by multiplying the calculated dose by 93.1/127.6, which is the ratio of the molecular weights of aniline and aniline hydrochloride. The doses are scaled between species by surface area scaling by multiplying the LAD by $(70/b.w.)^{-1/3}$ with b.w. equal to the the terminal body weights of animals in a particular dosed group. The surface area scaled LAD is listed in Table 1 and is used for dose-response modeling.

The tumor incidence data for the sites used in dose-response assessment are listed in Table 1. The multistage model was fit to the data in Table 1 and the 95% upper confidence limit on the linear term is used as the estimate of carcinogenic potency for each site. The potencies are listed in Table 2. There is no need for an adjustment for less than lifetime exposure because the experiment lasted longer than the nominal 104 week lifespan of the rat.

The carcinogenic potency for the male rat spleen hemangiosarcoma is the most sensitive of the sites analyzed and is used for calculation of a unit risk value for inhalation exposure. The nonneoplastic pathology reported in the spleen in this study is not considered to be sufficient to invalidate the dose-response assessment, in view of the low spontaneous incidence at this site. The carcinogenic potency at this site is 2.48×10^{-2} $(mg/kg/d)^{-1}$.

The unit risk for inhalation exposure is calculated assuming a 70 kg person breathing $20 m^3/d$ at a concentration of 1 ug/m^3 as follows:

$$\frac{2.48 \times 10^{-2}}{(mg/kg/d)^{-1}} \times \frac{20\ m^3}{d} \times \frac{1}{70\ kg} \times \frac{1\ mg}{1000\ ug} = 7.09 \times 10^{-6}\ (ug/m^3)^{-1}.$$

Discussion

The unit risk calculation for aniline was consistent with DEP procedures (Appendix D) and EPA guidelines (EPA, 1986b). Aniline has been shown to be carcinogenic in only one species and is classified by IARC as group 3. According to the EPA guidelines (EPA, 1986b) and the DEP procedures, chemicals in weight-of-evidence Group C are assessed on a case-by-case basis with regard to the adequacy of the data for quantitative dose-response assessment. In this case, the evidence is strengthened by the occurrence of relatively rare tumors in both male and female rats at multiple sites, and with positive dose-response at both doses at each site. Therefore the data are considered to be adequate for dose-response assessment. There are no additional data to account for dose, route, or species-specific effects on carcinogenic potency. It is therefore assumed that low-to-high dose, route-to-route, and species-to-species extrapolations are valid. This approach is consistent with the DEP position that these assumptions are a reasonable approach to dose-response assessment in the absence of additional data. Because the assumption of direct route-to-route extrapolation was made, the carcinogenic potency calculated here can be applied to oral exposures.

The unit risk value derived by CAG is very similar to the DEP value and is probably based on the same study. Because the documentation of this calculation has not been reviewed, the DEP value is adopted.

Table 1. Tumor Incidences and Dose Calculation for Dose-Response Assessment of Aniline Using NCI Feeding Study

	Male rat			Female rat		
	Dose			Dose		
Dose Calculation	Control	Low	High	Control	Low	High
Diet concentration (ppm)	0	3000	6000	0	3000	6000
LAD (mg/kg/d)	0	109	221	0	145	297
Surface area adjusted LAD (mg/kg/d)	0	18.5	37.1	0	20.9	41.2
Tumor Incidences						
Spleen hemangiosarcoma	0/25	19/50	20/46			
Spleen fibrosarcoma or sarcoma NOS	0/25	7/50	9/46			
Multiple organs fibrosarcoma or sarcoma NOS	0/25	2/50	9/48			
Spleen, body cavity, or multiple organs fibrosarcoma or sarcoma NOS				0/24	1/50	7/50

Table 2. Carcinogenic Potency Estimates for Aniline Using the NCI Feeding Study

Tumor Site	Potency $(mg/kg/d)^{-1}$
Male Rat	
Spleen hemangiosarcoma	2.48×10^{-2}
spleen fibrosarcoma or sarcoma NOS	9.84×10^{-3}
multiple organs fibrosarcoma or sarcoma NOS	5.91×10^{-3}
Female Rat	
Spleen, body cavity, or multiple organ fibrosarcoma or sarcoma NOS	3.78×10^{-3}

Carcinogenicity Dose-Response Assessment for Asbestos

Summary

The weight-of-evidence for asbestos is Group A for carcinogenicity and ND for mutagenicity. The data on carcinogenicity have been reviewed and cancer risk estimated by the EPA (EPA, 1986d), the CalDHS (CalDHS, 1986b), and others. The EPA uses the available epidemiological data to provide separate estimates of risk of mesothelioma and lung cancer for males and females according to smoking habits. Risk estimates are calculated based on age at first exposure and duration of exposure for different asbestos concentrations. The DEP elected to use the approach used by the EPA/OAQPS to establish a cancer unit risk value. The value used by the OAQPS and adopted by the DEP is $7.6 \times 10^{-3} (ug/m^3)^{-1}$ or $2.3 \times 10^{-1} (f/ml)^{-1}$. This value is based on the combined risks of lung cancer and mesothelioma due to lifetime exposure starting at birth, using the average values for males and females and without considering smoking habits. This value is adopted by the DEP for use in risk assessment of inhalation exposure.

Background and Discussion

The weight-of-evidence classification for carcinogenicity is based on the demonstration of cancer in humans exposed by inhalation to asbestos in several epidemiological studies. The carcinogenicity data are reviewed by IARC (IARC, 1977) and in the EPA Airborne Asbestos Health Assessment Update (EPA, 1986d). This document was prepared for the EPA by Dr. William J. Nicholson. There are 14 different studies cited with data that are useful for quantitative dose-response assessment of asbestos. The studies and methods used are described in detail in the EPA document. The unit risk is calculated for lung cancer from 14 studies and for mesothelioma from 4 studies. Based on these results a single unit risk value was chosen for each form of cancer and used to calculate lifetime cancer risk for males and females according to smoking habits for different exposure scenarios. The exposure scenarios considered included 2 exposure concentrations, five different ages of onset of exposure, and five different exposure durations.

For the purpose of selection of a unit risk value for use in deriving an AAL, the procedure and calculations used by the EPA/OAQPS were adopted by the DEP. This information was obtained from Brenda L. Riddle of the EPA/OAQPS in a phone conversation (3-11-87) and from a copy of a memo written by Brenda Riddle and dated 2-19-87. The details of this calculation are presented below.

The cancer risks listed in table 6-3 of the EPA document (EPA, 1986d) are used. For lifetime exposure to 0.01 (f/ml) with an age of onset of exposure at birth, the following lifetime risks per 100,000 persons are reported:

	Males	Females
Lung cancer	192.8	275.2
Mesothelioma	170.5	52.5
Total	363.3	327.7

The average of the values of total risk (lung cancer and mesothelioma) is obtained with the values weighted for the composition of the current U.S. population (49% male and 51% female):

$$(363.3 \times 0.49) + (327.7 \times 0.51) = 345.2.$$

This is the risk from lifetime exposure to 0.01 f/ml per 100,000 persons, which is equal to a lifetime risk of 0.345 $(f/ml)^{-1}$. To obtain the values listed in Table 6-3 (EPA, 1986b) the 40 hr/wk risks calculated from the epidemiological exposures were multiplied by 4.2 (=168hr/wk / 40hr/workweek). The EPA/OAQPS prefers to scale from occupational exposure to environmental exposure based on the relative dose received, which is calculated based on estimates of the amount of air breathed. The OAQPS assumes that 140 m^3 of air is breathed per week (20 m^3/d) and that 50 m^3/wk is breathed during the occupational time period (10 m^3/d). The lifetime risk value is therefore converted back to an occupational exposure by dividing by 4.2 and then scaled to a continuous exposure by multiplying by 140/50. The resulting value for the lifetime cancer risk is 2.3×10^{-1} $(f/ml)^{-1}$.

This risk value is expressed as per fiber per ml based on counting of asbestos fibres by phase contrast microscopy (PCM) because this method of measurement was used in most of the epidemiological studies. Based on an assessment of the data relating fibre counts to mass, the EPA recommends the use of a conversion factor of 30 $(ug/m^3)/(f/ml)$. This value is the geometric mean of 6 studies and the range of values was 5 to 150, showing the uncertainty of this conversion. Despite this uncertainty the EPA recommends the use of this value at this time. Using this value, the lifetime cancer risk for asbestos is:

$$2.3 \times 10^{-1}(f/ml)^{-1}/30(ug/m^3)/(f/ml) = 7.7 \times 10^{-3}\ (ug/m^3)^{-1}.$$

The calculations done here are based on optical fiber counts using phase contrast microscopy. This is done because the epidemiological investigations for the most part use PCM measurements. Most recent environmental measurements have been made using transmission electron microscopy (TEM). Comparisons

of PCM and TEM fibre counts yield very poor correlations and there is no concensus about how to convert between these two measures of asbestos concentration (EPA, 1986b and per Brenda Riddle). The EPA has not yet made a decision on this issue. The EPA/OAQPS will use a unit risk value expressed as mass of asbestos in the NESHAP process because emission estimates are obtained in mass units. The California asbestos assessment (CalDHS, 1986b) estimates that there are 100-1000 TEM fibres per PCM fibre. The PCM measurement generally includes only fibers more than 5 um long or more than 0.3 um wide and the TEM measurement includes much smaller fibres.

The cancer risk presented here is calculated to represent the average over the U.S. population. It is known that a significant positive interaction occurs between smoking and asbestos exposure such that the risk of lung cancer is increased disproportionately with exposure to both agents. Thus, this unit risk value will overestimate the risk to some members of the population while underestimating the risk to others. The risk to male smokers, female smokers, and males (without regard to smoking habits) is 15, 11, and 5% greater than this level, based on the data in the EPA document. Similarly, the risk to female and male nonsmokers are 84 and 70% respectively of the risk value as obtained above.

The risk values recommended by the EPA are not 95% upper confidence limits. Although the EPA policy is normally to use the 95% upper confidence limit, the maximum likelihood estimate is often used when the unit risk is based on human data. The California DHS presents the MLE and the 95% UCL as the range of unit risk values when human data are the basis of the dose-response assessment. The DEP policy is to adopt EPA recommendations in most cases. The DEP will therefore adopt the unit risk value and conversion factor recommended by the EPA, as calculated by the EPA/OAQPS, for assessment of inhalation exposure. The unit risk value for asbestos inhalation should not be used to derive a unit risk for ingestion exposure.

Carcinogenicity Dose-Response Assessment for Benzene.

Summary

The weight-of-evidence classifications for benzene are Group A-Human Carcinogen and Sufficient for mutagenicity. The CAG unit risk value is 8.1×10^{-6} $(ug/m^3)^{-1}$. This value is based on epidemiological studies of exposed workers (EPA, 1985l). The California Department of Health Services (CalDHS, 1984) elected to calculate a unit risk value based on the NTP gavage study because of unresolved questions about the epidemiological studies used by the CAG. The CalDHS unit risk value is 5.3×10^{-5} $(ug/m^3)^{-1}$. The unit risk value adopted by the DEP for risk assessment of inhalation exposure is the CAG value, 8.1×10^{-6} $(ug/m^3)^{-1}$.

Background and Discussion

The designation of weight-of-evidence for carcinogenicity of benzene as Group A derives from the finding of leukemia in exposed humans as reviewed by IARC (IARC, 1974b). The IARC concluded that sufficient human evidence exists (IARC, 1982c) and the EPA used an epidemiological study as the basis of their quantitative dose-response assessment. There is also sufficient animal evidence as shown by the positive carcinogenic response in male and female rats and male and female mice in the NTP study (NTP, 1986f).

The dose-response assessment done by the CAG is based on human studies. The current value for unit risk is provided in the table of relative carcinogenic potencies in the recent Health Assessment Documents (EPA, 1985d) and was confirmed in a phone conversation with Charles Ris of CAG (12-9-86). The documentation of this value has not yet been obtained by the DEP. The current CAG recommended value is a change from the previous value of 7.4×10^{-6} $(ug/m^3)^{-1}$ which was recommended in the Superfund Health Assessment Document for benzene (EPA, 1984h) and listed in the older Health Assessment Documents (EPA, 1984g), and the value of 1.5×10^{-5} $(ug/m^3)^{-1}$ which is discussed in the Water Quality Criteria document (EPA, 1980a).

The CalDHS reviewed the CAG assessment (CalDHS, 1984; EPA 1979c) and elected to use the NTP animal study for dose-response assessment. The CalDHS cited several criticisms of the CAG assessment, including choice of population for calculation of background rates, the use of total leukemias as an endpoint, and uncertainties in the exposure data, as reasons for their decision not to use the human data for dose-response assessment. The CalDHS unit risk value is based on the male mouse prepubital

gland tumors.

The CAG unit risk value is preferred by DEP because it is based on human data. The EPA has recommended different carcinogenic potency values for oral and inhalation exposure and it is therefore not recommended that the value derived from inhalation exposures be used to derive unit risk values for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Benzyl Chloride

Summary

The weight-of-evidence classifications for benzyl chloride are Group B2-Probable Human Carcinogen and Sufficient for mutagenicity. The evidence for carcinogenicity was reviewed by IARC (IARC, 1982b) and was classified as limited at that time. The current weight-of-evidence classification was assigned by DEP based on the finding of malignant tumors in rats and mice exposed by gavage (Lijinsky, 1986). No dose-response assessment is available from the EPA at this time. The CAG preliminary assessment (EPA, 1979b) found no data sufficient for quantitative dose-response assessment. The EPA stated at that time that benzyl chloride was a suspect carcinogen and a direct-acting alkylating agent. The Rhode Island DEM has a draft unit risk value of 7.1×10^{-5} $(ug/m^3)^{-1}$ which is based on thyroid C cell carcinoma in female rats fed benzyl chloride (Lijinsky, 1986). The DEP has not obtained the documentation of this value at the time of this writing. The value was obtained in a telephone conversation with Barbara Morin (2-2-87) and the documentation is forthcoming. The DEP will review the Rhode Island assessment and may adopt it contingent on its consistency with the DEP procedures. There is no unit risk value adopted by the DEP at this time.

Carcinogenicity Dose-Response Assessment for Beryllium

Summary

The weight-of-evidence classifications for beryllium are Group B1-Probable Human Carcinogen and ND for mutagenicity. The Group B1 weight-of-evidence for carcinogenicity is based on multiple positive animal experiments and several human epidemiological studies, as reviewed by IARC (IARC, 1980, 1982c). The IARC concluded that there is limited human evidence and CAG judged the human evidence to be "limited to inadequate" with the final classification being Group B2. The most recently published information from CAG was the draft Health Assessment Document for Beryllium (EPA, 1986a). In this draft document the human data are determined to be inadequate for quantitative dose-response assessment, but are used to calculate a plausible upper bound. The upper bound risk calculated by EPA is 2.4×10^{-3} $(ug/m^3)^{-1}$ and is based on occupational exposures to Be compounds of low solubility. The human data are preferred by CAG because the animal data are not consistent with the human experience in that the potencies resulting from the animal studies are much higher. The CAG considered the difference in human and animal results to be due to the chemical form. Animal studies with different Be compounds show that the carcinogenic potency is related to the solubility, with the less soluble Be compounds being less potent carcinogens. The potency estimated from animal studies using less soluble Be compounds agrees more closely with the estimated human upper bound. The recommendation in the draft HAD is that the human upper bound of 2.4×10^{-3} $(ug/m^3)^{-1}$ be used unless the emission contains more than a small fraction of more soluble forms, in which case "consideration should be given to noting the animal based estimates". The HAD also notes that 95% of atmospheric Be is from coal fired power plants and is emitted as an insoluble oxide.

The information in the draft HAD is currently under review by the EPA Science Advisory Board. The DEP will follow the final recommendations of CAG when they are released. In the interim the upper bound unit risk of 2.4×10^{-3} $(ug/m^3)^{-1}$ will be used for risk assessment of inhalation exposure with recognition that this number may change in the next year, and that the number applies to "less soluble" Be compounds. If soluble Be compounds are emitted the carcinogenic potency should be evaluated based on the CAG calculations using animal data (EPA, 1986a). More soluble forms of Be include, but are not limited to, the fluoride, phosphate, sulfate and chloride. Less soluble forms include, but are not limited to, beryl ore and beryllium oxides.

The dose-response assessment is based on an inhalation

exposure. The carcinogenic activity from other routes of exposure would be expected to be considerably different and the carcinogenic potency value should not be used for other routes of exposure.

Carcinogenicity Dose-Response Assessment for 1,3-Butadiene

Summary

The weight-of-evidence classifications for 1,3-butadiene are Group B2- Probable Human Carcinogen and ND for mutagenicity. The CAG unit risk value for 1,3-butadiene is 2.9×10^{-4} $(ug/m^3)^{-1}$ ($0.64\ ppm^{-1}$) (EPA, 1985k), and is based on the NTP inhalation study (NTP, 1984b). The DEP will adopt the CAG unit risk value (2.9×10^{-4} $(ug/m^3)^{-1}$) for risk assessment of inhalation exposure to 1,3-butadiene.

Background and Discussion

The weight-of-evidence designation of Group B2 was assigned by the EPA (EPA, 1985k) and is based on the finding of tumors in multiple species and at multiple sites in animal studies. The NTP currently has in progress a chronic inhalation study in mice and pre-chronic inhalation studies in rats (NTP, 1987).

The NTP inhalation study in mice (NTP, 1984b) provides information on which to base a dose-response assessment. Inhalation of 625 and 1250 ppm caused significant elevation of tumors at multiple sites in both male and female mice. Specifically, the CAG assessment uses tumor incidence data based on the pooled incidences from several sites that had significantly elevated tumor incidence, as proposed in the EPA Guidelines (EPA, 1986b). The CAG assessment also uses empirical data relating the exposure concentration to the internal dose, based on a study being done for NTP at the Lovelace Inhalation Toxicology Research Institute (NTP, 1985c; cited in EPA, 1985k). The CAG assessment also uses the geometric mean of the potency from male and female mice.

The CAG assessment assumes that absorption of 1,3 butadiene in humans at low concentrations will be 54%. This is derived from the Lovelace Study (NTP, 1985c; cited in EPA, 1985k) in which mice exposed to 7 ppm (the lowest concentration used) for 6 hours retained 54% of the inhaled dose. As discussed in Appendix D, and by Anderson (1981), the theoretical maximum retention at very low concentrations is approximately 70% for chemicals with low water solubility and high blood:air partition coefficient. This theoretical maximum results from a nearly complete absorption of the alveolar ventilation (70% of the total ventilation) at low concentrations. The 54% absorption thus slightly underestimates the dose and hence the risk at a given air concentration. However, as stated by EPA-CAG, the use of 54% absorption "will not cause a large underestimate of the risk" and the CAG unit risk value will be used without adjustment.

Carcinogenicity Dose-Response Assessment for Cadmium

Summary

The weight-of-evidence classifications for cadmium are Group B1- Probable Human Carcinogen and ND for mutagenicity. This weight-of-evidence classification was assigned by EPA. CAG derived a unit risk value for cadmium of 1.8×10^{-3} $(ug/m^3)^{-1}$ (EPA, 1985c) based on a study of respiratory cancer in smelter workers (Thun et al., 1985). The California Department of Health Services (CalDHS, 1986a) calculated a unit risk value of 1.6×10^{-3} $(ug/m^3)^{-1}$ based on the same study. The DEP will adopt the CAG unit risk value (1.8×10^{-3} $(ug/m^3)^{-1}$) for use in risk assessment of inhalation exposure.

The CAG assessment of a positive animal study of inhalation exposure to rats resulted in a potency which was much higher than the potency from the epidemiological study. The basis for this difference is not known and the CAG recommends use of the potency from the epidemiological data.

There is currently no basis on which to distinguish the carcinogenic potency for different chemical forms of cadmium. The CAG value will be applied to total airborne cadmium.

The available data suggest that the carcinogenic potency of ingested cadmium is at least 50 fold less than by inhalation exposure. The unit risk value cited should therefore not be used to derive unit risk values for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Carbon Tetrachloride

Summary

The weight-of-evidence classifications for carbon tetrachloride are Group B2-Probable Human Carcinogen and Suggestive for mutagenicity. The CAG unit risk value is 1.5 x 10^{-5} $(ug/m^3)^{-1}$ (EPA, 1984f). The DEP will adopt the CAG unit risk value (1.5 x 10^{-5} $(ug/m^3)^{-1}$) for use in risk assessment of inhalation exposure to carbon tetrachloride.

Background and Discussion

Carbon tetrachloride is designated as a Probable Human Carcinogen based on the occurrence of liver cancer in exposed animals of multiple species (IARC, 1982c; 1979b) and on the IARC conclusion that there is sufficient animal evidence (IARC, 1982c). This classification was also assigned by EPA.

The basis for the CAG unit risk value is described in the Health Assessment Document for Carbon Tetrachloride (EPA, 1984f). The unit risk value is the geometric mean value from four animal studies including two using mice, one using hamsters and one using rats (Della Porta et al., 1961; Edwards et al., 1942; NCI, 1976a, 1976b, 1977a). Three of these studies would be inadequate for quantitative dose-response assessment based on currently accepted criteria. The Della Porta et al. (1961) study had only 19 animals in the treated group and in the Della Porta et al. (1961) and Edwards et al. (1942) studies, the durations of exposure and duration of experiment were too short for use in dose-response assessment (i.e. not a majority of the lifespan). In the NCI rat study, only low-dose females had significantly increased tumors and the CAG assessment pooled male and female rats which were exposed to different dose levels. The NCI mouse study is also less than ideal for quantitative assessment because the response was 100% in the low-dose group and 97% in the high-dose. This pattern results in a poor fit with the multistage model and gives no information about the shape of the dose-response curve (EPA, 1984f).

A unit risk value is calculated for carbon tetrachloride to be consistent with the DEP policy to use quantitative dose-response assessment for chemicals which have weight-of-evidence designation of Group B. It is understood that the data have some limitations with regard to their use for quantitative dose-response assessment but the limitations are not considered to be substantial enough to invalidate the quantitative assessment.

Carcinogenicity Dose-Response Assessment of Chlordane

Summary

The weight-of-evidence classifications for chlordane are Group B2-Probable Human Carcinogen and Limited Evidence for mutagencity. The CAG calculated a carcinogenic potency of 1.61 $(mg/kg/d)^{-1}$ as part of the Ambient Water Quality Criteria Document for Chlordane (EPA 1980f) based on the IRDC mouse study (Epstein, 1976). The current EPA unit risk value is based on the results from both the IRDC study and the 1977 NCI mouse study. The EPA unit risk value for inhalation is 3.7×10^{-5} $(ug/m^3)^{-1}$ and is based on the geometric mean from four data sets (EPA, 1987a). The DEP will asopt the current EPA unit risk value for use in risk assessment of inhalation exposures: 3.7×10^{-5} $(ug/m^3)^{-1}$.

Background and Discussion

The carcinogenicity weight-of-evidence is based on the increase in liver tumors in mice in two studies (NCI,1977b; Epstein, 1976), as reviewed by IARC (1979b). Two other studies showing evidence of carcinogenicity for chlordane were reviewed by EPA (1987a). The animal evidence had been classified as "limited" by IARC (1982c), but EPA has concluded that the animal evidence is "sufficient", resulting in the classification of chlordane as Group B2- Probable Human Carcinogen.

The EPA calculation of unit risk is summarized in IRIS (EPA, 1987a). Four studies showing evidence of liver tumors in exposed animals were reviewed. The unit risk value is derived as the geometric mean using four data sets from two studies. The data sets used were the liver carcinomas in male and female mice in the IRDC and NCI studies.

The liver tumors in both studies occurred with high incidence, were malignant, and exhibited good dose-response at two dose levels. These studies may be considered less than ideal for dose-response assessment because:

- tumors occurred at a site which has a high spontaneous incidence and which is a target organ for the agent.
- tumors occurred in a single species
- tumors occurred at a single site.

However, the first point is mitigated by the fact that one study showed increased tumors in a strain of mice that does not have a high historical incidence of liver tumors (EPA, 1987a). Benign tumors or neoplastic nodules have been observed in rats exposed

to chlordane and malignant tumors were observed in several strains of rats, indicating that the response is not species-or strain-specific. The data are therefore considered to be adequate for dose-response assessment.

The CAG assessment uses gavage studies to calculate a unit risk value for inhalation exposure. This assumes that there are no route-specific effects on carcinogenic potency. As described in Appendix D, this assumption is considered reasonable. Because the potency value is based on a gavage study, it can be used to derive unit risks for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Chlorobenzene

Summary

The weight-of-evidence classifications for chlorobenzene are Group C-Possible Human Carcinogen and ND for mutagenicity. There is no dose-response assessment from CAG or from any other source known to the DEP at this time. According to the EPA guidelines and DEP procedures, chemicals in weight-of-evidence Group C are evaluated on a case-by-case basis with regard to their adequacy for dose-response assessment. Based on the criteria used by DEP, the NTP study is not considered to give a reliable estimate of the carcinogenic potency of chlorobenzene and no unit risk value is adopted by the DEP at this time.

Background and Discussion

The weight-of-evidence designation for chlorobenzene is assigned by DEP based on the production of rat liver neoplastic nodules in the NTP gavage study (NTP, 1985a). There has not been a review of carcinogenicity data for chlorobenzene by IARC and there are no other studies which are adequate for dose-response assessment known to DEP at this time. The designation Group C is based on the production of tumors in a single species, and on the fact that only neoplastic nodules were produced and these lesions are not considered to be a malignant response.

The DEP performed a quantitative dose-response assessment using the standard procedures (see Appendix D). The male rat showed the only increase in tumors and the incidences of neoplastic nodules was 2/50, 4/49 and 8/49 in rats dosed with 0, 60 and 120 mg/kg/d for 5 days per week for 103 weeks. The surface area adjusted lifetime average daily doses were 0, 8.01 and 16.02 and the carcinogenic potency was 1.90×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for inhalation exposure based on this site was 5.43×10^{-6} $(ug/m^3)^{-1}$.

Consistent with the EPA guidelines (EPA, 1986b), the DEP procedure is to evaluate chemicals with Group C weight-of-evidence on a case-by-case basis with regard to the adequacy of the data for quantitative dose-response assessment. The NTP study is considered to be inadequate for dose-response assessment because:

- tumors at a single site/single sex/single species
- only liver neoplastic nodules which are considered to be nonmalignant
- increase in tumors in the high-dose group only

Based on these considerations, the unit risk calculated based on the NTP study is not considered to be a quantitatively reliable estimate of the carcinogenic risk due to chlorobenzene and is not adopted for use.

Carcinogenicity Dose-Response Assessment for Chloroform

Summary

The weight-of-evidence classifications for chloroform are Group B2-Probable Human Carcinogen and Suggestive for mutagenicity. The CAG unit risk value is 2.3×10^{-5} $(ug/m^3)^{-1}$ (EPA, 1985i). The CAG value is based on data sets from male and female mouse liver tumors from the NCI study (NCI, 1976a). Adjustments are also made to incorporate pharmacokinetic data relating administered dose to metabolized dose in the CAG analysis. The DEP adopts the CAG unit risk value (2.35×10^{-5} $(ug/m^3)^{-1}$) for risk assessment of inhalation exposure.

Background and Discussion

The designation of weight-of-evidence Group B for chloroform is based on positive responses in rats and mice in the NCI study (NCI, 1976a) as reviewed by IARC (IARC, 1979b). The IARC concluded that there was sufficient animal evidence for chloroform (IARC, 1982c). The basis for the CAG unit risk value is described in the final Health Assessment Document for Chloroform (EPA, 1985i). The CAG evaluated five data sets including male and female mouse liver tumors and male rat kidney tumors from the NCI study (NCI, 1976a) and two other gavage studies resulting in kidney tumors in male mice (Roe et al., 1979) and kidney tumors in male rats (Jorgenson et al., 1985). The CAG elected to use the geometric mean of the male and female mouse liver tumors from the NCI study. The CAG also incorporated a limited amount of pharmacokinetic data describing the amount of gavage dose which is excreted unmetabolized.

The CAG uses the mean potency value of two data sets and uses data which define the amount of the gavage dose that is metabolized. The CAG unit risk value assumes 100% absorption of inhaled doses at low air concentrations. As discussed in the DEP procedures (Appendix D), this may overestimate the true absorption of a partially soluble gas. The data from the studies analyzed by CAG and DEP are less than ideal for use in quantitative dose-response assessment because both the kidney and the liver show extensive nonneoplastic pathology and the mouse liver has a high spontaneous tumor rate. However, consistent with DEP and EPA policy, quantitative dose-response assessment is generally done for chemicals which are categorized as Probable Human Carcinogens. The CAG value is adopted for use because the CAG assessment incorporates metabolism data and because the DEP agrees with the CAG use of these data.

The CAG assessment uses gavage studies to calculate a unit

risk value for inhalation exposure. This assumes that there are no route-specific effects on carcinogenic potency. As described Appendix D, this assumption is considered to be reasonable. Because the carcinogenic potency is based on a gavage study, it can be used to derive unit risks for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Chromium and Chromium Compounds

Summary

The weight-of-evidence classifications for Chromium III and Chromium metal are D-Not Classifiable as to Human Carcinogenicity and ND for mutagenicity. The carcinogenicity weight-of-evidence classification is Group A-Human Carcinogen for hexavalent chromium and is Group B1-Probable Human Carcinogen for chromic acid. The CAG unit risk value for hexavalent chromium is 1.2 x 10^{-2} $(ug/m^3)^{-1}$ (EPA, 1984e). This value is based on an epidemiological study (Mancuso, 1977). The DEP will adopt the CAG unit risk value for use in risk assessment of inhalation exposure to hexavalent chromium.

Background and Discussion

The designation of weight-of-evidence for hexavalent chromium is based on positive epidemiological data showing cancer in chromium-exposed workers and on the basis of positive animal studies with several chromium compounds as reviewed by IARC (IARC, 1980). The data regarding carcinogenicity due to chromium metal were found by IARC to be inadequate for evaluation (IARC, 1980). The studies reviewed by IARC show positive animal evidence for several hexavalent chromium compounds. Evidence for carcinogenicity of several chromium III compounds and several other chromium VI compounds were also found to be inadequate.

The epidemiological data demonstrate the carcinogenicity of chromium exposure in humans. Although the carcinogenicity of different chemical forms or oxidation states cannot be distinguished on the basis of these studies, it is believed that various hexavalent chromium compounds are the etiologic agent in human cancer (IARC, 1980; EPA, 1984e). The CAG unit risk for hexavalent chromium of 1.2 x 10^{-2} $(ug/m^3)^{-1}$ is based on the Mancuso et al. (1977) study and assumes that the exposures were to hexavalent chromium. The California Department of Health Services recommends a unit risk for hexavalent chromium of 1.2 x 10^{-2} $(ug/m^3)^{-1}$ with an upper limit of 1.5 x 10^{-1} $(ug/m^3)^{-1}$ (CalDHS, 1985b). The California value is also based on the Mancuso 1977 study and the upper limit is based on the assumption that the exposures in the Mancuso study were comprised of 1/7th hexavalent chromium and that hexavalent chromium was responsible for the carcinogenic effect.

DEP will consider that the CAG unit risk is reasonably applicable to any chemical form of hexavalent chromium. There is

no evidence for carcinogenicity of inhaled metallic chromium or chromium III compounds. Chromium carbonyl was listed as approved for toxicology study in the 6-86 NTP management status report, but was not listed on the 1-87 report. The carcinogenic potency is derived from inhalation exposure. The carcinogenic activity of hexavalent chromium would be expected to be considerably different if exposure is by other routes and the potency value discussed here should not be extrapolated to other routes of exposure.

Carcinogenicity Dose-Response Assessment for 1,4-dichlorobenzene

Summary

The weight-of-evidence classifications for 1,4-dichlorobenzene are Group B2- Probable Human Carcinogen and Limited Evidence for mutagenicity. DEP has calculated a unit risk value based on the NTP gavage study (NTP, 1986i) using the data from the male rat renal tubular adenocarcinoma or adenoma, and the male mouse liver adenoma or carcinoma. The unit risks calculated on the bases of these studies are 2.4×10^{-6} $(ug/m^3)^{-1}$ for renal tumors in rats and 6.1×10^{-6} $(ug/m^3)^{-1}$ for mouse liver tumors. The EPA has calculated a unit risk value which is also based on the liver tumors in male mice from the NTP study. The EPA value is 5.7×10^{-6} $(ug/m^3)^{-1}$. This value is currently in the process of being formally adopted by the Agency, but has not yet been verified for inclusion in the Integrated Risk Information System (IRIS) database. The value was obtained from CAG staff. Since the DEP and CAG values are virtually the same, and formal adoption of the CAG value by EPA is imminent, the EPA unit risk value of 5.7×10^{-6} $(ug/m^3)^{-1}$ will be used by DEP for risk assessment of inhalation exposures.

Background

The carcinogenicity weight-of-evidence was determined by DEP based on the NTP gavage study which showed significant increases in tumors of both rats and mice (NTP, 1986i). At the time of the IARC assessments of 1,4-dichlorobenzene (IARC, 1974b; 1982b, 1982c) there were no positive carcinogenicity studies and the evidence was considered inadequate for evaluation by IARC. The recent NTP gavage study is adequate for use in quantitative dose-response assessment and this assessment is presented below.

Calculation of Unit Risk for 1,4-dichlorobenzene using the NTP Study

In the NTP study, groups of male F344 rats were administered 0, 150, or 300 mg/kg/d of 1,4-dichlorobenzene and groups of female F344 rats and both sexes of B6C3F1 mice were administered 0, 300, or 600 mg/kg/d of 1,4-dichlorobenzene. The doses were administered by gavage on 5 days/week for 104 weeks, starting at 5 weeks of age.

No significant dose-related effects on body weight in any group occurred. There was a significant decrease in survival in the male rat high dose group but no dose-related effects on mortality in the other groups. Significant increases in tumors occurred in male and female mouse livers and in male rat kidneys.

In the mouse, the incidences of both benign and malignant tumors were statistically significant and the combination of these tumors is used for dose-response assessment (McConnell et al. 1986). The incidences of these tumors are presented in Table 1. Although the incidences of both benign and malignant tumors were increased, only the combined incidences are presented and used for dose-response modeling. The adjusted incidences are derived from the NTP reported adjustments for early mortality. A statistically significant increase in leukemia in male rats was not considered to be biologically significant by the NTP because it was not different than the historical control incidence.

Nonneoplastic pathology was observed at all sites of increased tumors. Male rats showed a dose-related increase in nephropathy and renal epithelial cell hyperplasia, focal hyperplasia of tubular epithelium, and mineralization of medullar collecting tubules. Mice of both sexes showed a dose-related increase in liver lesions including cytomegaly, karyomegaly, and hepatocellular degeneration and necrosis.

The lifetime average daily dose (LAD) was calculated as follows:

$$\text{LAD} = \text{daily dose} \times 5/7 \times 104/104.$$

For extrapolation to human equivalent dose the surface area adjusted dose was calculated as follows:

$$\text{Surface area adjusted dose} = \text{LAD} \times (70/bw)^{-1/3}$$

with bw equal to the average terminal body weight of the group of animals. The dose calculations are shown in Table 2. The multistage model was fit using the incidences in Table 1 and the doses in Table 2. The 95% upper confidence limit on the linear term is used as the estimate of carcinogenic potency and this parameter is listed in Table 1.

Discussion

The use of quantitative dose-response assessment for 1,4-dichlorobenzene is consistent with the DEP position that this assessment will generally be done for chemicals in weight-of-evidence Group B. The NTP study is considered to be adequate for dose-response assessment and no other studies were available. It is noted that all of the sites of tumor development in this study show nonneoplastic pathology and/or high spontaneous tumor incidence. The carcinogenic potency of 1,4-dichlorobenzene based on the male mouse liver tumors is 2.13×10^{-2} $(mg/kg/d)^{-1}$. The DEP calculation of the unit risk for lifetime exposure to $1 ug/m^3$ of 1,4-dichlorobenzene in air is done as follows:

$2.13x10^{-2}$ $(mg/kg/d)^{-1}$ x $20m^3/d$ x 1mg = $6.1x10^{-6}$ $(ug/m^3)^{-1}$

The EPA unit risk value is also calculated using the male mouse liver tumors from the NTP study. The unit risk calculated by EPA is 5.7×10^{-6} $(ug/m^3)^{-1}$. The difference between the EPA and DEP values is due to minor differences in the method used to calculate the human equivalent dose. The EPA value for unit risk is adopted by DEP in order to be consistent with EPA risk assessment procedures and because the EPA and DEP values do not differ significantly.

The calculation of a unit risk value for air based on a gavage study assumes that there are no route-specific differences in carcinogenic potency. There were no additional data used in this calculation describing the species-, dose-, or route-specific pharmacokinetics of 1,4-dichlorobenzene. The calculation of unit risk based on administered dose is consistent with DEP procedures and is based on the assumption that administered dose provides a reasonable measure of the effective dose in the absence of data showing otherwise. Because this dose-response assessment is based on a gavage study and there is assumed to be no difference between routes of exposure, the potency calculated here can be used for other routes of exposure.

Table 1. Tumor Incidences and Potency Values for 1,4-dichlorobenzene Dose-Response Assessment Using the NTP Study

		Tumor Incidence Control	Low	High	Potency $(mg/kg/d)^{-1}$
Rat male					
Renal tubular adenoma or adenocarcinoma	actual	1/50	3/50	8/50	5.46×10^{-3}
	adjusted	2	5	14	8.26×10^{-3}
Mouse male					
Hepatocellular adenoma or carcinoma	actual	17/50	22/49	40/50	2.13×10^{-2}
Mouse female					
Hepatocellular adenoma or carcinoma	actual	15/50	10/48	36/50	7.44×10^{-3}

Table 2. Dose Calculation for Dose-Response Assessment of 1,4-dichlorobenzene Using the NTP Study

		administered dose mg/kg/d	LAD mg/kg/d	surface area adjusted LAD mg/kg/d
Male rat	low dose	150	107	20.3
	high dose	300	214	40.1
Male mouse	low dose	300	214	18.2
	high dose	600	428	36.4
Female mouse	low dose	300	214	16.5
	high dose	600	428	33.4

Carcinogenicity Dose-Response Assessment for 1,2-dichloroethane

Summary

The weight-of-evidence classifications for 1,2-dichloroethane are Group B2-Probable Human Carcinogen and Sufficient for mutagenicity. The CAG unit risk value for inhalation exposure is $2.6 \times 10^{-5}(ug/m^3)^{-1}$(EPA, 1985a). The California Department of Health Services calculated an upper limit unit risk of $2.2x10^{-5}$ $(ug/m^3)^{-1}$ (CalDHS, 1985a). Each of these unit risk values is based on the NCI gavage study and they differ in the details of the calculation. The DEP will adopt the CAG unit risk value ($2.6 x10^{-5}(ug/m^3)^{-1}$) for use in risk assessment of inhalation exposure.

Background and Discussion

The designation of weight-of-evidence for 1,2-dichloroethane as Group B2 is based on the occurrence of a positive response in both sexes of mice and rats in the NCI gavage study (NCI, 1978c) as reviewed by IARC (IARC, 1979b). The EPA assigned 1,2-dichloroethane to Group B2 (EPA, 1985a). The toxicology of 1,2-dichloroethane has been thoroughly reviewed in health assessments performed by EPA (1985a) and the California Department of Health Services (CalDHS, 1985a).

The carcinogenic potency recommended by CAG is based on the male rat hemangiosarcoma in the NCI gavage study. The assessment was performed using an adjustment to convert administered dose to metabolized dose based on published data, and using a multistage model with a time-to-response term, which was considered to be a more appropriate model due to the presumed fatality of this tumor. The potency calculated at this site was converted to unit risk for air in the CAG assessment by assuming 100% absorption and metabolism of the inhaled dose at low concentrations (EPA, 1985a).

Both the CAG and the California DHS also presented assessment of the Maltoni et al. (1980) inhalation study. Maltoni et al. found no increase in cancer in rats exposed to 1,2-dichloroethane. Using this study, the upper bound of carcinogenic unit risk was calculated by CAG to be $1x10^{-6}$ $(ug/m^3)^{-1}$ and by CalDHS to be $7x10^{-7}$ $(ug/m^3)^{-1}$. The apparently lower carcinogenic potency in the inhalation study could be due to a difference in potency between routes of exposure, or due to the much higher transient peak levels due to gavage exposure. However, it cannot be ruled out that the lower apparent potency in the Maltoni et al. (1980) study is due to a difference in sensitivity among species or due to an inadequate conversion of the inhalation exposure to metabolized dose. It is therefore

preferable to use the assessment based on the NCI gavage study.

The CAG assessment assumes that the absorption and metabolism at low doses will be 100%. As discussed in Appendix D, the absorption of a partially soluble gas with a high blood gas partition coefficient would be expected to approach a theoretical maximum of 70%, based on the complete absorption of the alveolar ventilation which is approximately 70% of the total ventilation. The blood-gas partition coefficient of 1,2-dichloroethane is approximately 20 (EPA, 1985a) and it would be expected to follow this relationship. This adjustment is not made by the CAG and is not added in the DEP assessment in the interest of consistency with EPA recommendations, and because this adjustment would have a minor effect on the unit risk value. Because the carcinogenic potency is based on a gavage study, and there is assumed to be no difference between routes of administration, the potency value cited may be used for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Dichloromethane (Methylene Chloride)

Summary

The weight-of-evidence classifications for methylene chloride are Group B2-Probable Human Carcinogen (EPA, 1985b) and Substantial Evidence for mutagenicity. The current CAG unit risk value for inhalation exposure is 4.1×10^{-6} $(ug/m^3)^{-1}$ (EPA, 1985b). In two recent draft documents however, the EPA has reevaluated the data and incorporated information and models regarding the pharmacokinetics of dichloromethane (EPA, 1987b, 1987c). Based on this analysis the EPA has proposed to adjust the unit risk value to 4.7×10^{-7}. This change has been reviewed by the SAB but has not yet been formally adopted by the agency. The DEP will therefore use the existing CAG value (4.1×10^{-6} $(ug/m^3)^{-1}$) until the new value has been adopted by EPA.

Background and Discussion

The designation of weight-of-evidence for carcinogenicity as Group B2 is based primarily on the NTP inhalation study (NTP, 1986g). At the time of the IARC review, this study was not available and the IARC concluded that the evidence for carcinogenicity in animals was inadequate for evaluation (IARC, 1979b). The toxicity of methylene chloride is reviewed in the EPA Health Assessment Document (EPA, 1985f) and the data on carcinogenicity are discussed in the HAD (EPA, 1985f), and in an addendum to the HAD (EPA, 1985b). Dichloromethane is assigned to Group B2 by EPA (1985b). The addendum primarily reviews the NTP inhalation study and pharmacokinetic data which were not included in the HAD. The NTP has a gavage study in progress; the original gavage study was not released (NTP, 1987).

In an update to the HAD and Addendum, and in an accompanying technical analysis, the EPA discusses new data pertaining to the risk assessment of dichloromethane, and the use of pharmacokinetic modeling in the derivation of a unit risk value. A pharmacokinetic model was used to calculate a dose at the target site and a human equivalent dose using an extensive database on the metabolism, disposition, and mechanism of action of dichloromethane. Based on this analysis, CAG has proposed to reduce the unit risk value by a factor of 8.7 from the previously adopted value.

The new CAG value, which is based on a more complete and sophisticated analysis of the available data, will be adopted by DEP as soon as it has been adopted by EPA.

Carcinogenicity Dose-Response Assessment for 1,2-dichloropropane

Summary

The weight-of-evidence classifications for 1,2-dichloropropane are Group B2- Probable Human Carconogen, and Suggestive Evidence for mutagenicity. The CAG unit risk value for inhalation exposure is $1.8 \times 10^{-5}(ug/m^3)^{-1}$. The documentation for this value was not available at the time of this writing, and the value was obtained in a telephone conversation with Charles Ris of the CAG. The CAG is currently reviewing the quantitative data for 1,2-dichloroprane and a final EPA value is not available. Therefore, DEP calculated a unit risk value on the basis of the NTP gavage study (NTP, 1986d). The DEP value is 1.87×10^{-5} $(ug/m^3)^{-1}$. The DEP unit risk value is adopted for use in risk assessment of inhalation exposure.

Background

The weight-of-evidence designation for carcinogenicity of Group B2 is based on evidence of increased tumors in multiple species. The NTP study showed increased mammary adenocarcinomas in female rats, increases in benign liver tumors in male and female mice, and non statistically significant increases in malignant liver tumors. These are considered to represent "clear" evidence of carcinogenicity by NTP. The increased tumors in multiple species leads to a designation of sufficient animal evidence- Group B2. There is no evaluation of 1,2-dichloropropane by IARC. The NTP study is considered adequate for quantitative dose-response assessment, and no other study was used.

Unit Risk Calculation from NTP Gavage Study

Male F344 rats were administered 0, 62 or 125 mg/kg/d and female rats and male and female mice were administered 0, 125 or 250 mg/kg/d by gavage. Doses were administered 5 days per week for 103 weeks beginning at 5 weeks of age. There was a significant dose-related effect on body weight in rats of each sex and there was a significant dose related effect on survival in female rats and female mice.

There were no elevated tumors in male rats. In female rats a significantly elevated incidence of mammary adenocarcinomas occurred. Significantly elevated incidences of liver adenoma and liver adenoma or carcinoma were observed in male and female mice. The incidence of liver carcinoma was not statistically significantly elevated. The incidence of tumors at these sites are shown in Table 1. Adjusted incidences are presented as

reported by NTP for the groups which had a significant mortality effect.

There was a dose-related increase in hepatocytomegaly and liver necrosis in male rats and in mammary gland hyperplasia in female rats.

The lifetime average daily doses (LAD) were calculated as follows:

$$\underset{(mg/kg/d)}{LAD} = \underset{(mg/kg/d)}{\text{gavage dose}} \times \frac{5}{7} \times \frac{103}{104}$$

The surface area adjusted LAD was calculated using surface area scaling as follows:

$$\text{surface area adjusted LAD} = LAD \times (70/bw)^{-1/3}$$

with b.w. equal to the terminal body weight of the group of animals. The calculated doses are shown in Table 2. The dose-response curve was estimated using the multistage model fit to the tumor incidences and the surface area adjusted lifetime average daily doses in Table 1. The 95% upper confidence limits for these tumor sites are given in Table 3. There was no adjustment for less than lifetime exposure because the experiment lasted the full lifetime of the animals.

The carcinogenic potency for the male mouse liver tumors was chosen for use in calculation of a unit risk for air. The potency for this site is 6.55×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for lifetime exposure to 1 ug/m^3 is calculated using the assumption of a 70 kg human breathing 20 m^3/d as follows:

$$\underset{Risk}{\text{Unit}} = 6.89 \times 10^{-3} \times \frac{20\ m^3/d}{70\ kg} \times \frac{1\ mg}{1000\ ug} = 1.97 \times 10^{-6} (ug/m^3)^{-1}$$

The most sensitive site for calculation of carcinogenic potency is the male mouse liver tumors. The carcinogenic potency based on this site is 6.55×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for inhalation exposure is 1.87×10^{-5} $(ug/m^3)^{-1}$.

Discussion

The documentation for the CAG unit risk value is not yet available, although the CAG and DEP values are virtually identical. The calculation of a unit risk value for 1,2-dichloropropane is consistent with the policy that quantitative dose-response assessment is generally performed for

chemicals in weight-of-evidence category Group B. The DEP value is based on the male mouse liver tumors. The selection of this site is consistent with DEP policy to use the most sensitive site for calculation of unit risk value. It is noted that this site is less than ideal because of the occurrence of nonneoplastic pathology and high spontaneous incidence at this site. Likewise, female rat mammary adenocarcinoma is less than ideal for quantitative dose-response assessment due to effects on body weight and survival. The choice of site in this study is not clear, and mouse liver tumors are chosen in order to be consistent with DEP policy to use the most sensitive site. The fact that the male mouse liver does not show a significant increase in malignant tumors is not a strong argument against using this site because there is a consistent (nonsignificant) increase in malignant tumors, supported by a dose-related significant increase in benign tumors.

This assessment is made without any ancillary data regarding dose, route or species dependent differences in pharmacokinetics or carcinogenic potency. As such, the assumption is made that the potency is the same between routes of exposure, and the calculated potency value can be applied to other exposure routes.

TABLE 1 Tumor Incidences Used for Dose-Response Assessment of 1,2-dichloropropane Using the NTP Gavage Study

		Control	Low	High
Female Rat				
Mammary adenocarcinoma	actual	1/50	2/50	5/50
	adjusted	1	2	13
Male Mouse				
Liver adenoma		7/50	10/50	17/50
Liver carcinoma		11/50	17/50	16/50
Liver adenoma or carcinoma		18/50	26/50	33/50
Female Mouse				
Liver adenoma	actual	1/50	5/50	5/50
	adjusted	1	9	10
Liver carcinoma	actual	1/50	3/50	4/50
	adjusted	1	5	6
Liver adenoma or carcinoma	actual	2/50	8/50	9/50
	adjusted	3	13	15

TABLE 2. Dose Calculation for Dose-Response Assessment of 1,2-dichloropropane Using NTP Gavage Study.

		Administered Dose mg/kg/d	Lifetime Average Daily Dose mg/kg/d	Surface Area Adjusted LAD mg/kg/d
Female Rat	Low	62	43.9	8.16
	High	125	88.4	16.1
Male Mouse	Low	125	88.4	7.49
	High	250	177	14.8
Female Mouse	Low	125	88.4	7.63
	High	250	177	14.7

TABLE 3. Upper Confidence Limits of Carcinogenic Potency for 1,2-dichloropropane Using the NTP Gavage Study

Site		Potency $(mg/kg/d)^{-1}$
Female Rat mammary adenocarcinoma	actual	5.42×10^{-3}
	adjusted	6.89×10^{-3}
Male Mouse liver adenoma or carcinoma	actual	6.55×10^{-2}
Female Mouse liver adenoma or carcinoma	actual	2.09×10^{-2}
	adjusted	3.45×10^{-2}

Carcinogenicity Dose-Response Assessment for
Di(ethylhexyl)phthalate
(DEHP)

Summary

The weight-of-evidence classifications for di(ethylhexyl)phthalate (DEHP) are Group B2-Probable Human Carcinogen and Substantial for mutagenicity. There is no CAG recommended unit risk value for DEHP at this time. The DEP calculation of carcinogenic potency is based on the NTP feeding study (NTP, 1982a). The unit risk value adopted for risk assessment of inhalation exposure is 1.30×10^{-6} $(ug/m^3)^{-1}$.

Background

The weight-of-evidence designation for DEHP is based on the positive response in rats and mice of both sexes in the NTP study (NTP, 1982a) as reviewed by IARC (IARC, 1982b). This weight-of-evidence classification was assigned by DEP and no EPA evaluation is available. There is no dose-response assessment from any other source known to the DEP at this time. The DEP performed a dose-response assessment using the NTP feeding study as described below.

Calculation of the Unit Risk Using the NTP Feeding Study.

In this study male and female F344 rats were fed diets containing 0, 6000, or 12000 ppm DEHP, and male and female B6C3F1 mice were fed diets containing 0, 3000, or 6000 ppm DEHP for 103 weeks starting at 6 weeks of age. There was a significant dose related effect of DEHP on weight gain in male and female rats and in female mice and no significant effect of DEHP treatment on survival in any group.

Significant increases in the incidences of liver carcinoma, neoplastic nodule, and combined carcinoma or neoplastic nodule were observed in males and females of both species. The NTP study reported only minor nonneoplastic pathology of the liver, but in other studies severe liver pathology occurred at doses equal to the doses used in the NTP study including hepatomegaly, necrosis, and peroxisome proliferation in rodents. The incidences of liver tumors in the NTP study are shown in Table 1.

The NTP report includes a calculation of lifetime average dose (LAD) based on measurements of food consumption made during the study. These values are converted to human equivalent dose using surface area scaling as follows:

Surface Area Adjusted Dose = LAD x $(b.w./70)^{1/3}$

with b.w. equal to the average terminal body weight of the group of animals. The calculated doses are shown in Table 1. The dose-response curve was estimated by fitting the multistage model to the doses and incidences listed in Table 1. The 95% upper confidence limit on the linear term is used as the estimate of carcinogenic potency and this value is listed in Table 2.

The female mouse liver carcinoma or neoplastic nodule is considered to be the most appropriate site for dose-response assessment and is used to calculate a unit risk value for inhalation exposure. The carcinogenic potency based on this site is $4.53 \times 10^{-3}(mg/kg/d)^{-1}$. The risk from lifetime exposure to 1 ug/m^3 of DEHP is calculated assuming a standard 70 kg person breathing 20 m^3 of air per day as follows:

$$\frac{4.53\times10^{-3}}{mg/kg/d} \times \frac{20\ m^3}{d} \times \frac{1}{70\ kg} \times \frac{1\ mg}{1000\ ug} = 1.30\times10^{-6}\ (ug/m^3)^{-1}.$$

The unit risk value for inhalation exposure is 1.3×10^{-6} $(ug/m^3)^{-1}$.

Discussion

It is the policy of DEP that dose-response assessment will generally be performed on chemicals in carcinogenicity weight-of-evidence Group B. The carcinogenic potency was therefore calculated based on the NTP feeding study. The potency value from the female mouse liver tumor is selected in preference to the male mouse liver because the male mouse has a much higher spontaneous tumor incidence at this site.

The use of liver tumors for quantitative dose-response assessment is less than ideal because of the liver toxicity of this compound and the possibility of promoting activity due to tissue regeneration, and of initiating activity secondary to peroxisome proliferation and generation of active oxygen species. The calculation of a unit risk for DEHP is consistent with the position stated in the DEP procedures that initiating activity cannot be ruled out based on the evidence for other effects and that carcinogenic potency will be calculated based on the best evidence available.

The calculation of a unit risk for air exposure based on a feeding study assumes that there are no route specific differences in carcinogenic potency. This assumption is consistent with the DEP position that direct route-to-route extrapolation is considered to be a reasonable method in the absence of inhalation studies. As a result, the carcinogenic potency calculated here may be used for other routes of exposure.

Table 1. Incidences and Dose Calculations for Dose-Response Assessment of Di(ethylhexyl)phthalate Using the NTP Feeding Study.

	Diet Conc. ppm	LAD mg/kg/d	Surface Area	Liver Tumors neo-plastic nodule	carcinoma	carcinoma or neoplastic nodule
Rat-male						
Control	0	0	0	2/50	1/50	3/50
Low dose	6000	332	53.6	5/49	1/49	6/49
High dose	12000	674	118	7/49	5/49	12/49
Rat-female						
Control	0	0	0	0/50	0/50	0/50
Low dose	6000	394	61.8	4/49	2/49	6/49
High dose	12000	774	117	5/50	8/50	13/50
Mouse-male						
Control	0	0	0	6/50	9/50	14/50
Low dose	3000	672	56.7	11/48	14/48	25/48
High dose	6000	1325	110	10/50	19/50	29/50
Mouse-female						
Control	0	0	0	1/50	0/50	1/50
Low dose	3000	799	64.6	5/50	7/50	12/50
High dose	6000	1821	140	1/50	17/50	18/50

Table 2. Carcinogenic Potencies (q_1^*) for Di(ethylhexyl)phthalate Using the NTP Feeding Study

	Carcinogenic Potency $(mg/kg/d)^{-1}$		
	Neoplastic nodule	Carcinoma	Carcinoma or neoplastic nodule
Rat male	1.97×10^{-3}	1.10×10^{-3}	2.86×10^{-3}
female	1.76×10^{-3}	1.75×10^{-3}	3.41×10^{-3}
Mouse male	2.51×10^{-3}	4.45×10^{-3}	8.24×10^{-3}
female	7.05×10^{-4}	3.72×10^{-3}	4.53×10^{-3}

Carcinogenicity Dose-Response Assessment for 1,4-dioxane

Summary

The weight-of-evidence classifications for 1,4-dioxane are Group B2-Probable Human Carcinogen and ND for mutagenicity. There is no carcinogenic potency assessment from the CAG at this time. The DEP carcinogenic potency value is based on the NCI study (NCI, 1978f). The DEP unit risk value is 4.11×10^{-6} $(ug/m^3)^{-1}$ and is adopted for use in assessment of inhalation exposure.

Background

The designation of the weight-of-evidence for carcinogenicity of dioxane as Group B2 is based on positive responses in multiple species as reviewed by IARC (IARC, 1976; IARC, 1982c) and on the positive response in rats and mice in the NCI study (NCI, 1978f). The IARC concluded that there is sufficient animal evidence (IARC, 1982c). EPA has also concluded that the animal evidence is sufficient. There is no quantitative dose-response assessment from any other source known to the DEP at this time, so an assessment was performed using the NCI study in which dioxane was administered in drinking water.

Calculation of Unit Risk

In this study, OM rats and B6C3F1 mice were administered dioxane as 0, 0.5, or 1.0 percent in the drinking water. Mice were administered this agent for 90 weeks and rats for 110 weeks. There was no dose-related effect on body weight in any group but there was a dose-related decrease in survival in male and female rats and in female mice. There were increases in nasal turbinate squamous cell carcinonas in male and female rats and increases in liver hepatocellular carcinoma in male and female mice. A variety of dose-related nonneoplastic pathology was reported, including kidney tubular degeneration, liver cytomegaly, nasal turbinate inflammation and tracheal inflammation in rats, and pneumonia, rhinitis, and liver necrosis in mice. Tumor incidences used for quantitative dose-response assessment are listed in Table 1.

The NTP report provides estimates of the daily dose based on measurement of water consumption during the study. For rats, the reported value is the lifetime average dose. For mice the dose is averaged over the 96 week lifetime of the animals in this study. The lifetime average dose (LAD) is converted to a human equivalent dose by scaling to surface area as follows:

Surface area adjusted LAD = LAD x $(70/b.w.)^{-1/3}$

with b.w. equal to the terminal average body weight of the group of animals. The doses calculated are presented in Table 2. The dose-response curve is estimated by fitting the multistage model to the incidences in Table 1 and the doses in Table 2. The 95% upper confidence limit on the linear term is taken as the estimate of carcinogenic potency and these values are shown in Table 1. The last column in Table 1 (adjusted q1*) shows the adjustment of the potency to account for less than lifetime exposure (LLE). This factor is applied to the mouse potencies because the mouse lifetime was only 96 weeks in this study. Therefore the potency is adjusted by a factor of $(104/96)^3$ to get the final potency value. The potency value from the male mouse liver hepatocellular carcinoma is selected by the DEP to calculate a unit risk value for air exposure. The potency at this site is 1.44×10^{-2} $(mg/kg/d)^{-1}$. The unit risk value for air exposure is calculated as described in Appendix D as follows:

1.44×10^{-2} $(mg/kg/d)^{-1}$ x $20m^3/70kg$ x 1mg/1000 ug =

4.11×10^{-6} $(ug/m^3)^{-1}$

The unit risk value for lifetime exposure to 1 ug/m^3 of 1,4-dioxane in air is 4.11×10^{-6}.

Discussion

The calculation of a unit risk value was performed consistent with the DEP procedures and with the policy to calculate a unit risk value for chemicals in weight-of-evidence Group B. The NCI drinking water study was considered to be adequate for quantitative dose-response assessment. Among the sites showing a positive carcinogenic response in this study, the male mouse liver carcinoma was selected as the most appropriate site for dose-response assessment. Selection of this site is consistent with the procedure to use the most sensitive site among the sites considered appropriate for dose-response assessment. This site is also preferred because only the male mouse showed no effect on survival in this study and because the nonneoplastic pathology at this site was minor.

This assessment was performed using the standard DEP-ORS procedure and there were no additional data describing dose-dependent effects on pharmacokinetics, or possible route or species-related differences in carcinogenic potency. The potency value calculated here can be used for other routes of exposures.

Table 1. Tumor Incidences and Carcinogenic Potency for Dose-Response Assessment of 1,4-dioxane Using the NCI Drinking Water Study.

	Tumor Incidence			LLE	Potency $(mg/kg/d)^{-1}$	
	Control	Low	High	adj.	q_1*	adjusted q_1*
_Male rat Nasal turbinate	0/33	12/33	16/34	1	9.54×10^{-3}	
Female rat Nasal turbinate	0/34	10/35	8/35	1	4.96×10^{-3}	
Male mouse Liver	2/49	18/50	24/47	1.27	1.13×10^{-2}	1.44×10^{-2}
Female mouse Liver	0/50	12/48	29/37	1.27	9.36×10^{-3}	1.19×10^{-2}

_ adjusted q1* = adjustment based on length of study (see Appendix D)

Table 2. Dose Calculation for Dose-Response Assessment of 1,4-dioxane Using the NCI Drinking Water Study.

		administered dose % in drinking water	LAD mg/kg/d	Surface Area Adjusted LAD mg/kg/d
_Male rat	Low dose	0.5	240	50.4
	High dose	1.0	530	105
Female rat	Low dose	0.5	350	62.6
	High dose	1.0	640	109
Male mouse	Low dose	0.5	675	54.1
	High dose	1.0	778	64.6
Female mouse	Low dose	0.5	356	28.9
	High dose	1.0	806	60.8

Carcinogenic Dose-Response Assessment for Epichlorohydrin

Summary

The weight-of-evidence classifications for epichlorohydrin are Group B2-Probable Human Carcinogen (EPA, 1984a) and Sufficient for mutagenicity. The CAG recommended unit risk value for inhalation exposure is 1.2×10^{-6} $(ug/m^3)^{-1}$ (EPA, 1984a). The CAG assessment is based on an inhalation study with rats that showed a significant increase in nasal cavity carcinoma or papilloma. The EPA assessment notes that the carcinogenicity of epichlorohydrin is considered to be route- and site-specific and a different potency value is recommended for oral exposure. With regard to the inhalation exposure, the EPA notes that the use of a model which includes time dependent criteria to account for high dose intervals resulted in a higher estimate of risk than the multistage model and that the dose rate effects should be considered in using the unit risk value. No other dose-response assessments are known to the DEP at this time. The DEP will adopt the CAG unit risk value (1.2×10^{-6} $(ug/m^3)^{-1}$) for use in risk assessment of inhalation exposure.

Carcinogenicity Dose-Response Assessment for Ethyl Acrylate

Summary

The weight-of-evidence classifications for ethyl acrylate are Group B2-Probable Human Carcinogen and ND for mutagenicity. This designation was determined by DEP based on the positive responses in both sexes of rats and mice in the NTP gavage study (NTP, 1986c). At the time of the IARC review, this study was not available and the IARC designated the animal evidence as inadequate for evaluation (IARC, 1979a).

The NTP study is not considered to be adequate for quantitative dose-response assessment by the DEP. The only tumors which were considered to be significantly elevated by the NTP were tumors of the fore-stomach. Because the fore-stomach is the site of deposition in a gavage study, the site will be exposed to a highly concentrated solution of the chemical. The production of tumors at the site is clear evidence of carcinogenic action but it is not clear that the tumor incidence can be related to the dose on a body weight or body surface area basis. It is more likely related to the high local concentration of the gavage solution, as noted by the NTP, or to the dose per surface area of fore-stomach. Because of likely substantial differences in the dose-response relationship, it would not be appropriate to quantitatively extrapolate this information to inhalation exposure or to low dose ingestion exposure. Therefore, there is no unit risk adopted for inhalation exposure to ethyl acrylate. No quantitative dose-response assessment from EPA or any other source is known to the DEP at this time.

Carcinogenicity Dose-Response Assessment for Formaldehyde

Summary

The weight-of-evidence classifications for formaldehyde are Group B1- Probable Human Carcinogen and Substantial for mutagenicity. The EPA-OTS recommended value for unit risk is $1.3x10^{-5}$ $(ug/m^3)^{-1}$ (EPA, 1985e) and is based on the results from the CIIT rat study (Swenberg et al., 1980; Kerns et al., 1983). The unit risk has also been calculated by Starr and Buck (1984) based on incorporation of the data of Casanova-Schmitz et al., (1984) for the dose calculation in the CIIT study. The value calculated by Starr and Buck is $5.1x10^{-7}$ $(ug/m^{-3})^{-1}$. The use of the Casanova-Schmitz et al. data remains controversial and the EPA-OTS unit risk value (1.3×10^{-5} $(ug/m^3)^{-1}$) is adopted by DEP for use in risk assessment of inhalation exposure.

Background and Discussion

The weight-of-evidence designation for formaldehyde is based on the EPA designation as Group B1 indicating limited evidence in humans and sufficient evidence of carcinogenicity in animals. The available toxicology and carcinogenicity data are reviewed in the EPA Office of Toxic Substances draft assessment of health risks (EPA, 1985e). The EPA is currently considering changing the weight-of-evidence designation to Group A- Human Carcinogen (Elizabeth Margosches, CAG, 1/6/87, personal communication). Documentation of this change has not yet been received by DEP. Several reports of epidemiological studies of formaldehyde exposure have been released in the last year showing evidence of carcinogenicity in humans. However, there is no dose-response assessment available which is based on a human epidemiological study as yet.

The carcinogenic potency is based on the CIIT study (Kerns et al., 1983; Swenberg et al., 1980). The current EPA unit risk value is calculated based on the results from the CIIT study and at the time of this writing the final documentation of the EPA unit risk value was not available. In a phone conversation on 1-6-87, George Semeniuk of the OTS said that the current unit risk values calculated by the EPA-OTS is $1.3x10^{-5}$ $(ug/m^3)^{-1}$ based on malignant tumors in the CIIT study and $1.8x10^{-4}$ $(ug/m^3)^{-1}$ based on total tumors. In two draft documents from EPA-OAQPS the value of $1.8x10^{-4}$ $(ug/m^3)^{-1}$ was used. One of these was a draft list of unit risk values dated 7-23-85, and the other was a memo dated 4-3-86 regarding calculations of additive individual risk in several urban areas. The final documentation of the EPA-OTS review was in final senior level review and is due to be released in the near future (per George Semeniuk of EPA-OTS).

There has been a great deal of controversy surrounding the interpretation of the CIIT study in terms of human carcinogenicity. The basis of the controversy is the shape of the dose-response curve and the use of the Casanova-Schmitz et al. (1984) data to define the relationship between the exposure concentration and the delivered dose. The results of the CIIT study show a distinctly non-linear response with tumor incidences of 2/200 and 103/199 in groups exposed to 5.6 and 14.3 ppm of formaldehyde. There have been several possible factors suggested which could account for the non-linear response. Inhibition of mucociliary clearance occurs at high doses and exhibits a threshold. Formaldehyde is known to react with components of mucous including a glycoprotein, and the reduction or elimination of mucous flow at high concentrations could allow the consumption of formaldehyde reactive sites allowing more formaldehyde to reach the tissue. Increased cell proliferation also occurs at high doses. Proliferation could increase the incidence of tumors by acting as a promotor or by allowing increased reaction of DNA with formaldehyde because, as shown in in vitro studies, formaldehyde reacts preferentially with single-stranded DNA.

The controversy about the EPA-OTS risk assessment revolves around whether the data of Casanova-Schmitz et al. (1984) should be used to adjust the exposure concentration to a measure of delivered dose. In this study rats were exposed to doubly labeled formaldehyde, nasal mucosal DNA was isolated, and incorporation of label was measured. This study demonstrated a non-linear relationship between formaldehyde concentration and the amount of formaldehnyde determined to be covalently bound to DNA. It is the contention of the authors and of other scientists at CIIT that this information should be incorporated into the dose-response assessment of formaldehyde carcinogenicity by using the relationship between the exposure concentration and DNA binding to define the relationship between exposure concentration and effective dose in the carcinogenicity study (Casanova-Schmitz et al., 1985; Swenberg et al., 1983; Starr and Buck, 1984). The other point of view is that the data of Casanova-Schmitz et al. should not be considered to be a reliable estimate of the exposure concentration-delivered dose relationship because of various difficulties in the interpretation of the study which could not be satisfactorily resolved (Cohn et al., 1985).

In order to attempt to resolve the outstanding issues the EPA convened an expert review panel to review the pharmacokinetic data. This panel concluded that the available data on pharmacokinetics were not adequate for use in quantitative risk assessment. The panel notes that the study was an important step toward defining the administered-delivered dose relationship for formaldehyde.

The CIIT response to the expert panel evaluation addresses many of the issues raised by the panel with new data and with the available data. The CIIT group maintains that the use of the pharmacokinetic data is valid and is an improvement over the EPA use of the lifetime average exposure concentration. The EPA unit risk value is derived using a five stage multistage model because the usual use of the multistage with the number of stages limited to the number of dose groups minus one gives a very poor fit to the data. Although the fit is much better using the five stage multistage model and the maximum likelihood slope estimate is much lower, the 95% upper confidence limit differs only slightly in the two approaches. The unit risk value calculated by Starr and Buck (1984) of 5.08×10^{-7} $(ug/m^3)^{-1}$ is 1/26 of the EPA value.

Because the controversy regarding the use of the data of Casanova-Schmitz et al. has not been resolved and the EPA and other federal regulatory agencies intend to use the EPA cancer risk assessment, DEP elects at this time to adopt the EPA-OTS unit risk value. Because the evidence for carcinogenicity and other effects demonstrate a non-linear response at high doses and because the theoretical mechanism for this effect is reasonable, it is likely that the use of the linearized multistage model overestimates the true risk substantially. It is the opinion of the DEP that the incorporation of data such as that of Casanova-Schmitz et al. will improve the accuracy of the dose-response assessment and that such data should be incorporated when the various issues regarding the interpretation of the study are further resolved. DEP will continue to monitor the discussion of this issue.

Because formaldehyde is reactive and causes effects at the site of deposition, the carcinogenic potency calculated for inhalation exposure should not be used for other routes of exposure.

Carcinogenicity Dose-Response Assessment for Heptachlor

Summary

The weight-of-evidence classifications for heptachlor are Group B2-Probable Human Carcinogen and Limited Evidence for mutagenicity. This weight-of-evidence classification was determined by CAG. The CAG calculated a carcinogenic potency of 3.37 $(mg/kg/d)^{-1}$ as part of the Ambient Water Quality Criteria Document for Heptachlor (EPA, 1980c) based on the NCI feeding study (NCI, 1977c). The unit risk for inhalation exposure based on this study would be 9.64×10^{-4} $(ug/m^3)^{-1}$. In a more recent analysis the CAG has calculated a potency value of 4.5 $(mg/kg/d)^{-1}$. This value is based on the geometric mean of four data sets from two studies showing significant increases in liver carcinomas in mice exposed orally to heptachlor (USEPA 1987d). The EPA unit risk value based on the more recent evaluation is 1.3×10^{-3} $(ug/m^3)^{-1}$. This value will be adopted by DEP for risk assessment of inhalation exposure to heptachlor.

Background and Discussion

The carcinogenicity weight-of-evidence is based on the positive response in mice in the NCI study (NCI, 1977c) as reviewed by IARC (IARC, 1979b). The designation as Group B is based on the occurrence of tumors at a single site in a single species, in multiple studies, and in both sexes.

The data for heptachlor are considered to be adequate for quantitative assessment because the liver tumors occurred with a high incidence, were malignant, showed good dose-response at two dose levels, and occurred in two studies. The data are less than ideal because:

- tumors occurred at a site which has a high spontaneous incidence
  and which is a target of heptachlor acute and chronic toxicity
- tumors occurred at a single site
- tumors occurred in a single species
- there is little supportive evidence from short term studies

The CAG evaluation reviews two studies which show increases in liver carcinomas in both male and female mice. The final CAG value for unit risk is the geometric mean of unit risks from these four data sets. Although it is generally the policy of DEP to use the most sensitive site, the EPA value is adopted by DEP in this case in the interest of consistency with EPA and because the DEP value (based on male mouse liver tumors would be 1.96×10^{-3} $[ug/m^3]^{-1}$) would not differ substantially from EPA's value.

Carcinogenicity Dose-Response Assessment for Hexachloroethane

Summary

The weight-of-evidence classifications for hexachloroethane are Group C- Possible Human Carcinogen and No Data for mutagenicity. The carcinogenicity weight-of-evidence classification was determined by CAG. The CAG has calculated a carcinogenic potency of 1.4×10^{-2} $(mg/kg/d)^{-1}$ (EPA, 1980b) based on the NCI gavage study (NCI, 1978d). This results in an inhalation unit risk value of 4.0×10^{-6} $(ug/m^3)^{-1}$ (USEPA, 1986e). According to EPA (1986b) and DEP guidelines, carcinogenicity data for chemicals in Group C are evaluated on a case-by-case basis with regard to their adequacy for quantitative dose-response assessment. Based on the criteria discussed in Appendix D, the NCI study is considered adequate for dose-response assessment. The EPA unit risk value of 4.0×10^{-6} $(ug/m^3)^{-1}$ is adopted for use in risk assessment of inhalation exposure.

Background and Discussion

The carcinogenicity weight-of-evidence is based on the NCI gavage study as reviewed by IARC (IARC, 1979b). The designation of Group C is based on the occurrence of tumors at a single site in a single species. The EPA unit risk value is based on the liver tumors in male mice in the NCI study.

The study is considered to be adequate for dose-response assessment because the liver tumors occurred with high incidence, were malignant, and showed good dose-response at two dose levels. The study is less than ideal however, because:

- tumors occurred at a site which has a high spontaneous incidence
- tumors occurred at a single site
- tumors occurred in a single species

The EPA unit risk value is adopted by DEP in the interest of consistency with EPA.

Carcinogenicity Dose-Response Assessment for Hydrazine

Summary

The weight-of-evidence classifications for hydrazine are Group B2-Probable Human Carcinogen and Suggestive for mutagenicity. This designation for carcinogenicity is based on positive responses in mice with multiple exposure routes and positive responses in rats, as reviewed by IARC (IARC, 1982c; IARC, 1974a). IARC concluded that there was sufficient animal evidence for carcinogenicity of hydrazine (IARC, 1982c). CAG determined the weight-of-evidence classification to be Group B2, but has not recommended a unit risk value for hydrazine at this time. No study of hydrazine has been performed in the NTP carcinogenicity bioassay program and there is no current activity (NTP, 1987). The Rhode Island DEM is currently working on a dose-response assessment and the results will be assessed by the DEP when available. At this time there is no unit risk value adopted by DEP for hydrazine.

Carcinogenicity Dose-Response Assessment for Lead Subacetate

Summary

The weight-of-evidence classifications for lead subacetate are Group B2-Probable Human Carcinogen and ND for mutagenicity. This designation for carcinogenicity is recommended by CAG and is based on the production of renal tumors in rats and mice with oral or i.p. administration as reviewed by IARC (IARC, 1982c; IARC, 1980). The IARC concluded that there is sufficient animal evidence of carcinogenicity due to lead subacetate (IARC, 1982c). No quantitative dose-response assessment is available from CAG or from any other source at this time. Based on the information provided in the IARC review, the studies which show carcinogenic effect would not be adequate for quantitative dose-response assessment due to inadequate length of study or number of animals used or other technical details. There is no NTP study of lead subacetate either completed or in progress (NTP, 1987). No unit risk value for lead subacetate is adopted by DEP at this time.

Carcinogenicity Dose-Response Assessment for Lindane

Summary

The weight-of-evidence classifications for lindane are Group C-Possible Human Carcinogen and Suggestive for mutagenicity. The designation of Group C for carcinogenicity is based on studies showing mouse liver tumors after oral exposure as reviewed by IARC (IARC, 1979b). The IARC concluded that there was limited animal evidence (IARC, 1982c).

Background and Discussion

The NCI conducted a feeding study in rats and mice and found small increases in liver tumors (mice) and thyroid tumors (rats) but did not consider the changes to be biologically significant, and concluded that there was no evidence of carcinogenicity in that study (NCI, 1977e). The current CAG recommended carcinogenic potency is 1.3 $(mg/kg/d)^{-1}$, based on mouse liver tumors in another feeding study (Thorpe and Walker, 1973) (EPA, 1984d; 1980f). This value has not been formally adopted and was obtained from CAG staff.

Based on EPA (1986b) and DEP guidelines, the carcinogenicity data for chemicals in Group C are evaluated on a case-by-case basis with regard to their adequacy for quantitative dose-response assessment. The carcinogenicity data are considered adequate because positive effects have been seen in three strains of mouse, all with a high incidence of tumors. The Thorpe and Walker study is considered less than ideal for quantitative assessment because there was only one dosed group and too few animals per group.

The EPA unit risk value of 3.8×10^{-4} $(ug/m^3)^{-1}$ is adopted by DEP for inhalation exposure in order to be consistent with EPA and because no other unit risk value is available at this time. There is currently no activity in the National Toxicology Program regarding lindane (NTP, 1987).

Carcinogenicity Dose-Response Assessment for Mirex

Summary

The weight-of-evidence classifications for Mirex are Group B2-Probable Human Carcinogen and ND for mutagenicity. The designation for carcinogenicity was determined by DEP based on positive responses in rats and mice after oral administration and in mice after subcutaneous administration as reviewed by IARC (1979b). The IARC concluded that there was sufficient animal evidence (IARC, 1979b). There is no currently recommended carcinogenic potency from the EPA-CAG. Based on the information presented in the IARC review, the studies reviewed would not be considered to be adequate for quantitative dose-response assessment based on the DEP procedures (Appendix D). An animal bioassay has been performed by the NTP and the report of this study is currently being drafted (NTP, 1986a). This study will be reviewed by the DEP when it has been peer reviewed and released by the NTP. There is no unit risk value adopted by DEP for mirex at this time.

Carcinogenicity Dose-Response Assessment for Naphthalene

Summary

The weight-of-evidence classifications for naphthalene are Group D-Not Classifiable as to Human Carcinogenicity and ND for mutagenicity. The data on carcinogenicity have not been reviewed by the IARC. There is no currently recommended CAG value for carcinogenic potency and the CAG is in the process of developing a dose-response assessment at this time (personal communication - Charles Ris). There is no dose-response assessment from any other source or any study on which to base a dose-response assessment known to the DEP at this time. There are no completed NTP studies on naphthalene, but there is an inhalation study in mice with the chronic histopathological in progress (NTP, 1987). The DEP will review the CAG assessment and the NTP study when they are available. There is no unit risk value adopted for inhalation at this time.

Carcinogenicity Dose-Response Assessment for Nickel and Nickel Compounds

Summary

The weight-of-evidence classification for carcinogenicity varies for different nickel compounds. For nickel metal the weight-of-evidence is Group C-Possible Human Carcinogen and ND for mutagenicity. For nickel oxide the weight-of-evidence is Group B1-Probable Human Carcinogen and ND for mutagenicity. For several other nickel compounds, the weight-of-evidence for carcinogenicity is described below. The weight-of-evidence for mutagenicity for several other nickel compounds is ND. The CAG recommends a unit risk value for inhalation exposure of 4.8 x $10^{-4}(ug/m^3)^{-1}$ for nickel refinery dust. There are no unit risk values recommended by CAG for other nickel compounds at this time.

Background and Discussion

The IARC review of the carcinogenicity data for nickel and nickel compounds (IARC, 1982c) is summarized as follows:

Human Evidence - sufficient for nickel refining dust and limited for nickel and certain nickel compounds.

Animal Evidence - Sufficient for nickel and certain nickel compounds.

In this assessment, the IARC apparently assigns equal weight to studies in which only injection site sarcomas are produced. Many of the studies with various nickel compounds use intramuscular injection (IM) and produce only injection site sarcomas. The available data regarding toxicity and carcinogenicity of nickel and nickel compounds are reviewed by the EPA in the Health Assessment Document for Nickel (EPA, 1985d). The EPA provides qualitative assessment of individual nickel compounds after reviewing the applicable studies. In the EPA assessment, studies showing only injection site tumors are considered to provide limited evidence and agents with only injection site tumors in animal studies would be placed in Group C. Based on the reviews of EPA (1985d) and IARC (1976), the weight-of-evidence was evaluated by DEP for several nickel compounds by examining only the studies using each specific compound. This assessment takes the position that studies showing injection site tumors only will be considered to be limited evidence of carcinogenicity. The weight-of-evidence for each nickel compound is listed in Table 1 with a brief description of the evidence including the response (+ or -),

route, and species. The weight-of-evidence for nickel subsulfide and nickel refinery dust were assigned by EPA and the remaining classifications were done by DEP.

The CAG calculation of unit risk for nickel is based on the use of 2 mathematical models and several data sets for epidemiological midpoint of the range of values obtained. The value for nickel subsulfide is equal to the value for nickel refinery dust multiplied by 2 because nickel subsulfide is assumed to be about half of refinery dust. With regard to the use of these unit risk values for other nickel compounds, the EPA states that "while nickel oxide and nickel sulfate are two other important nickel compounds in refinery dust, their possible carcinogenic potencies relative to the subsulfide have not been established and the above estimate cannot be used for either the oxide or the sulfate from" (EPA, 1985d). In the Draft HAD, the EPA states that "since respiratory tract cancer occurred in facilities that are diverse metallurgically in their operations, human carcinogenicity probable resides in several compounds of nickel" and that "this would be consistent with the experimental models" (EPA, 1983b). Based on the EPA discussion, the DEP considers that there is limited evidence of carcinogenicity in humans for nickel oxide and nickel sulfate.

Besides the CAG unit risk values for inhalation exposure to nickel refinery dust and nickel subsulfide, there are no other unit risk values adopted for inhalation exposure to nickel compounds. There are no completed NTP studies with any nickel compounds. The NTP currently has pre-chronic inhalation studies in progress for nickel oxide and nickel sulfate and has completed pre-chronic inhalation studies for nickel subsulfide (NTP, 1986a).

TABLE 1

Carcinogenicity Weight-of-Evidence for Nickel Compounds

Compound	Weight of Evidence	Summary of Evidence
Nickel metal	Group C	+ rat IM, + hamster IM - rat inh, - hamster inh
Nickel oxide (NiO)	Group B1	limited human data + rat IM, + mouse IM
Nickel oxide (Ni_2O_3)	Group D	- rat IM, 2 studies
Nickel sub-sulfide (Ni_3S_2)	Group A	+ human inhalation
Nickel monosulfide (NiS) crystalline	Group C	+ IM, intrarenal, - rat
amorphous	Group D	
Nickel nitrate (NiNO)	Group D	
Nickel sulfate ($NiSO_4$)	Group B1	limited human data - IM rats, - ingestion rats
Nickel chloride ($NiC1_2$)	Group D	
Nickel acetate ($Ni(CH_3COO)_2$)	Group C	+ IP (lung tumors), - implantation
Nickel hydroxide ($Ni(OH)_2$)	Group C	
Nickel carbonyl ($Ni(CO)_4$)	Group B2	+ inhalation + IV, + IM
Nickel fluoride (NiF_2)	Group D	
Nickel carbonate ($NiCO_3$)	Group C	+ IM
Nickel refinery dust	Group A	+ human inhalation

Carcinogenicity Dose-Response Assessment for Nitrobenzene

Summary

The weight-of-evidence classifications for nitrobenzene are Group D-Not Classifiable as to Human Carcinogenicity and ND for mutagenicity. There is no recommended carcinogenic potency from EPA-CAG. In a preliminary risk assessment, the CAG found no data suitable for risk assessment (EPA, 1979a). No studies of carcinogenicity of nitrobenzene, or dose-response assessment from other sources are known to the DEP at this time. No NTP studies with nitrobenzene are either completed or in progress (NTP, 1987). There is no recommended unit risk value for inhalation of nitrobenzene at this time.

Carcinogenicity Dose-Response Assessment for Pentachlorophenol

Summary

The weight-of-evidence classifications for pentachlorophenol are Group D-Not Classifiable as to Human Carcinogenicity and Limited for mutagenicity. CAG has not recommended a unit risk value at this time. There is no completed NTP study of pentachlorophenol. Two NTP studies of pentachlorophenol administered in feed to mice are in progress with the chronic pathology working group (NTP, 1987). These studies will be reviewed by the DEP when they are released by the NTP. There is no unit risk value adapted for pentachlorophenol at this time.

Carcinogenicity Dose-Response Assessment for PCB

Summary

The weight-of-evidence classifications for PCB are Group B2-Probable Human Carcinogen and No Data for mutagenicity. The EPA potency value is $7.7(mg/kg/d)^{-1}$. The unit risk for air exposure is 2.2×10^{-3} $(ug/m^3)^{-1}$. The recommended value for use in risk assessment of inhalation exposure is 2.2×10^{-3} $(ug/m^3)^{-1}$. The EPA is currently reevaluating the PCB carcinogenic potency value and the value given above was obtained from Dr. of EPA. Documentation for this value is not yet available. DEP will review any changes when the documentation becomes available. The potency value is based on a lifetime study reported by (1985) in which rats were exposed by ingestion & Arochlor 1260.

Background and Discussion

The carcinogenicity weight-of-evidence for PCB is based on liver tumors in multiple species (rats and mice) after oral exposure, as reviewed by IARC (1982c; 1978). Several other studies reviewed by IARC (1978) which show evidence of carcinogenicity, including benign and malignant tumors, are inadequate for quantitative dose-response assessment due to short duration of dosing and small numbers of animals used. The NCI reported a feeding study (NCI, 1978b) using Arochlor 1254 which caused no significant increases in malignant tumors and significant increases only in liver neoplastic modules in male and female rats. The negative results in this study compared to the positive results in the Kimbrough study may be due to the use of fewer animals (24 compared to 184), different rat strains, a different PCB congenes. The NTP has no current activity for any PCB (NTP, 1987).

Comparative studies of PCBs show that the acute and chronic toxicity increases with increasing chlorination. There is not sufficient evidence to determine whether this relationship extends to the carcinogenic effects. In the absence of better information on the structure - activity relationship of PCBs with regard to carcinogenicity, and PCB mixture will be considered to act with the same potency.

The data from the Kimbrough study used for the dose-response assessment by EPA will also be used by DEP, consistent with the policy that this assessment will generally be carried out for chemicals in Group B. The potency value was verified by EPA for inclusion in the Integrated Risk Information System (IRIS) database for the oral route. The inhalation unit risk has not been reviewed by EPA and is based on the assumptions that a 70kg

person inhales $20m^3$ of air per day over a 70-year lifetime, and that the PCB is completely absorbed.

The use of this study for quantitative dose-response evaluation for inhalation assumes that the potency of PCB will be identical when administered via different routes of exposure. This is presumed to be the case in the absence of information to the contrary. It follows from this assumption and from the fact that this analysis is based on an oral ingestion study that the potency value can be used in both oral and inhalation exposures.

Carcinogenicity Dose-Response Assessment for Propylene Oxide

Summary

The weight-of-evidence classifications for propylene oxide are Group B2 Provable Human Carcinogen and Suggestive Evidence for mutagenicity. There is no quantitative risk assessment available from CAG or any other source at this time. The DEP has performed a dose-response assessment based on the male mouse nasal turbinate tumors in the NTP inhalation study (NTP, 1985b). The DEP adapts a risk value of 6.67×10^{-7} $(ug/m^3)^{-1}$ for use in risk assessment of inhalation exposure.

Background

The carcinogenicity weight-of-evidence is based on the positive response in female rats and in male and female mice in the NTP study (NTP, 1985b), and on the positive response in rats as reviewed by the IARC (IARC, 1976). The recent IARC review of the data for propylene oxide concludes that there is sufficient animal evidence (IARC, 1985). No dose-response assessment from any other source is known to the DEP at this time. The NTP inhalation study of propylene oxide (NTP, 1985b) is considered to be adequate for quantitative dose-response assessment based on DEP procedures and the DEP quantitative dose-response assessment is based on this study.

Calculation of Unit Risk

In this study, male and female F344 rats and male and female B6C3F1 mice were exposed to 0, 200 or 400 ppm of propylene oxide for 6 hours, 5 days/week for approximately 98 weeks starting at 7-8 weeks. The actual numbers of days of exposure were 491 days for rats and high-dose mice and 495 days for low-dose mice or 98.2 and 99 weeks respectively (5 days/week) over a 103 week period. No significant treatment-related effect on survival or body weight occurred in rats. There was a significant treatment-related effect on body weight and on survival in male and female rats.

Increases in nasal turbinate papillary adenomas in female rats, and increases in nasal turbinate hemangioma or hemangiosarcoma in male and female mice were reported. In male mice, the increase in nasal turbinate hemangiosarcoma was statistically significant, while in the female mouse only the combined benign and malignant tumors were statistically significant The NTP considers benign tumors at this site to be biologically significant. The incidences of these tumors are shown in Table 1. The adjusted incidences shown are based on NTP

reported adjustment for early mortality. There were several tumor sites which were statistically significantly increased, but were not considered to be biologically significant by the NTP including rat female thyroid C-cell, rat female uterine tumors and female mouse mammary adenocarcinoma.

There was a dose-related increase in nasal epithelial nonneoplastic pathology including inflammation and squamous metaplasia in rats, and inflammation in mice.

The dose used for dose-response assessment was calculated as the lifetime average exposure concentration (LAC) as follows for rats and high-dose female mice:

$$\text{LAD} = \text{exposure concentration} \times \frac{6}{24} \times \frac{5}{7} \times \frac{98.2}{104}$$

For low-dose male mice, the last term was 99/104 because of differences in the number of days of exposure. The exposure concentration was expressed as mg/m^3 and the conversion from ppm is done as follows:

$$mg/m^3 = ppm \times \frac{mw}{24.455}$$

The volume of a mole of gas at 25^o C and standard pressure is 24.455 L. No further adjustment is needed for surface area scaling because the ventilation rate is approximately proportional to surface area so the exposure concentration is an equivalent dose metameter between species. The calculated lifetime average exposure concentrations are shown in Table 2.

The dose-response curve was estimated by fitting the multistage model to the incidence in Table 1 and the lifetime average exposure concentration in Table 2. The 95% upper confidence limit on the linear term is shown in Table 1 (q1*). There is no adjustment of this value necessary to account for less than lifetime exposure because the length of the experiment was longer than the nominal 104 week lifespan of rats and mice.

Discussion

The calculation of a unit risk value for propylene oxide is consistent with the DEP policy that unit risk value will generally be calculated for chemicals in weight of evidence Group B. The NTP inhalation study is considered to be an adequate study for quantitative dose-response assessment by the DEP. In this study, the preferred site for use in quantitative dose-response assessment is the male mouse nasal turbinate. This is the preferred site because it is the only site at which there is a significant increase in malignant tumors alone. The

combination of malignant and benign tumors at this site is consistent with NTP guidelines for combination of tumors (McConnell et al., 1986; NTP, 1984a). The unit risk for inhalation exposure to 1 (ug/m^3) of propylene oxide is 6.63×10^{-7} $(ug/m^3)^{-1}$. It is noted that the potency values for the three tumor sites are very similar.

There are no additional data describing dose-related or species-related effects on carcinogenic potency. It is therefore implicitly assumed that the relationship between the exposure concentration and the effective dose at the target is the same at high and low doses and in different species. This is consistent with the DEP policy that in the absence of additional data, these assumptions are reasonable. Because the toxicity of propylene oxide occurs at the site of contact, it is likely that there are significant route-dependent differences in toxicity and carcinogenicity and therefore this carcinogenic potency calculated on the basis of an inhalation study should not be used for assessment of risk from oral exposure.

TABLE 1. Incidences and Potency For Dose-Response Assessment of Propylene Oxide Using the NTP Inhalation Study.

Site	Incidence			Potency
	Control	Low	High	$(mg/m^3)^{-1}$
Female Rat				
Nasal turbinate papillary adenoma	0/50	0/50	3/50	4.79×10^{-4}
adjusted	0	0	5	6.17×10^{-4}
Male mouse				
Nasal turbinate hemangioma or hemangiocarcinoma	0/50	0/50	10/50	6.58×10^{-4}
adjusted	0	0	16	6.58×10^{-4}
Female mouse				
Nasal turbinate hemangioma or hemangiocarcinoma	0/50	0/50	5/50	6.17×10^{-4}
adjusted	0	0	16	6.63×10^{-4}

TABLE 2. Dose Calculation for Dose-Response Assessment of Propylene Oxide Using the NTP Inhalation Study.

	Exposure Concentration		LAC (mg/m^3)	
	low	high	low	high
Female rat	200	400	80.1	160
Male mouse	200	400	80.7	160
Female mouse	200	400	80.7	160

Carcinogenicity Dose-Response Assessment for Resorcinol

Summary

The weight of evidence classifications for resorcinol are D-Not Classifiable as to Human Carcinogenicity and Limited Evidence for mutagenicity. There is no dose-response assessment from any source, or any study on which to base a dose-response assessment, known to the DEP at this time. There are NTP gavage studies in rats and mice for which the chronic histopathology is in progress (NTP, 1987). These studies will be reviewed by DEP when released by NTP. There is no unit risk value adopted by DEP at this time.

Carcinogenicity Dose-Response Assessment for Selenium Sulfide

Summary

The weight of evidence classifications for selenium sulfide are Group B2-Probable Human Carcinogen and ND for mutagenicity. There is no quantitative dose-response assessment from the CAG or any other source known to the DEP at this time. The DEP has performed a dose-response assessment based on the NCI gavage study (NCI, 1980). The recommended unit risk for inhalation exposure to 1 (ug/m^3) is the DEP value which is 2.02×10^{-5} $(ug/m^3)^{-1}$.

Background

The weight of evidence designation for selenium sulfide is based primarily on tumors in rats and mice in the NCI study (NCI, 1980). CAG has assigned a weight of evidence classification of Group B2 to selenium disulfide. At the time of the IARC assessment of selenium and selenium compounds, the NCI study was not available and the animal and human evidence was considered inadequate by the IARC (IARC, 1975).

There is no dose-response assessment from any other source known to the DEP at this time. The NCI gavage study of selenium sulfide (NCI, 1980) is considered to be adequate for quantitative dose-response assessment based on DEP procedures and the assessment is presented below.

Calculation of Unit Risk Using the NCI Gavage Study

In this study, F344 rats were administered 0,3 or 15 mg/kg/d and B6C3F1 mice were administered 0, 20 or 100 mg/kg/d of selenium sulfide by gavage or 7 days per week for 103 weeks, starting at 4 weeks of age. There were no treatment-related effects on body weight or survival in any of the animal groups.

Significant increases in liver carcinoma and in combined liver carcinoma or neoplastic nodule were observed in the male and female rat and in the female mouse. There was also a significant increase in lung carcinoma and in combined adenoma or carcinoma of the lung in female mouse. The incidences of the tumors observed in this study are shown in Table 1. Some treatment-related nonneoplastic changes were reported in high-dose animals including "focal cellular changes" in rat liver and accumulation of dark pigment in interstitial and peribronchiolar areas of the lung.

The dose is characterized by the NCI study as being primarily

selenium monosulfide, and the elemental analysis is consistent with a mixture of selenium monosulfide and selenium disulfide, or selenium and sulfur, or both. For the purpose of this assessment the dose will be considered to be selenium sulfide because no adjustment is possible to account for other constituents. The dose is calculated as the surface area adjusted lifetime average daily dose. The lifetime average daily dose (LAD) is the daily dose x 103/104. The surface area adjusted dose is obtained by multiplying the LAD by $(70/bw)^{-1/3}$ with bw equal to the mean terminal body weight of the group of animals in kilograms. The adjusted doses are shown in Table 2. The dose-response relationship was estimated by fitting the multistage model to the tumor incidences in Table 1 and the surface area adjusted doses in Table 2. The resulting 95% upper confidence limits (q1*) are shown in Table 1. The tumor site with the highest potency is the female rat liver hepatocellular carcinoma or neoplastic nodule, and the carcinogenic potency at this site is 7.08×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for inhalation exposure is calculated assuming a 70kg person inhaling 20 m^3 of air per day and assuming that the absorption of the inhaled dose is the same as absorption of the gavage dose. The unit risk for 1 (ug/m^3) air concentration is:

$7.08 \times 10^{-2} \times 20m^3 \times 1/70kg \times 1mg/1000mg = 2.02 \times 10^{-5}$ $(ug/m^3)^{-1}$.

Discussion

The unit risk value for selenium sulfide is calculated using the NCI gavage study by the standard DEP procedure. The NCI study is considered adequate for dose-response assessment. There is not sufficient reason to exclude any of the tumor sites, so the site with the highest potency (the most sensitive site) was used. It is noted that the potency (the most sensitive site) was used. It is noted that the potency values from all sites fall within less than a two-fold range. The data from this study are less than ideal for quantitative dose-response assessment because the low dose used was only one-fifth of the high dose and because there were only significant increases in tumors in the high dose group.

There were no additional data to account for dose, route, or species-specific effects on carcinogenic potency. In accord with the DEP policy, the use of direct extrapolation of administered dose, and direct route-to-route and species-to-species extrapolation is reasonable in the absence of additional information. In this study, the high incidence of tumors in the high dose compared with the low dose group suggests a nonlinear response at high doses. However, the low dose was only one fifth of the high dose and the response in the low dose group, assuming a linear relationship, might not be distinguishable from zero. It is noted that the lung tumors in female mice increase

proportionately with dose. The DEP-ORS considers that the linear extrapolation to low dose is reasonable for this study.

The extrapolation from gavage to inhalation exposure is also made with the assumption that there are no differences between routes in absorption and distribution. More soluble selenium compounds are known to be quickly absorbed from lung and from gastrointestinal exposure. Selenium sulfide is relatively insoluble forms are absorbed to a large extent. At this time, the DEP-ORS will consider that the assumption of the similarity of carcinogenic potency for a dose given via different routes is reasonable. On this basis, the carcinogenic potency calculated for selenium sulfide may be used for inhalation or oral exposure.

TABLE 1. Incidences and Potencies for Dose-Response Assessment of Selenium Sulfide Using the NCI Gavage Study.

Tumor Site	Tumor Incidences Control	Low	High	Potency $q1^*$ $(mg/kg/d)^{-1}$
Male rat				
Liver carcinoma	0/50	0/50	14/49	6.26×10^{-2}
Liver carcinoma or neoplastic nodule	1/50	0/50	24/49	6.26×10^{-2}
Female rat				
Liver carcinoma	0/50	0/50	21/50	7.08×10^{-2}
Liver carcinoma or neoplastic nodule	1/50	0/50	37/50	7.08×10^{-2}
Female mouse				
Liver carcinoma	0/49	1/50	22/49	3.99×10^{-2}
Liver carcinoma or neoplastic nodule	0/49	2/50	25/49	6.31×10^{-2}
Lung carcinoma	0/49	1/50	4/50	
Lung carcinoma or adenoma	0/49	3/50	12/49	5.58×10^{-2}

TABLE 2. Dose Calculation for Dose-Response Assessment of Selenium Sulfide Using the NCI Gavage Study

	Administered dose (mg/kg/d)		LAD	Surface area adj. LAD (mg/kg/d)
Male Rat	low	3	2.97	0.542
	high	15	14.86	2.68
Female Rat	low	3	2.97	0.482
	high	15	14.86	2.33
Male Mouse	low	20	19.81	1.60
	high	100	99.04	8.01
Female Mouse	low	20	19.81	1.56
	high	100	99.04	7.51

Carcinogenicity Dose-Response for Styrene

Summary

The weight-of-evidence classifications for styrene are Group B2 - Probable Human Carcinogen and Sufficient Evidence for mutagenicity. The EPA has recently completed an analysis of the carcinogenicity data for styrene and calculated an inhalation unit risk value of 5.7×10^{-7} $(ug/m^3)^{-1}$ (EPA, 1987e) based on an inhalation study in rats. The EPA unit risk value is adopted by DEP for use in risk assessment of inhalation exposures.

Background and Discussion

The weight-of-evidence designation for styrene is based on the results of three studies which show increased tumor incidence in animals dosed with styrene or exposed by inhalation In 1982 IARC concluded that there was limited animal evidence (1982c) on the basis of increased lung tumors in mice in the 1979 NCI study. A study at DOW found increased leufemia/lymphosarcomas in rats after lifetime inhalation exposures. Another study showed increased incidence and decreased age of onset for lung tumors in mice exposed by gavage.

The EPA value is being adopted in the interest of consistency with EPA, and based on DEP and EPA policy to carry out quantitative cancer risk assessment for chemicals in Group B. Since the unit risk value is based on inhalation exposure, it should not be used for other routes of exposure.

Carcinogenicity Dose-Response Assessment for 1,1,2,2,-tetrachloroethane

Summary

The weight of evidence classifications for 1,1,2,2-tetrachloroethane are Group C-Possible Human Carcinogen and Suggestive Evidence for mutagenicity. The CAG calculated a carcinogenic potency of 0.20 $(mg/kg/d)^{-1}$ as part of the Water Quality Criteria Document (EPA, 1980b) based on the NCI gavage study (NCI, 1978a). The unit risk value for inhalation exposure based on this potency value is 5.8×10^{-5} $(ug/m^3)^{-1}$ (EPA, 1986f). The DEP has calculated a unit risk value for inhalation exposure based on the NCI study (NCI, 1978a). The DEP unit risk value for inhalation exposure is 7.70×10^{-5} $(ug/m^3)^{-1}$. According to the EPA Guidelines (EPA, 1986b) and the DEP procedures, the carcinogenicity data for chemicals in weight-of-evidence Group C are evaluated on a case-by-case basis with regard to their adequacy for dose-response assessment. the NCI study is considered to be adequate for dose-response assessment, and the EPA unit risk value of 5.8×10^{-5} $(ug/m^3)^{-1}$ is adopted by DEP for risk assessment of inhalation exposures.

Background and Discussion

The carcinogenicity weight-of-evidence is based on the positive response in mouse liver in the NCI gavage study as reviewed by IARC (1979b). The IARC designated the evidence as "limited". Weight-of-evidence Group C is assigned on the basis of increased tumor incidence at a single site in a single species. The NCI study is considered less than ideal for dose-response assessment because:

- -tumors only occurred at a single site
- -tumors only occurred in a single species
- -tumors occurred at a site with a high spontaneous incidence
- -high dose groups showed reduced survival

However, the tumors of the mouse liver in the NCI study occurred with a high incidence, were malignant, and were increased in a dose-dependent pattern. Based on these considerations, the unit risk value calculated using this study is considered to be a reasonable estimate of carcinogenic potency and is adopted for use.

The EPA unit risk estimate is based on the female mouse liver tumors (EPA, 1986f). This value is adopted by DEP in the interest of consistency with EPA.

Carcinogenicity Dose-Response Assessment for Tetrachloroethylene

Summary

The weight of evidence classifications for tetrachloroethylene are Group B2 for carcinogenicity and Suggestive Evidence for mutagenicity. The CAG has calculated a unit risk value for tetrachloroethylene based on the NCI gavage study and incorporating data describing the relationship between administered dose and metabolized dose and data describing the relationship between human inhaled dose and metabolized dose. The CAG recommended unit risk value for inhalation exposure is 4.8×10^{-7} $(ug/m^3)^{-1}$ (EPA, 1985h. The CAG has also updated the 1985 document with an addendum (EPA, 1986c) which includes a quantitative assessment of the NTP inhalation study (NTP, 1986h) using pharmacokinetic modelling. The unit risk values resulting from this assessment are not considered by CAG to be substantially different than the value obtained using the NCI gavage study. The DEP has calculated a unit risk which is also based on the NCI gavage study and using the pharmacokinetic data discussed in the EPA document. The DEP unit risk value is 5.52×10^{-5} $(ug/m^3)^{-1}$. The DEP has also calculated a unit risk value based on the NTP inhalation study, using disposition/metabolism data presented in the EPA document to estimate metabolized data presented in the EPA document to estimate metabolized dose. The unit risk value based on this analysis is 6.0×10^{-5} $(ug/m^3)^{-1}$. The unit risk value adopted by DEP for risk assessment of inhalation exposure is the DEP value of 5.52×10^{-5} $(ug/m^3)^{-1}$ based on the NCI gavage study. The details of the calculation of these values and the reasons for the choice of values are discussed below.

Background

The weight of evidence designation for carcinogenicity is based on the positive response in mice in the NCI gavage study (NCI, 1977) as reviewed by IARC (IARC, 1979b; 1982c), and the positive responses in rats and mice in the NTP inhalation study (NTP, 1986h). The EPA had classified the weight of evidence for carcinogenicity for tetrachloroethylene as Group C in the 1985 document, but changed that designation to Group B2 in the 1986 addendum on the basis of the NTP inhalation study. The EPA Scientific Advisory Board has recommended that the weight of evidence be designated Group C, but the EPA response is to maintain the Group B2 designation. The designation of tetrachloroethylene as a Group B2-Probable Human Carcinogen is consistent with EPA guidelines. The toxicology and carcinogenicity of tetrachloroethylene are reviewed in the EPA Health Assessment Document for Tetrachloroethylene are reviewed

in the EPA Health Assessment Document for Tetrachloroethylene (EPA, 1985h). This document also reviews many of the pharmacokinetic, metabolism but does not use pharmacokinetic modelling in the risk assessment in the Health Assessment Document. The DEP has performed a dose-response assessment based on the same study used by the CAG (NCI gavage study) and using the metabolism and disposition data discussed by EPA. The DEP unit risk value differs from the CAG value due mainly to differences in assumptions made about the amount of inhaled dose which is metabolized in humans. The only other study which is suitable for dose-response assessment for tetrachloroethylene is the NTP inhalation study (NTP, 1986h). The CAG assessment of this study, described in the addendum to the health assessment document (EPA, 1986c) includes dose calculation based on direct use of disposition/metabolism data and based on pharmacokinetic modelling. The DEP has also used the NTP inhalation study for dose-response assessment using metabolism and disposition data reviewed by the EPA. The CAG dose-response assessment is briefly reviewed below and the DEP unit risk calculations are described in detail.

CAG Dose-Response Assessment Using the NCI Gavage Study

The CAG dose-response assessment is based on the female mouse liver tumors from the NCI gavage study. The dose calculation used by the CAG uses the data of Buben and O'Flaherty (1985) showing a relationship between urinary and gavage dose through a range of concentrations which encompassed the doses used in the NCI study. The Buben and O'Flaherty study showed a pattern characteristic of a saturating effect, with metabolism measured as total urinary metabolites deviating from linearity at doses greater than 200 mg/kg. These data were fit to an equation with the Michaelis-Menton from equation and this equation was used to calculate metabolized dose from the gavage doses used in the NCI study. The resulting lifetime average dose for female mice used by the CAG are 0, 31.1, and 45.4 mg/kg/d and are expressed as dose metabolized to urinary metabolites. The CAG preferred to use a dose measurement based on urinary metabolites rather than adjusting the data to total metabolism because the data used later in their assessment to estimate human metabolism are based on measurements of urinary metabolites. The incidences used in the CAG dose-response assessment are 0/20, 19/48, and 19/48 for the control, low, and high dose groups respectively. The 95% upper confidence limit on the linear term in the multistage model fit to this tumor incidence and metabolized dose data set is 2.5×10^{-1} $(mg/kg/d)^{-1}$. this value includes a scaling factor for surface area. The conversion of this carcinogenic potency to a unit risk value for air exposure is made by the CAG using the study by Bolanowska and Golacka (1972). In this study 5 human subjects were exposed to approximately 50ppm (390,000 ug/m^3) of

tetrachloroethylene for 6 hours and urine metabolites were measured during exposure and for 14 hours after exposure. Using the data presented, the CAG estimates that the total metabolites in urine were about 13mg for this exposure. Using direct linear extrapolation from the results of the Bolanowska and Golacka study to low exposure concentration and 24 hour exposure, the CAG estimates that the metabolized dose due to 1 ug/m^3 of tetrachloroethylene is 1.33×10^{-4} mg/d or 1.9×10^{-6} (mg/kg/d) for a 70kg person exposed continuously. Based on the common assumption that a 70kg person inhales $20m^3$ of air per day, the total inhaled dose due to 1 ug/m^3 of tetrachloroethylene in air would be $1\ ug/m^3 \times 20\ m^3 \times 1/70kg \times 1mg/1000ug = 2.86 \times 10^{-4}$ mg/kg/d. The metabolized dose used in the CAG assessment is then 0.66% of the inhaled dose. The CAG assessment therefore assumes that 0.66% of the total inhaled dose in humans is metabolized to urinary metabolites at low concentrations of tetrachloroethylene in air, and this assumption is based on the results of a study with five human subjects exposed to 50 ppm of tetrachloroethylene. Based on this use of the data, the final CAG unit risk for inhalation exposure is 2.5×10^{-5} $(mg/kg/d)^{-1}$ x 1.9×10^{-6} $(mg/kg/d)/1\ ug/m^3 = 4.8 \times 10^{-7}$ $(ug/m^3)^{-1}$.

CAG Dose-Response Assessment Using the NTP Inhalation Study

The CAG has also assessed the results of the NTP inhalation study (NTP, 1986h) and calculated the inhalation unit risk based on this study (EPA, 1986c). In this study, male and female F344 rats were exposed to 0, 200, or 400 ppm of tetrachloroethylene and male and female B6C3F1 mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 6 hours/day, 5 days/week, for 103 weeks. There were increases in liver hepatocellular carcinoma in male and female mice and increases in mononuclear cell leukemia in male and female rats. The increase in kidney tubular cell tumors in male rats was not statistically significant, but may be biologically significant due to the rare spontaneous incidence of this tumor. The tumor incidences are shown in Table 3. No significant effect on body weight occurred in rats or mice. There were significant dose-related effects on survival in male rats and in male and female mice. Significant increases in several nonneoplastic pathologies were observed including kidney karyomegaly in male and female rats, kidney hyperplasia in male rats, adrenal hyperplasia in male and female rats, lung necrosis in mice and liver degeneration and necrosis in male and female mice.

The CAG used three approaches to calculation of the dose for use in dose-response modeling. The first approach involved direct estimation using metabolism/disposition data. The other two approaches used a physiologically-based pharmacokinetic model to estimate dose.

For direct estimation of dose in rats CAG uses the data of Pegg et al. (1979) in which SD rats were exposed to 10 or 600 ppm of tetrachloroethylene for 6 hours and exhaled or excreted radioactivity was measured for 72 hours after exposure. During this time, 32% and 12% of the body burden was metabolized at 10 and 600 ppm respectively. These data were used to estimate the metabolized dose at the concentrations used in the NTP study (200 and 400 ppm). To do this, CAG fits an equation of the Michaelis-Menton from to the data. The equation has the form $M = (V \times d)/(K + d)$ with M = urinary metabolites (mg/kg), and d = exposure concentration in ppm. The value of M is used as urinary metabolites so the human metabolism data of Bolanowska and Bolacka, reported as urinary metabolites, can be used to calculate human unit risk as described previously. The values of V and K are said by CAG to have been estimated from the data. Using the equation derived, CAG estimates dose metabolized to urinary metabolites in rats to be 11.9 and 16.05 mg/kg/d for the low and high exposure concentrations in the NTP study. Since it is not possible to solve an equation for two variables given only two data points without some other information, and no other information is cited in the CAG assessment, it is not clear how the equation used by CAG was derived. Because of this uncertainty, the DEP will not use this dose estimate, and will use an alternative procedure as described below.

For mice, the only data available for dose calculation for inhalation exposure are the data of Schumann et al. (1980) which show the disposition of tetrachloroethylene after exposure to 10 ppm for 6 hours. The CAG assumes that mice metabolized 5 times more than rats at the levels used in the NTP study. This is based on interpolation between a factor of 10 difference at low concentrations and a factor of 2-3 difference at high concentrations. The factor of 10 based on comparison of the data of Pegg et al. for rats and the data of Schumann et al. for mice, both at 10 ppm for 6 hour, in which the urinary metabolites in mice were 10 times greater than in rats on a mg/kg basis. This is not a reasonable comparison because at 10 ppm the rat was near saturation (68% of body burden exhaled unchanged) while the mouse was apparently not near saturation (12% of body burden exhaled unchanged). The factor of 2-3 is based on the assumption that the V max scales to surface area between species. There is no evidence that this is the case for tetrachloroethylene. This assumption is supported by CAG by evidence from gavage exposure to 500 mg/kg in mice and rats (Pegg et al., 1979; Schumann et al., 1980) but these studies do not give any information about the shape of the dose-response curve and it is therefore not reasonable to assume that this relationship is the same for mice and rats. This assumption is made by the CAG and the values for urinary metabolites for mice are obtained by multiplying by 5 the values obtained using the equation derived for rats. The DEP used a substantially different approach as described later. The

unit risks calculated are based on the surface area adjusted dose and use the human data of Bolanowska and Golacka as described for the NCI gavage study.

The CAG also used two different approaches to calculation of the dose based on pharmacokinetic modeling. The first method uses human metabolized doses calculated from the pharmacokinetic model and the second method uses the model to predict the mouse metabolized dose and then incorporates the data of Bolanowska and Golacka to calculate the human unit risk. The CAG risk estimates for these three methods used to calculate dose are:

a.) 2.9×10^{-7} to 9.5×10^{-7} $(ug/m^3)^{-1}$
b.) 2.9×10^{-6} to 1.1×10^{-5} $(ug/m^3)^{-1}$
c.) 9.6×10^{-7} to 3.6×10^{-6} $(ug/m^3)^{-1}$

Based on this analysis, CAG considers the unit risk estimates using the pharmacokinetic model to be unreliable due to uncertainties about several of the model inputs. The CAG states that the unit risk values from method 1, using direct estimation of dose from metabolism studies, are the most certain estimates. Since this range of values includes the value derived by CAG based on the NCI gavage study, the CAG does not change its recommendation regarding the unit risk value.

DEP Calculation of Unit Risk Based on NCI Gavage Study

The DEP calculated a unit risk value based on the male and female mouse liver tumors found in the NCI gavage study. The tumor incidences reported are shown in Table 1. The dose calculation used by the DEP is summarized in Table 2. The administered dose (Column 1) is used to calculate the dose metabolized to urinary trichloroacetic acid (TCA) (Column 2) using the equation derived by the CAG using the Buben and O'Flaherty data. Column 3 is the metabolized dose expressed as mg of tetrachloroethylene (Column 3 x MW PERC/MW TCA = Column 3 x 165.8/163.4). The lifetime average daily dose (LAD, Column 4) is calculated as metabolized dose x 5/7 x 78/95. The final term derives from the fact that the animals were dosed for 78 weeks and were killed at 95 weeks of age. The LAD is similar to the doses cited in the CAG analysis. A further adjustment is made to convert LAD based on urinary metabolites (Column 4) to total metabolites (Column 5). This adjustment is based on the assumption that the urinary metabolites are 80% of the total metabolism. This derives from the EPA analysis of the data of Schumann et al. (1980), Pegg et al. (1979) and Buben and O'Flaherty (1985). This adjustment was not used by the CAG. The LAD is then converted to equivalent human doses based on surface area scaling by multiplying the LAD by $(bw/70)^{1/3}$ with body weight

equal to the average terminal body weight of the animal group. The CAG assessment applies this adjustment to the carcinogenic potency after fitting the multistage model to the incidences in Table 1 and the surface area adjusted lifetime average dose in Column 6 of Table 2. The resulting carcinogenic risk values are shown in Table 1 for each site. The carcinogenic risk ($q_{1*)}$ is the 95% upper confidence limit on the linear term in the multistage model. The q1* value is adjusted for less than lifetime exposure by multiplying it by $(104/95)^3 = 1.31$. This is based on a 104 week nominal lifetime for mice and the fact that the mice were killed at 95 weeks of age in the NCI study. The carcinogenic potency value for the female mouse using the incidence cited by EPA is selected as the most appropriate value and the unit risk for inhalation exposure is based on the potency at this site which is 2.76×10^{-1} $(mg/kg/d)^{-1}$.

The DEP conversion to inhalation exposure assumes that the metabolized dose is equal to 70% of the inhaled dose. This assumption is substantially different than the approach used in the CAG assessment and is discussed below. Based on this assumption, the metabolized dose during exposure to 1 ug/m^3 is 1 $ug/m^3 \times 20m^3 \times 1/70kg \times 1/1000 \times .70 = 2.00 \times 10^{-4}$ (mg/kg/d). The unit risk for inhalation exposure to 1 mg/m^3 is then 2.76×10^{-1} $(mg/kg/d)^{-1} \times 2.00 \times 10^{-4}$ $(mg/kg/d)/(ug/m^3) = 5.52 \times 10^{-5}$ $(ug/m^3)^{-1}$.

DEP Unit Risk Calculation Using NTP Inhalation Study

The dose calculation used by the DEP relies on the data reviewed in the EPA document (EPA, 1985h). The dose calculation for the rat study uses the data of Pegg et al. (1979) as presented by the EPA. Rats were exposed to 10 or 600 ppm for 6 hours and the expired air, urine and feces were collected for 72 hours after exposure ended, and analyzed for tetrachloroethylene and metabolites. The amount of tetrachloroethylene recovered in any form was 5.92 mg/kg and 310 mg/kg in the 10 and 600 ppm groups respectively. This will be referred to as the body burden at the end of exposure. When normalized to exposure concentrations, the body burden of 0.592 and 0.517 (mg/kg)/ppm were obtained. The average value is 0.554 (mg/kg)/ppm and is used to approximate the body burden for the exposures used in the NTP study for rats (200 and 400 ppm). This use of the body burden data assumes a linear relationship between body burden and exposure concentrations exists through the range of concentrations used by Pegg et al. This is considered to be a reasonable approximation because the ratio of body burden to exposure concentrations for 10 and 600 ppm differ by less than 15% of their mean. Using this value, the body burden for the concentrations used in the NTP study are calculated and are shown in Table 4, Column 2. The data from Pegg et al. (1979) show that the proportion of the body burden that is metabolized is 32% and 12% in the 10 and 600 ppm groups respectively. Using linear

interpolation of the relationship between inhaled concentration and % of body burden metabolized to approximate the metabolism at the concentrations used by the NTP results in the values in Table 4, Column3. Column 4 gives the resulting estimate of metabolized dose. This is likely to be an overestimate of the proportion of the body burden metabolized, resulting in an overestimate of metabolized dose and an underestimate of carcinogenic potency. However, this is considered to be a reasonable dose estimate and is preferred to the CAG estimates for the reasons cited previously. Assuming that urinary metabolites are 50% of the total metabolites, the values obtained by the DEP (Table 4) and by CAG (cited previously) are comparable. Using this as the metabolized dose, the lifetime average dose is calculated a metabolized dose x 5/7 and shown in Table 4, Column 5; and the surface area adjusted LAD is shown in Column 6 of Table 4. The doses shown in Table 4, Column 6 are used for dose-response modeling for rats.

This dose calculation is based on a study in which metabolites were measured after a 6 hour exposure in rats. The metabolism during the exposure period was not measured and must be assumed to be small. This is considered to be a reasonable assumption based on the slow metabolism of tetrachloroethylene in the rats.

For mice, there are fewer data useful for dose calculation and the calculation is less certain. For this assessment, only the data of Schumann et al. (1980) are available. In contrast to the approach used by CAG (method 1), which assumes that the mouse dose metabolism curve approaches saturation with a form similar to the rat, the DEP assumes that the exposure concentration used in the NTP inhalation study do not result in metabolic saturation. This assumption is supported by the animal data. As discussed previously, the data of Pegg et al. (1979) show that the body burden at the end of exposure increases linearly with exposure concentration in in rats exposed to 10 to 600 ppm tetrachloroethylene for 6 hr. It appears reasonable to assume that this is also true of mice. Schumann et al. (1980) measured tetrachloroethylene and metabolites in the expired air, urine and feces in mice after 6 hr exposure to 10 ppm of tetrachloroethylene. In the Schumann et al. study, the body burden at the end of exposure is 16.5 mg/kg and 88% of the body burden is metabolized. There is no similar information available for other exposure concentrations.

Assuming a linear increase, the body burden at 100 and 200 ppm would be 165 and 330 mg/kg. The data of Buben and O'Flaherty show that the relationship between gavage dose and urinary metabolites is linear in Swiss-Cox mice up to a dose of 500 mg/kg. It can be assumed that the gavage dose is equivalent to the body burden at the end of a 6 hr inhalation exposure with

regard to its eventual disposition, and that the Swiss-Cox mice used by Buben and O'Flaherty are representative of the B6C3F1 mice used in the NTP study. It follows that the doses received in the NTP study are on the linear part of the dose metabolism curve and that the value of 88% metabolized is reasonable at these levels. This is used to calculate the metabolized dose as shown in Table 5. If the urinary metabolites are assumed to be half of the total, then the values used for metabolized dose by CAG are about 1/2 of the values obtained by DEP, because the CAG assumed that the levels used were on the nonlinear part of the dose-metabolism curve.

In this calculation, the actual dose could be underestimated because the data do not account for metabolism during the exposure, and could be overestimated due to extrapolation from the low concentration used by the NTP. The net effect of these potential errors on the dose estimation and hence on the risk estimate is not known. This dose calculation also assumes that the metabolized dose for a single 6-hour exposure will be the same when doses are given chronically. Because the metabolism of tetrachloroethylene is slow, the dose given on one day is probably not completely cleared before the next day's exposure, leading to accumulation of tetrachloroethylene, and increased body burden. This would lead to an underestimate of the actual metabolized dose. It is not possible to know if this is the case because only one dose level is available but this is considered to be a reasonable approach.

The risk estimates for rats and mice were calculated using the surface area adjusted doses presented in Table 4 and 5 and the incidences in Table 3. The unit risk estimate is taken as the 95% upper confidence limit on the linear term of the multistage model and is presented in Table 6.

The unit risk for inhalation exposure to 1 ug/m^3 based on the male rat kidney tumor is 9.1×10^{-6} $(ug/m^3)^{-1}$. This value is based on the assumption that a 70kg person breathes 20 m^3/d and that a 70% of the inhaled tetrachloroethylene is metabolized. The most sensitive site in this analysis is the male rat mononuclear cell leukemia which gives a unit risk for inhalation exposure of 6.01×10^{-5} $(ug/m^3)^{-1}$. The unit risk value for female mouse liver is 1.47×10^{-5} compared with 5.5×10^{-5} from the gavage study. The unit risk for the male mouse liver is 4.1×10^{-5} compared with 9.7×10^{-5} in the gavage study.

Discussion

The unit risk value calculated for the NTP inhalation study is not considered by DEP to be a reasonable quantitative estimate of the carcinogenic potency of tetrachloroethylene because of the uncertainty in the calculations of metabolized dose. The

calculation of metabolized dose for the gavage study is more reliable because the data of Buben and O'Flaherty provide information on the metabolism of a range of doses that include the doses used in the NCI gavage study. The data on metabolism of tetrachloroethylene after inhalation exposure are limited to a single group of animals for mice and two groups for rats. The DEP analysis used only the data provided in the EPA Health Assessment Document and did not use pharmacokinetic modeling.

The unit risk calculation based on the NCI gavage study done by the DEP is preferred for inhalation exposure to low concentrations. The calculation of the human equivalent doses are very similar in the DEP and the CAG assessments of the NCI gavage study. The resulting carcinogenic potency values are 2.5×10^{-1} $(mg/kg/d)^{-1}$ in the CAG assessment and 2.76×10^{-1} $(mg/kg/d)^{-1}$ in the DEP assessment. the major difference in the CAG and DEP unit risk values for inhalation exposures are due to the assumptions made about the extent of absorption and metabolism of inhaled tetrachloroethylene in humans. The CAG calculations use the data of Bolanowska and Golacka (1972) in which metabolism was measured in humans after exposure to 390,000 ug/m^3 of tetrachloroethylene for 6 hours. Based on the EPA analysis of this study, and the assumption of 20 m^3/d inhaled for a 70kg person, this study showed that 0.66% of the inhaled dose was metabolized This result is assumed in the CAG calculation of unit risk for air exposure. Use of the CAG risk estimate for estimation of risk at ambient exposure levels assumes that the results of this study can be extrapolated over five orders of magnitude of dose.

The DEP assessment considers it more likely that the proportion of the inhaled dose which is metabolized varies with the dose and that at low enough doses nearly all of the absorbed chemical is metabolized. If all tissues are assumed to have some metabolizing capacity, then it is reasonable to assumed to have some metabolizing capacity, then it is reasonable to assume that at some low airborne concentration none of the tissues are saturated (capacity limited). Under this condition, the metabolism in most tissues would be flow limited and 100% of the absorbed dose would be metabolized. The blood concentration would then be zero in the pulmonary artery and the absorption would be a function of the blood;air partition coefficient. Anderson et al. (1981) have presented a theoretical curve showing that under these conditions the proportion of the inhaled dose that is metabolized approaches a maximum of 67% at blood:air partition coefficient greater than 10. This is based on the use by these authors of alveolar ventilation equal to 67% of the total ventilation and the assumption that the absorption of inhaled gases occur at the alveolar level. The DEP assessment assumes that the levels of tetrachloroethylene that are of concern due to environmental exposure will be too low to cause

metabolic saturation in any tissue and that the metabolized dose will be equal to 70% of the inhaled dose. This is considered to be a more reasonable quantitative dose-response assessment for ambient air exposure.

The final unit risk estimate for the NCI gavage study was 5.52×10^{-5} $(ug/m^3)^{-1}$. The unit risk values calculated for the NTP inhalation study ranged from 6×10^{-5} to 9×10^{-5} $(ug/m^{3\ -1}$. The result for the NTP inhalation study must be considered to be uncertain at this time because of the limited amount of data that are available for calculation of metabolized dose. Nevertheless, the results from the two studies agree fairly well, lending confidence to the unit risk based on the gavage study.

Table 1. Tumor Incidences and Potencies from the NCI Gavage Study of Tetrachloroethylene

	Incidences			Potency	
	Control	Low Dose	High Dose	q1*	q1* LLE adjusted
Mouse					
Male	2/20	32/49	27/48	2.578×10^{-1}	3.38×10^{-1}
Female	0/20	19/48	19/48	2.004×10^{-1}	2.63×10^{-1}
CAG	0/20	19/48	19/45	2.106×10^{-1}	2.76×10^{-1}

Table 2. Dose Calculation for Dose-Response Assessment of Tetrachloroethylene Using the NCI Gavage Study.

		(1) admin. dose mg/kg/d	(2) metab. mg TCA/ kg/d	(3) metab. mg PERC/ kg/d	(4) LAD mg/ kg/d	(5) LAD adj. urinary to total metabol.	(6) surface area adj. mg/kg/d
mouse							
male	low	536	60.95	61.84	36.27	45.34	3.46
	high	1072	84.18	85.42	50.10	62.63	4.77
female	low	386	50.19	50.93	29.87	37.34	2.65
	high	772	73.32	74.40	43.63	54.54	3.87

Table 3. Incidences for Dose-Response Assessment of Tetrachloroethylene Using the NTP Inhalation Study

		Control	Low dose	High dose
Male rat				
Mononuclear cell leukemia	actual	28/50	37/50	37/50
	adj.	32	40	45
Kidney tubular cell	actual	1/49	3/49	4/50
	adj.	2	5	11
Female rat				
Mononuclear cell leukemia	actual	18/50	30/50	29/50
	adj.	27	36	33
Male mouse				
Hepatocellular carcinoma	actual	7/49	25/49	26/50
	adj.	7	29	29
Hepatocellular adenoma or carcinoma	actual	17/49	31/49	41/50
	adj.	18	36	45
Female mouse				
Hepatocellular carcinoma	actual	1/48	13/50	6/50
	adj.	1	18	46
Hepatocellular adenoma or carcinoma	actual	4/48	17/50	38/50
	adj.	5	23	46

Table 4. Dose Calculation for Rats for Dose-Response Assessment of Tetrachloroethylene Using the NTP Inhalation Study.

(1) exposure conc. ppm	(2) body burden mg/kg	(3) % of b.b. metabol.	(4) metabolized dose mg/kg/d	(5) LAD mg/kg/d	(6) Surface area adjusted LAD mg/kg/d	
					Male	Female
200	110.8	25.6	28.4	20.3	3.80	3.36
400	221.6	18.8	41.7	29.8	5.58	4.95

Table 5. Dose Calculation for Mice for Dose-Response Assessment of Tetrachloroethylene Using the NTP Inhalation Study.

Exposure Concentration (mg/kg/d)	Body burden (mg/kg/d)	Metabol. dose (mg/kg/d)	LAD (mg/kg/d)	Surface area adjusted dose (mg/kg/d)	
				male	female
100	165	145	104	8.45	8.05
200	330	290	207	16.8	15.5

Table 6. Carcinogenic Potency From Dose-Response Assessment of Tetrachloroethylene Using the NTP Inhalation Study.

Site	Potency $q1^*$ $(mg/kg/d)^{-1}$
Male rat	
Mononuclear cell leukemia	3.00×10^{-1}
Kidney tubular cell	4.57×10^{-2}
Female rat	
Mononuclear cell leukemia	1.66×10^{-1}
Male mouse	
Hepatocellular carcinoma	7.31×10^{-2}
Hepatocellular adema or carcinoma	1.43×10^{-1}
Female mouse	
Hepatocellular carcinoma	3.16×10^{-2}
Hepatocellular adema or carcinoma	5.15×10^{-2}

Carcinogenicity Dose-Response Assessment for Tetrahydrofuran

Summary

The weight of evidence classifications for tetrahydrofuran are D-Not Classifiable as to Human Carcinogenicity and ND for mutagenicity. There is no quantitative dose-response assessment available from any other source and no study on which to base a dose-response assessment known to the DEP at this time. An NTP inhalation study in rats and mice has been assigned to a lab for toxicology study (NTP, 1987). There is no unit risk value adopted by DEP at this time.

Carcinogenicity dose-Response Assessment for Toluene

Summary

The weight of evidence classifications for toluene are Group D-Not Classifiable as to Human Carcinogenicity and non-positive for mutagenicity. There is no dose-response assessment available from any source or any study on which to base a dose-response assessment known to the DEP at this time. The EPA evaluated the carcinogenicity data available for toluene concluded that there were insufficient data to evaluate carcinogenicity or to calculate carcinogenic potency (EPA, 1980d). There is an NTP inhalation study with rats and mice for which the quality assessment is in progress (NTP, 1987). The DEP will review this study when it is released by the NTP. There is no unit risk value adopted by DEP at this time.

Carcinogenicity Dose-Response Assessment for Toluene Diisocyanate

Summary

The weight of evidence classifications for toluene diisocyanate are Group B2-Probable Human Carcinogen and ND for mutagenicity. There is no dose-response assessment from CAG or any other source known to the DEP at this time. The DEP dose-response assessment based on the NTP gavage study (NTP, 1986b) is presented herein. The unit risk value adopted by DEP for risk assessment of inhalation exposure is 6.79×10^{-6} $(ug/m^3)^{-1}$.

Background

The carcinogenicity weight of evidence classification assigned by DEP is based primarily on the NTP gavage study in which tumors were observed in rats and mice. At the time of the IARC review of the data for toluene diisocyanate (IARC, 1979a), there were no adequate data on which to base an assessment of carcinogenicity. The NTP study is the only study known to the DEP which is adequate for dose-response assessment. The CAG is currently in the process of performing a quantitative dose-response assessment for toluene diisocyante (Charlis Ris, 8-26-86, personal communication). The DEP assessment is presented below.

Unit Risk Calculation Based on NTP Study

In this study F344 rats and B6C3F1 mice were dosed by gavage with toluene diisocyante 5 days per week for 106 weeks (rats) or 105 weeks (mice). The dose levels were 0, 30, or 60 mg/kg/d for male rats 0, 120, or 240 mg/kg/d for male mice, and 0. 60, or 120 mg/kg/d for female rats and mice. Statistically significant dose-related effects on body weight occurred in males and females of both species. There was also a dose-related decrease in survival in male and female rats and male mice, but not in female mice.

Increased tumor incidences were reported at several sites in both rats and mice. The incidences used in this assessment are shown in Table 1. Adjusted incidences are reported by the NTP to account for treatment-related effects on survival.

The lifetime average daily dose (LAD) is obtained by multiplying the administered dose by 5/7. The LAD is converted to an equivalent human dose by surface area scaling as follows:

$$\text{Surface Area Adjusted LAD} = \text{LAD} \times (70/\text{b.w.})^{-1/3}$$

with b.w. equal to the the mean terminal body weight of the group of animals. The dose calculations are presented in Table 2.

The dose-response curve was estimated by fitting the multistage model to the incidences in Table 1 and the surface area adjusted lifetime average daily dose in Table 2. The 95% upper confidence limit on the linear term is taken as the estimate of carcinogenic potency for each site This parameter (q1*) is listed in Table 1.

The female mouse circulatory hemangioma or hemangiosarcoma is the preferred site for carcinogenic potency estimation as discussed below. The carcinogenic potency at this site is 2.37 x 10^{-2} $(mg/kg/d)^{-1}$. This potency value is used to calculate a unit risk for lifetime exposure to 1 ug/m^3 in air, assuming a 70 kg person inhaling 20 m^3 of air, as follows:

$$\frac{2.37 \times 10^{-2}}{(mg/kg/d)^{-1}} \times \frac{20m^3}{d} \times \frac{1}{70kg} \times \frac{1mg}{1000ug} = 6.79 \times 10^{-6} \ (ug/m^3)^{-1}$$

Discussion

The calculation of the unit risk value for toluene diisocyante is consistent with the DEP policy to perform dose-response assessment on chemicals in Group B. The NTP gavage study is the only carcinogenicity study for toluene diisocyanate known to the DEP and this study was the basis for the dose-response assessment.

The female mouse circulatory tumors were selected as the most appropriate site for use in dose-response assessment. The female mouse tumor is preferred to the rat because the rat data were were compromised due to decreased survival in the treated animals. The circulatory tumors in the female mouse are preferred to the liver tumors because there was no significant increase in liver hepatocellular carcinomas. It is the policy of the DEP that only sites with significantly elevated malignant tumors will be considered appropriate for dose-response assessment. The criteria for site selection are discussed in detail in Appendix D.

There were no additional data to account for dose, route, or species specific effects on carcinogenic potency. This assessment is therefore based on the assumption that high-dose to low-dose, route-to-route, and species-to-species extrapolations are valid. The basis for the use of these assumptions is discussed in detail in Appendix D. Because this assessment is based on the use of direct route-to-route extrapolation, the unit risk value can be used for oral or inhalation exposure.

Table 1. Tumor Incidences and Carcinogenic Potencies for Toluene Diisocyanate Based on the NTP Study

		Tumor Incidence		Potency
	Control	Low	High	q_1*
Dose Dose	(mg/kg/d)$^{-1}$			
Male rat				
Subcutaneous fibroma or fibrosarcoma[1]	3/50	6/50	12/50	4.30×10^{-2}
Adjusted	4	17	33	1.41×10^{-1}
Pancreatic Acinar Cell Adenoma	1/47	3/47	7/49	2.86×10^{-2}
Adjusted	1	9	29	6.47×10^{-2}
Female Rat				
Subcutaneous fibroma or fibrosarcoma[2]	2/50	1/50	5/50	8.88×10^{-3}
Adjusted	3	3	26	1.31×10^{-2}
Pancreatic islet cell adenoma	0/50	6/49	2/47	1.60×10^{-2}
Adjusted	0	12	16	5.10×10^{-2}
Liver neoplatic nodule	3/50	8/50	8/48	2.22×10^{-2}
Adjusted	4	15	29	7.21×10^{-2}
Mammary gland and subcutaneous fibroadenoma	7/50	25/50	21/50	3.70×10^{-2}
Adjusted	22	44	46	2.58×10^{-1}
Female mouse				
Circulatory hemangioma or hemangiosarcoma[1]	0/50	1/50	5/50	2.07×10^{-2}
Adjusted	0	1	7	2.37×10^{-2}
Liver hepatocellular or carcinoma[2]	4/50	5/50	15/50	4.35×10^{-2}
Adjusted	5	6	22	4.08×10^{-2}

[1] Malignant tumors were significantly elevated.
[2] Malignant tumors were not significantly elevated.

Table 2. Dose calculations for Dose-Response Assessment of Toluene Diisocyanate Using the NTP Study

Dose		Administered Dose	LAD	Surface Area Adjusted Dose
		mg/kg/d	mg/kg/d	mg/kg/d
Male Rat	Low dose	30	21.4	3.77
	High dose	60	42.9	7.19
Female Rat	Low dose	60	42.9	6.23
	High dose	120	85.7	11.96
Male Mouse	Low Dose	120	85.7	6.90
	High dose	240	171	13.4
Female Mouse	Low dose	60	42.9	3.37
	High dose	120	85.7	6.57

Carcinogenicity Dose-Response Assessment for o-toluidine

Summary

The weight-of-evidence classifications for o-toluidine are Group B2-Probable Human Carcinogen and Suggestive for mutagenicity. There is no CAG recommended unit risk value at this time and there is no dose-response assessment from any other source known to the DEP at his time. The Rhode Island DEM is currently performing a dose-response assessment for o-toluidine. The DEP-ORS will review this work when it is finished. The DEP has calculated the carcinogenic potency for o-toluidine using the NCi study in which the chemical was administered in the feed (NCI, 1979a). The unit value recommended for inhalation exposure is the DEP value of 5.72×10^{-6} $(ug/m^3)^{-1}$.

Background

The carcinogenic weight-of-evidence classification for o-toluidine is assigned by DEP and is based on positive responses in rats and two strains of mouse after oral exposure, as reviewed by IARC (IARC, 1982a). The IARC concluded that there is sufficient evidence that o-toluidine causes cancer in animals (IARC, 1982c). The DEP dose-response assessment is based on the NCI feeding study and is presented below. The IARC review also discusses the Weisburger et al. (1978(study which showed increases in tumors in rats and mice. The Weisburger et al. study was not reviewed by the DEP. There is no current activity in the NTP bioassay program regarding o-toluidine (NTP, 1987).

Discussion

The calculation of a unit risk value for o-toluidine is performed because the weight of evidence for carcinogenicity is Group B and because the NCI study is considered to be adequate for quantitative dose-response assessment. The female mouse liver was selected as the most appropriate site for use in quantitative dose-response assessment. The mouse was preferred to the rat in this study because of dose related effects on rat survival. The site selected is the most sensitive site showing increased tumors in the mouse.

There were no additional data describing dose, route, or species-specific effects on carcinogenic potency. This assessment therefore assumes that there are no high-dose effects on carcinogenic potency, that the oral and inhalation routes are equivalent with regard to the carcinogenic potency, and that direct interspecies extrapolation is valid. The basis for the use of these assumptions is discussed in detail in Appendix D.4

Because equivalence of routes of exposure is assumed, the carcinogenic potency derived here can be used for oral or inhalation exposure.

Calculation of Unit Risk from NCI Study

In this study, F344 rats were fed diets containing 0, 3000 or 6000 ppm of o-toluidine and B6C3F1 mice were fed diets containing 0, 1000 or 3000 ppm of o-toluidine. The diets were fed for 103 weeks in mice and 104 weeks in rats and all treatments were started at 6 weeks of age. Significant treatment-related effect on body weight was observed in all rats and mice of both sexes and there was a significant dose-related effect on survival in male and female rats. No significant effect on survival occurred in male or female mice.

There were significant increases in tumors at various sites in male and female rats and in male and female mice. The incidences of tumors which were considered by the NCI to provide evidence of carcinogenicity are shown in Table 1. The incidences were given to account for survival effects in rats. The combination of tumors at different sites and the combination of benign and malignant tumors at a single site are consistent with recent NTP recommendations (NTP, 1984; McConnell et al., 1986). Various nonneoplastic lesions were reported including proliferative lesions in mesenchymal tissue in spleen, other viscerla organs, and the peritoneal lining of the abdominal cavity and scrotum in rats, and proliferative lesions of the transitional epithelium of the urinary bladder and renal pelvis in rats.

The dose of o-toluidine was administered as o-toluidine hydrochloride. There was no information given in the NCI report on the measurement of consumption or the estimation of the dose in this study. In the absence of estimated dose, the DEP procedure is to use the equations developed by Crouch (1983) to estimate the lifetime average dose in a feeding study. The calculated doses are adjusted to be expressed as dose of o-toluidine by multiplying the calculated dose by the ratio of molecular weights of o-toluidine and o-toluidine hydrochloride (107.2/143.6). The lifetime average dose (LAD) derived in this way are scaled to human equivalent doses by surface area scaling as follows:

$$\text{surface area adjusted LAD} = \text{LAD (mg/kg/d)} \times (70/bw)^{-1/3}$$

with bw equal to the average terminal body weight in the group of animals. The dose calculations are shown in Table 2.

The dose-response curve was estimated by fitting the multistage model to the incidences in Table 1 and the surface

area adjusted lifetime average dose in Table 2. The 95% upper confidence limit on the linear term is taken as the estimate of carcinogenic potency and the values of this parameter (q1*) are shown in Table 1.

The result for the mouse female liver hepatocellular adenoma or carcinoma was selected as the best estimate of carcinogenic potency as discussed below. The carcinogenic potency at this site was 2.00×10^{-2} $(mg/kg/d)^{-1}$. Based on this value a unit risk for lifetime exposure to 1 ug/m^3 of o-toluidine is calculated assuming a 70 kg person breathing 20 m^3/day and 100% absorption of the inhaled dose. The unit risk value for air is 5.72×10^{-5} $(ug/m^3)^{-1}$.

Table 1. Incidence and Potency For Dose-Response Assessment of o-toluidine Based on NCI Study.

Site	Tumor Incidence Cont	Low	High	Potency q^{1*} $(mg/kg/d)^{-1}$
Male rat				
Spleen and other organs - sarcoma	0/20	15/50	37/49	2.21×10^{-2}
Abdominal cavity or scrotum - mesothelioma	0/20	17/50	9/49	1.48×10^{-2}
Female rat				
Spleen and other organs - sarcoma	0/20	3/50	21/49	4.46×10^{-3}
Bladder - transitional cell carcinoma	0/20	9/45	22/47	1.61×10^{-2}
Male mouse				
Various sites - hemangiosarcoma	1/19	1/50	10/50	8.78×10^{-3}
Various sites - hemangioma or hemangiosarcoma	1/19	2/50	12/50	1.21×10^{-3}
Female mouse				
Liver - adenoma or carcinoma	0/20	4/49	13/50	2.00×10^{-2}
Liver - carcinoma	0/20	2/49	7/50	1.14×10^{-2}

Table 2. Dose Calculation for Dose-Response Assessment of o-toluidine Using the NCI Study

	Administered, Dose ppm in diet	LAD as o-toluidine HCl (mg/kg/d)	LAD as o-toluidine (mg/kg/d)	Surface Area Adjusted LAD (mg/kg/d)
Male rat				
Low dose	3000	139	104	18.4
high dose	6000	288	215	36.8
Female rat				
low dose	3000	191	143	22.4
high dose	6000	383	286	43.1
Male mouse				
Low Dose	1000	109	81.3	7.02
High dose	3000	340	254	21.1
Female mouse				
Low dose	1000	115	86	6.95
High dose	3000	367	274	20.9

Carcinogenicity Dose-Response Assessment for
1,1,1-trichloroethane

Summary

The weight-of-evidence classifications for 1,1,1-trichloroethane are Inconclusive for carcinogenicity and Suggestive for mutagenicity. The CAG classification is Group D - not classifiable as to Human Carcinogenicity. The designation for carcinogenicity is based on the IARC review (IARC, 1979b) in which the only animal study was the NCI report (NCI, 1977a) which was inadequate for assessment. The more recent gavage study (NTP, 1987) is being drafted. This study showed some evidence of tumors in female mice; the male mice data were considered inadequate for assessment by the NTP. The rats in this study showed no tumors but exposures may have been below the MTD. There is no carcinogenicity dose-response assessment available from any source and there is no adequate study on which to base a dose-response assessment known to the DEP at this time. The CAG assessed the available data (EPA, 1980e) and concluded that there are no data available which could be used for quantitative dose-response assessment at that time. The NTP has performed another gavage study with 1,1,1-trichloroethane and the technical report is being drafted (NTP, 1987). The DEP will review the study when it is released by the NTP. There are also chemical disposition studies underway at the NTP (1987). There is no unit risk value adopted by DEP at this time.

Carcinogenicity Dose-Response Assessment for
1,1,2-trichloroethane

Summary

The weight-of-evidence classifications for 1,1,2-trichloroethane are Group C- Possible Human Carcinogen and No Data (ND) for mutagenicity. The CAG calculated a carcinogenic potency value as part of the Ambient Water Quality Criteria Document series (EPA, 1980b) based on the NCI gavage study (NCI, 1978e). The carcinogenic potency derived by CAG is 5.7×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for inhalation exposure based on this value is 1.6×10^{-5} $(ug/m^3)^{-1}$ (EPA, 1986g). According to EPA (1986b) and DEP policy, the carcinogenicity data for chemicals in Group C are evaluated on a case-by-case basis with regard to their adequacy for dose-response assessment. The NCI gavage study is considered to be adequate for quantitative assessment. The EPA unit risk value is adopted by DEP for use in risk assessment of inhalation exposures.

Background and Discussion

The weight of evidence designation for 1,1,2-trichloroethane is based on the positive response in mice in the NCI gavage study. The designation as Group C is based on the IARC designation of the evidence as limited (IARC, 1979b) and on the appearance of tumors in a single species; the evidence is strengthened by the increasing tumors at two sites in mice.

The CAG unit risk is based on male mouse liver tumors. The liver tumors are considered to be less than ideal for dose-response assessment because:

- -the tumors occur in a single species
- -the tumors occur at a site which has a high spontaneous incidence and which is a target organ for the agent
- -there are no supporting data from short-term tests

However, the liver tumors occurred with a high incidence, were malignant, and showed a dose-response at two dose-levels; the adrenal tumors were also malignant and were significantly elevated. The tumor incidences and doses are shown in Table 1.

Based on these considerations, the data from the NCI gavage study are considered to be adequate for dose-response assessment. The EPA unit risk value is adopted by DEP in order to ensure consistency with EPA.

Table 1. Tumor Incidences and Dose Calculations from Dose-Response Assessment of 1,1,2-trichloroethane Using the NCI Gavage Study.

	Admin. dose mg/kg/d	LAD mg/kg/d	Surface area adjusted dose	Incidence
Male mouse				
Liver	0	0	0	2/17
hepatocellular	195	119	9.48	18/49
carcinoma	390	239	18.8	37/49
Adrenal				
pheochromocytoma	0	0	0	0/18
	195	119	9.48	0/49
	390	239	18.8	8/48
Female mouse				
Liver	0	0	0	2/20
hepatocellular	195	119	9.48	16/48
carcinoma	390	239	18.8	40/45
Adrenal	0	0	0	0/20
pheochromocytoma	195	119	9.48	0/48
	390	239	18.8	12/43

Carcinogenicity Dose-Response Assessment for Trichloroethylene

Summary

The weight-of-evidence classifications for trichloroethylene are Group B2 for carcinogenicity and Sufficient for mutagenicity. The CAG has calculated a unit risk value for inhalation exposure based on the NCI and NTP gavage studies (NCI, 1976a; NTP, 1982b). The CAG recommended unit risk value is 1.3×10^{-6} $(ug/m^3)^{-1}$ (EPA, 1985j). The DEP has calculated a unit risk which is based on the NCI gavage study and uses the metabolism and disposition data discussed in the EPA document. The DEP unit risk value is 1.63×10^{-6} $(ug/m^3)^{-1}$. For comparative purposes, the unit risk value was calculated from the inhalation study of Bell et al. (1978) by the CAG and the DEP, and from the inhalation study of et al. (1983) by the DEP. These results are discussed. The unit risk value adopted for risk assessment of inhalation exposure is the DEP value based on the NCI gavage study which is 1.63×10^{-6} $(ug/m^3)^{-1}$. The details of the calculation and the reasons for this choice of unit risk value are discussed below.

Background

The weight-of-evidence designation for carcinogenicity is based on the positive responses in mice in multiple studies using different exposure routes as reviewed by the IARC (IARC, 1979b, 1982c), and the positive response in the Fukuda et al. study (Fukuda et al., 1983). The toxicology and carcinogenicity of trichloroethylene are reviewed in the EPA Health Assessment Document for Trichloroethylene (EPA, 1985j). This document also reviews much of the pharmacokinetic, metabolism, and disposition data that are available for trichloroethylene. The CAG unit risk calculation incorporated animal disposition studies and human studies of metabolism, but does not use pharmacokinetic modeling. The DEP dose-response assessments use the animal metabolism data presented in the EPA document. The EPA document reviews the literature and concludes that the NCI and NTP gavage studies and the Bell et al. (1978) inhalation studies are useful for quantitative risk assessment. In addition to these studies, the DEP has used the Fukuda et al. (1983) study for quantitative dose-response assessment. The study is not discussed in detail in the EPA document. In addition to these studies, a study by Maltoni et al, is cited in the EPA document as being recently completed, but the results of this study are not available to the DEP at this time. CAG currently has in progress an update of the trichloroethylene health assessment which includes the Maltoni inhalation and gavage studies and will presumable incorporate pharmacokinetic modelling in the dose calculation. This document should be available soon. The NTP has performed a gavage study in F344 rats and B6C3F1 mice (NTP, 1982b) which was reviewed by

the EPA and used in the CAG dose-response assessment. The NTP has also completed a gavage study in four stains of rats (NTP, 1986e). The 1986 study was considered to be inadequate by the NTP due to reduced survival, toxicity, and poor documentation of the results and is not used in this dose-response evaluation.

The details of the DEP unit risk calculations are presented below as well as a brief review of the CAG dose-response assessment.

Summary of the CAG Dose-Response Assessment

The CAG unit risk calculation uses liver tumors from male and female mice in the NCI (1976b) and NTP (1982b) gavage studies. In the NTP study, B6C3F1 mice were gavaged with 0 or 1000 mg/kg/d on 5 days per week for 103 weeks. The incidence of hepatocellular carcinoma is used in the CAG dose-response assessment and is 8/48 and 30/50 in male mice, and 2/48 and 13/49 in female mice in control and dosed group respectively. The dose conversion uses the data of Prout et al. (1984) which shows that the metabolized dose is 78% of the administered dose, and the data of Buben and O'Flaherty (1985) which shows that the dose used in the NTP study is on the linear part of the dose-metabolism curve for mice. The CAG analysis estimates the metabolized dose by fitting an equation of the Michaelis Menton form to the data of Prout et al. (1984) to describe the relationship between administered dose and metabolized dose, and uses this curve to estimate the metabolized dose for the doses used in the NTP study. This approach yields results that are very similar to the values obtained directly from the high-dose groups in the Prout et al. study (80% vs. 78% metabolism of the administered dose), which is not surprising because the data of Prout et al, and of Buben and O'Flaherty show that the dose used in the NTP study is on the linear part of the dose-metabolism curve. These metabolized doses are used to calculate the lifetime average dose which is then adjusted by the surface area to get the human equivalent dose. The human equivalent dose was 47.4 and 45.6 mg/kg/d in the dosed male and female respectively.

In the NCI study male mice were administered 0, 1169 and 2339 mg.kg.d and female mice were administered 0, 869 and 1739 mg/kg/d. These time-weighted average doses were administered for 78 weeks starting at 5 weeks of age and animals were killed at 90 weeks of age. Incidences of hepatocellular carcinoma were 1/20, 26/50 and 31/48 for male mice and 0/20, 4/50 and 11/47 for female mice. The dose adjustments made for the study were done in a similar manner to the approach used for the NTP study. However, according to the data of Buben and O'Flaherty, the high doses used for the NCI study were above the linear part of the dose-metabolism curve and the CAG analysis states that at the

high dose levels used, the urinary metabolites are 68% and 96% higher than at the low dose in male and female mice respectively. The CAG assessment states that the Buben and O'Flaherty data are important because they used a chronic dosing schedule, but these data cannot be used to calculate total metabolized dose because only urinary metabolites were measured. However, the CAG analysis does not use these data in the calculation of dose. The CAG assessment uses the metabolized dose calculated using the equation from the Prout et al. (1984) study, which is then converted to lifetime average daily dose and converted to human equivalent dose by surface area adjustment. The human equivalent doses used are 0, 45.1 and 85.8 mg/kg/d for male mice and 0, 31.7 and 61.4 for female mice.

The carcinogenic potency for trichloroethylene recommended by the CAG is the geometric mean value from the NCI and NTP male and female mouse data sets. The carcinogenic potency for each data set is the 95% upper confidence limit on the linear term of the multistage model. For the NCI study the potency vale is adjusted by a factor of $(104/90)^3 = 1.54$ to account for less than lifetime exposure. The potency value calculated in this way and expressed as metabolized dose is 1.3×10^{-2} $(mg/kg/d)^{-1}$. The potency values for male and female mouse were 2.1×10^{-2} and 6.9×10^{-3} for the NCI study and 2.2×10^{-2} and 9.5×10^{-3} for the NTP study (expressed as metabolized dose $(mg/kg/d)^{-1}$.

In order to convert this potency to a human unit risk for inhalation exposure, the CAG uses the data of Monster et al. (1976) in which the total metabolism was measured in four subjects who inhaled 70 ppm of trichloroethylene for 4 hours. The median amount metabolized in these subjects was 439 mg, and assuming a linear relationship between the amount metabolized and the exposure time and concentration, the CAG calculates that a continuous exposure to 1 ug/m^3 would result in 6.9×10^{-3} mg metabolized per day, or 9.9×10^{-5} (mg/kg/d). Using the standard assumption that a 70 kg human inhales 20 m^3 of air, an exposure concentration of 1 ug/m^3 would result in a dose of 2.86×10^{-4} mg/kg/d and 9.9×10^{-5} mg/kg/d would be 35% of the inhaled dose. The CAG assessment therefore assumes that 35% of the inhaled dose is metabolized in humans at low concentrations. Based on this assumption the CAG unit risk is 1.3×10^{-6} $(ug/m^3)^{-1}$.

The CAG also calculates a unit risk based on the inhalation study of Bell et al. (1978). The value so derived is 2.6×10^{-6} $(ug/m^3)^{-1}$. The CAG recommends use of the value based on the gavage study because of deficiencies in the Bell et al. study.

DEP Calculation of Unit Risk Based on NCI Gavage Study

The NCI gavage study serves as the basis for the DEP dose-response assessment. The NTP gavage study is not used

because only one dosed group of mice was used and this study is not considered to be adequate for quantitative assessment dose-response assessment for this reason. The increase in renal tumors in male rats was also considered to be less than adequate to evaluate due to reduced survival in treated animals. The NTP study does serve to show that the administration of epoxide-free trichloroethylene is carcinogenic and that the presence of epoxide stabilizers in the trichloroethylene in the NCI study (1976b) does not account for the observed carcinogenicity. The administered dose is shown in Column 1 of Table 1 and is converted to metabolized dose as follows. The low doses are multiplied by 0.78 because the EPA discussion of the Prout et al. (1984) data show that 78% of the administered dose is metabolized. The high dose levels are obtained by multiplying the low dose by 1.68 and 1.96 for male and female mice respectively. This is based on the EPA analysis of the data of Buben and O'Flaherty, which show that the high doses used in the NCI study are above the point where the dose metabolism curve deviates from linearity and the metabolized doses at the low dose for male and female mice respectively. The metabolized doses are shown in Column 2. The use of the Buben and O'Flaherty data in this way assumes that the ratio of urinary to total metabolites is independent of dose, and that the Swiss-Cox mice used by Buben and O'Flaherty are representative of B6C3F1 mice used in the NCI study. The lifetime average daily dose (LAD) is calculated and shown in Column 3 and the surface area adjusted lifetime average doses are in Column 4. The values obtained in this way similar to the values obtained and used by CAG. The only value that deviates by more than three percent from the CAG value is the high-dose group for male mice (74.4 vs. 85.8 mg/kg/d). This difference results from the use of the Buben and O'Flaherty data to calculate the metabolized dose in the high-dose group by DEP. The use of the Buben and O'Flaherty data is preferred because a range of administered doses was used which included doses above those used in the NCI study, and because they used a subchronic dosing regime.

The multistage model was fit to the incidence of hepatocellular carcinoma in Column 5 and the doses in Column 4. The carcinogenic potency is taken as the upper 95% confidence limit on the linear term. This value is adjusted by a factor of $(104/90)^3 = 1.54$ to account for the fact that the 90 week age of the mice at termination of this experiment was less than the nominal 104 week lifespan. The final potency values were 2.77×10^{-2} $(mg/kg/d)^{-1}$ and 8.16×10^{-3} $(mg/kg/d)^{-1}$ for male and female mice respectively. These values are very similar to the values obtained by CAG for these sites (2.1×10^{-2} and 6.9×10^{-3} $(mg/kg/d)^{-1}$. The value for the female mouse is considered to be the most appropriate value and is used to calculate the unit risk for inhalation exposure. This value was chosen over the male mouse liver because the female mouse has a lower spontaneous

liver tumor incidence in B6C3F1 mice.

The DEP conversion to inhalation exposure assumes that the metabolized dose is equal to 70% of the inhaled dose. The basis for this assumption is discussed later. Based on this assumption, the metabolized dose during exposure to $1ug/m^3$ is $1ug/m^3 \times 10m^3 \times 1/70kg \times 1/1000 \times 0.70 = 2.0 \times 10^{-4}$ mg/kg/d. The unit risk for inhalation exposure to $1ug/m^3$ is then 8.16×10^3 $(mg/kg/d)^{-1} \times 2.00 \times 10^{-4}$ $(mg/kg/d)/(ug/m^3) = 1.63 \times 10^{-6}$ $(ug/m^3)^{-1}$.

The resulting unit risk is very similar to the final CAG value. The calculation of the unit risk differs fro the CAG calculation in two ways. A single site is used by DEP rather than the mean of four data sets, resulting in a larger potency value being used by the CAG (by a factor of 1.6). The second difference is that the metabolism in humans assumed by DEP is twice the level used by CAG at low exposure concentrations.

Unit Risk Calculation Bases on Fukuda et al. Inhalation Study

In this experiment, female ICR mice and female SD rats were exposed to 0, 50, 150, or 450 ppm of trichloroethylene for 7 hours/d, 5 days/week for 104 weeks. There was a significant elevation in lung tumors in female mice and the incidence of tumors was 1/49, 3/50, 8/50, and 7/46 in control, low, medium, and high dose groups. There were no liver tumors reported in this study.

In order to calculate the dose for use in dose-response assessment, the data of Stott et al. (1982) as reviewed by the EPA (1985j) is used. Stott et al. exposed mice to 10 or 600 ppm of trichloroethylene for 6 hours and then measured the metabolites. These data show that 78.5 and 3138 umol/kg is recovered in animals exposed to 10 and 600 ppm, respectively, and the 77.9 and 3062 umol/kg was metabolized. The metabolism dose for these exposures expressed as a ratio of metabolized dose to ppm of exposure is 78 and 5.8 (umol/kg)/ppm for the 10 and 600 ppm exposures. This estimation of the body burden and metabolized dose is likely to underestimate the actual values because a significant amount of metabolism could have occurred during the exposure due to the rapid metabolism of trichloroethylene. It is not possible to estimate the extent of this error from the data provided, but it is likely to be substantial. This effect would be less at the lower level of exposure and the value based on the group of mice exposed to 10 ppm is used for dose adjustment. The metabolized dose for a six hour exposure is then 7.8 x (exposure concentration) and is shown in Column 2 of Table 2. This use of the data assumes that the metabolized dose is linearly related to the exposure concentration throughout the range of concentrations used in the Fukuda et al. study and that the slope of this relationship is

equal to the slope defined by the data from the group exposed to 10 ppm in the Stott et al. study. The metabolized dose is converted to a dose in mg/kg/d by multiplying it by mw/1000 = 0.1314 and this value is multiplied by 7/6 to account for the difference in the time of exposure in the FUkuda study and is shown in Column 3 of Table 2. The lifetime average daily dose is calculated (Column 4) and the surface area adjusted lifetime average daily dose is calculated assuming a 30 g body weight for female mice (actual body weights were not reported in the study) and is shown in Column 5.

The dose-response curve was estimated by fitting the multistage model to the incidences listed in Column 6 and the doses in Column 5 of Table 2. The carcinogenic potency is the 95% upper confidence limit on the linear term and the carcinogenic potency for female mouse lung tumors in the Fukuda et al. study is 1.16×10^{-2} $(mg/kg/d)^{-1}$ expressed as metabolized dose. There is no adjustment necessary for less than lifetime exposure because the exposure time was 104 weeks. The conversion to a unit risk for inhalation exposure is done in the same way as for the NCI study. Based on the assumption that 70% of the inhaled dose is metabolized in humans at low doses, the unit risk value is 2.32×10^{-6} $(ug/m^3)^{-1}$.

Using a similar approach, the DEP calculated a unit risk based on the study of Bell et al. (1978) as reviewed by EPA. In this study, male mice were exposed to 0, 100, 300 or 600 ppm of trichloroethylene for 6 hrs/day, 5 days/wk for 24 months. The metabolized dose for the Bell et al. study are calculated based on the data from the Stott et al. study using the group exposed to 10 ppm and using the factor of 7.8 umole/kg metabolized per 6 hour exposure to 1 ppm as described for the Fukuda et al. study. The dose calculations are shown in Table 3. The surface area adjusted dose is calculated assuming a body weight of 35g. The dose-response curve was estimated by fitting the multistage model to the incidence of hepatocellular carcinoma listed in Column 6 of Table 3 and the doses in Column 5 of Table 3. The carcinogenic potency is taken as the 95% upper confidence limit on the linear term of the multistage model. The potency for the liver tumors in male mice from the Bell et al. study is 1.49×10^{-2} $(mg/kg/d)^{-1}$. The unit risk for inhalation exposure is calculated as described previously and is 2.98×10^{-6} $(ug/m^3)^{-1}$.

Discussion

The DEP unit risk calculation based on the NCI gavage study is considered to be the most appropriate unit risk value. The unit risk values calculated for the inhalation studies are not considered to be reasonable quantitative estimates because of uncertainty in the calculation of metabolized dose. The metabolized dose calculation used in both studies was based on

the data of Stott et al. (1982) in which groups of 4 mice were exposed to 10 or 600 ppm trichloroethylene for 6 hours and the metabolites were collected and measured for 50 hours after the exposure. These data are uncertain with regard to estimating total metabolized dose because it does not measure the metabolism that occurs during the exposure. This could result in significant underestimates of the total metabolized dose because of the rapid metabolism of trichloroethylene. This would result in an overestimate of the carcinogenic risk. It is noted that the potency estimates based on the inhalation study are 1.4 and 1.8 times higher than the potency based on the gavage study and these factors are larger when compared with the CAG unit risk value. However, if the male mouse liver were selected by DEP for calculation of unit risk, the unit risk values based on the inhalation study would be less than the values based on the NCI gavage study. The use of the Stott et al. (1982) data is also uncertain because it assumes that the metabolized dose is a linear function of exposure concentration over the rage of concentrations used in the Fukuda et al. study. This is unlikely to cause a large error because the study of Buben and O'Flaherty showed that for an equivalent dose given by gavage, only the highest dose level in the Fukuda et al. study is above the point where the dose-metabolism curve deviates form linearity. The EPA also discusses limitations in the technical adequacy of the Bell et al. study, which limit the usefulness of the study for quantitative dose-response assessment.

The use of the carcinogenic potency based on the NCI gavage study is preferred to the inhalation study for calculation of a unit risk for inhalation exposure. the DEP calculation differs from the CAG calculation in several respects. The CAG value is the geometric mean of values from four data sets (male and female mouse NTP study and male and female mouse for NCI study), while the DEP value is selected from the two data sets in the NCI study. The female mouse is selected by the DEP as the most appropriate site because the spontaneous incidence of liver tumors is lower in female mice compared with male mice (benign and malignant tumors). As a result, the potency value used by the DEP to calculate inhalation unit risk is less than the value used by CAG by about one half. There is also a slight difference in the dose adjustment used by DEP because the Buben and O'Flaherty data are used which show that the high doses in the NCI study are in the nonlinear part of the dose metabolism curve. The result is that the human equivalent dose calculated by the DEP is lower than the dose used by the CAG for the high-dose male mice. There is not a significant difference between the doses used by CAG and the DEP for female mice and low-dose male mice.

The other important difference between the CAG and the DEP calculations is the assumption made about the extent of absorption and metabolism of inhaled trichloroethylene in humans.

The CAG assessment uses the data of Monster et al. (1976), which show that 35% of the inhaled dose is metabolized. The DEP does not use these data because the relationship described is not likely to hold at ambient air levels. The DEP assessment considers it more likely that the portion of the inhaled dose that is metabolized varies with exposure concentration, and that at low enough doses all of the absorbed chemical will be metabolized. If all tissues are assumed to have some metabolizing capacity, then it is reasonable to assume that there is some air concentration below which none of the tissues are saturated. Under this condition, the metabolism in most tissues would be flow-limited and 100% of the absorbed dose would be metabolized. The blood concentration would then be zero in the pulmonary artery and the absorption would be a function of the blood:air partition coefficient. Anderson et al. (1981) have presented a theoretical curve showing that under these conditions the proportion of the inhaled dose that is metabolized approaches a maximum of 67% at blood:air partition coefficient to greater than 10. This is based on the use of alveolar ventilation of 67% of the total ventilation and the assumption that absorption of inhaled gases occurs at the alveolar level. The DEP assessment assumes that the levels of trichloroethylene that are of concern due to environmental exposure will be too low to cause metabolic saturation in any tissue and that the metabolized dose will be equal to 70% of the inhaled dose.

There are significant differences in the approaches used by the CAG and the DEP in the quantitative dose-response assessment of trichloroethylene. The effects of these differences on the final unit risk value vary in magnitude and direction, but the resulting unit risks for inhalation exposure calculated by the CAG (1.3×10^{-6} $(ug/m^3)^{-1}$) and by the DEP (1.63×10^{-6} $(ug/m^3)^{-1}$) are similar. The results of the DEP unit risk calculation based on the inhalation studies of Bell et al. (2.98×10^{-6} $(ug/m^3)^{-1}$) and of Fukuda et al. (2.32×10^{-6} $(ug/m^3)^{-1}$) also agree fairly well with the gavage study and lend confidence to the unit risk based on the gavage study.

The unit risk value calculated for trichloroethylene is based on a gavage study. The carcinogenic potency of 8.16×10^{-3} $(mg/kg/d)^{-1}$ can be used for oral exposure. The EPA addendum to the trichloroethylene health assessment document and the study by Maltoni will be reviewed when they are available to DEP.

TABLE 1. Tumor Incidences and Dose Calculation for Dose-Response Assessment of Trichloroethylene Using the NTP Gavage Study.

	(1) Administered dose mg/kg/d	(2) Metabolized dose mg/kg/d	(3) LAD mg/kg/d	(4) Surface area adjusted LAD mg/kg/d	(5) Incidence of Hepato-cellular carcinoma
Male					
control	0	0	0	0	1/20
low	1169	911	654	44.7	26/50
high	2339	1530	947	74.4	31/48
Female	0	0	0	0	0/20
low	869	678	420	30.9	4/50
high	1739	1329	823	60.6	11/47

TABLE 2. Tumor Incidences and Dose Calculations for Dose-Response Assessment of Trichloroethylene Using the Fukuda et al. (1983) Study.

(1) Exposure concentration ppm	(2) Metabol. dose in umol/kg	(3) Daily metabol. dose mg/kg/d	(4) LAD mg/kg/d	(5) Surface area adj. LAD mg/kg/d	(6) Incidence of lung adeno-carcinoma
0	0	0	0	0	1/49
50	390	59.8	42.7	3.22	3/50
150	1170	179.4	128	9.65	8/50
450	3510	538.1	384	29.0	7/46

TABLE 3. Tumor Incidences and dose Calculation for Dose-Response Assessment of Trichloroethylene Using the Bell et al. (1978) Study.

Exposure concentration	Metabol. dose	Metabol. dose	LAD	Surface area adj. LAD	Incidence of hepato-cellular carcinoma
ppm	umol/kg	mg/kg/d	mg/kg/d	mg/kg/d	
0	0	0	0	0	18/99
100	780	102.5	73.2	5.81	28/95
300	2340	307.5	219.6	17.4	31/100
600	4680	615.0	439.3	34.9	43/97

Carcinogenicity Dose-Response Assessment for
2,4,6-trichlorophenol

Summary

The weight-of-evidence classifications for 2,4,6-trichlorophenol are Group B2-Probable Human Carcinogen and Limited evidence for mutagenicity. The recommended CAG carcinogenic potency value for 2,4,6-trichlorophenol is 1.98 x 10^{-2} $(mg/kg/d)^{-1}$ (EPA, 1984c). The unit risk value for inhalation exposure is 5.66 x 10^{-6} $(ug/m^3)^{-1}$, assuming a 70kg person inhaling 20 m^3/d, and that the chemical is 100% absorbed. The DEP calculated a unit risk value for air based on the same study as used by the CAG. The DEP unit risk value for air exposure is 6.20 x 10^{-6} $(ug/m^3)^{-1}$. The unit risk value adopted by DEP for use in risk assessment of inhalation exposure is 6.20 x 10^{-6} $(ug/m^3)^{-1}$.

Background

The carcinogenicity weight-of-evidence classification for 2,4,6-trichlorophenol was determined by CAG and is based on the positive responses in rats and mice in the NCI feeding study (NCI, 1979b) as reviewed in IARC (IARC, 1979b, 1982c). There are no studies, other than the NCI study, which are adequate for dose-response assessment for carcinogenicity. The CAG dose-response assessment (EPA, 1984c) is based on male and female mouse liver tumors found in the NCI feeding study (NCI, 1979b). This assessment was published in the superfund health assessment document and was presented as a brief appendix to the document. The carcinogenic potency calculation is not presented in detail and it is not clear whether the assessment is consistent with current DEP procedures, so the DEP performed the following assessment.

Calculation of Unit Risk from NCI Feeding Study

In this study, male and female F344 rats and male B6C3F1 mice were fed diets containing 0, 5000 or 10,000 ppm of 2,4,6-trichlorophenol for 105 (mice) or 106 (rat) weeks starting at 6 weeks of age. Female mice were fed diets containing 0, 10,000 or 20,000 ppm from 6 to 44 weeks of age and 0, 2500 or 5000 ppm from 44 till 111 weeks of age. No significant effect on survival occurred in any of the treated groups, but there was a statistically significant treatment-related effect on body weight in males and females of both species.

Treatment-related increases in tumor incidence were observed in the male rat and in the male and female mouse. The tumor

incidences reported by the NCI are presented in Table 1. Several nonneoplastic lesions were reported by the NCI including peripheral blood leukocytosis and monocytosis, bone marrow hyperplasia, low incidences of mild liver lesions in the rat, and low incidences of liver hyperplasia in the mouse.

The dose of 2,4,6-trichlorophenol was administered by incorporation of the agent into the animal feed. No information is given in the NCI report on the measurement of food consumption or the estimate of actual doses used in this study. In the absence of estimates of dose, the DEP procedure is to use the equations developed by Crouch (1983) to estimate the lifetime average daily dose in a feeding study. The lifetime average daily doses (LAD) calculated in this way are shown in Table 2. The LAD for animals is scaled to an equivalent human LAD using surface area scaling as follows:

$$LAD \times (70/bw)^{-1/3} = \text{surface area adjusted LAD}$$

with b.w. equal to the mean terminal body weight of the group of animals. The resulting doses are shown in Table 2.

The dose-response curve is estimated by fitting the multistage model to the tumor incidences in Table 1 and the surface area adjusted LAD in Table 2. The 95% upper confidence limit on the linear term is taken as the estimate of carcinogenic potency and this value (q_1^*) is shown in Table 1.

The potency value from the male mouse liver tumor was selected as the most appropriate estimate of carcinogenic potency and this value is 2.17×10^{-2} $(mg/kg/d)^{-1}$. There is no adjustment necessary for less than a lifetime exposure since the exposure exceeded the nominal 104 week lifetime in both species. The potency value cited above is used to calculate a unit risk for inhalation exposure, assuming a 70kg person inhaling 20 m^3/d of air, as follows:

2.17×10^{-2} $(mg/kg/d)^{-1} \times 20$ $m^3/d \times 1/70kg \times 1mg/1000mg = 6.20 \times 10^{-6}$ $(ug/m^3)^{-1}$.

Discussion

The calculation of the unit risk value for 2,4,6-trichlorophenol was performed by DEP because the detailed documentation of the CAG assessment was not available. Therefore, it was not clear whether the CAG assessment was consistent with the current EPA guidelines (EPA, 1986b) or DEP procedures. The NCI feeding study is considered to be adequate for dose-response assessment and is used for both the CAG and DEP assessment. The male mouse liver was selected because it was the most sensitive site in this study. The unit risk values

calculated by CAG and DEP are very similar and are in fact identical if the CAG recommendation to consider only one significant figure is used. The DEP value is recommended in order to assure consistency with stated procedures.

The assessment uses no additional pharmacokinetic data to describe dose, route, or species specific effects on carcinogenic potency. As such, the assessment makes the following assumptions:

- direct high to low dose extrapolation is valid
- direct route extrapolation is valid (i.e., absorption and carcinogenic potency are identical for different routes of exposure)
- direct species-to-species extrapolation is valid

The basis for the use of these assumptions is described in detail in Appendix D. Because of the assumption of equivalence between routes of exposure, the potency value derived here can be used for oral or inhalation exposure.

Table 1. Tumor Incidences and Potency for Dose-Response Assessment of 2,4,6-trichlorophenol Using the NCI Feeding Study.

Site	Incidence control	low	high	Potency $(mg/kg/d)^{-1}$
Male Rat				
Lymphoma or leukemia	4/20	25/50	29/50	1.18×10^{-2}
Male mouse				
Liver hepatocellular carcinoma	1/20	10/49	7/49	3.04×10^{-3}
Liver hepatocellular adenoma or carcinoma	4/20	32/49	39/47	2.17×10^{-2}
Female mouse				
Liver hepatocellular carcinoma	1/20	12/50	24/48	6.87×10^{-3}
Liver hepatocellular adenoma or carcinoma	1/20	10/50	24/48	6.87×10^{-3}

Table 2. Dose Calculation for Dose-Response Assessment of 2,4,6-trichlorophenol Using the NCI Feeding Study.

		Administered Dose	LAD mg/kg/d	Surface Area Adjusted LAD (mg/kg/d)
Rat				
Male	low	5,000	248	44.0
	high	10,000	513	87.9
Female	low	5,000	332	52.1
	high	10,000	691	103
Mouse				
Male	low	5,000	567	48.6
	high	10,000	1182	96.4
Female	low	10,000/2,500	672	55.8
	high	20,000/5,000	1344	105.7

Carcinogenicity Dose-Response Assessment for Vinyl Chloride

Summary

The weight-of-evidence classifications for vinyl chloride are Group A-Human Carcinogen and Substantial evidence for mutagenicity. The designation for carcinogenicity is based on positive evidence in humans and in several species of animals as reviewed by IARC (1979a). The IARC concluded that there is sufficient human evidence of carcinogenicity. The recommended CAG unit risk value is 2.6×10^{-6} $(ug/m^3)^{-1}$. The documentation of this value has not yet been obtained by the DEP and the value was obtained in a phone conversation with Charles Ris of the CAG (7-24-86). This value also appears on a draft list of unit risk values dated 7-85. This value differs from the earlier published value of 7.15×10^{-6} $(ug/m^3)^{-1}$, which is documented in the superfund health assessment (EPA, 1984i). The recommended unit risk value adopted by DEP for risk assessment of inhalation exposure is the current CAG value of 2.6×10^{-6} $(ug/m^3)^{-1}$. A substantially different value has been derived using animal studies of orally administered vinyl chloride and the unit risk for inhalation exposure should not be used for other routes.

Carcinogenicity Dose-Response Assessment for Vinylidene Chloride

Summary

The weight-of-evidence classifications for vinylidene chloride are Group C-Possible Human Carcinogen and Suggestive evidence for mutagenicity. This weight-of-evidence designation was obtained by the EPA (EPA, 1985g). The recommended CAG unit risk value for inhalation exposure is 5.0×10^{-5} $(ug/m^3)^{-1}$. The toxicology and carcinogenicity data are reviewed in the EPA Health Assessment Document for Vinylidene Chloride (EPA, 1985g) and the calculation of the unit risk value is described in detail in that document. The unit risk value is based on an inhalation study using mice. The unit risk value adopted by DEP for use in risk assessment of inhalation exposure is the CAG value of 5.0×10^{-5} $(ug/m^3)^{-1}$.

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APPENDIX F

GUIDELINES FOR REPRODUCTIVE STUDIES FOR SAFETY EVALUATION OF DRUGS FOR HUMAN USE: U.S. FOOD AND DRUG ADMINISTRATION (1972)

APPENDIX F

GUIDELINES FOR REPRODUCTIVE STUDIES FOR SAFETY EVALUATION OF DRUGS FOR HUMAN USE

U.S. FOOD AND DRUG ADMINISTRATION

1972

1. Teratological Study Protocol

Treatment Period - cover period of organ formation

Untreated Males

Fetuses delivered by cesarean section 1-2d prior to parturition

Determine: Number fetuses

Placement in uterine horn

Correlation of fetuses with corpus

Number of live and dead fetuses

Number of early and late resorptions

Fetal weight

External anomalies

Internal anomalies:

- one-third for dissection or Wilson slicing method for visceral anomalies
- two-thirds for clearing and bone staining with alizarin

2. Fertility and Reproductive Performance

Study both males and females

Male Fertility

Rats - minimum age of 40 days before chemical exposure

Treatment 60-80 days before mating
Mated with treated females and/or untreated females

At least 10 males mated with 20 females

Female Fertility

Adult/sexually mature animals

Establish estrous cycles by daily vaginal smears

Drug administration 14 days before mating

Copulation established: vaginal inspection when evidence of copulatory plug consider this day zero of pregnancy

Daily dosing

Sacrifice one-half females on day 13 of pregnancy and examine dams for

a) Number and distribution of embryos
b) Presence of empty implantation sites
c) Embryos undergoing resorption
d) Abnormalities in uterus

Remaining dams continue on drug and allow

a) Examine duration of gestation
b) Examine litters - size, stillborn, live born, and gross anomalies, pup weight on days 1, 4, and 21
c) Examine skeletal anomalies on dead pups
d) Determine cause of adverse effects observed
e) Determine whether reproductive performance of offspring should be studied.

3. Perinatal and Postnatal Study

Drug Administration - (Dam) During final one-third of gestation and weaning

Observe labor and delivery
- Dystocia
- Prolonged Labor
- Delayed Labor

Calculate duration gestation

Observe litter size

- pup weight
- number of stillborn
- number of live born
- gross anomalies
- examine skeletal observation on dead pups
- pup weight on days 1, 4, and 21

Continued treatment through nursing period

- Observe effect on : lactation, nursing, instinct, toxic effects of newborn

- Examine litters between control + high dose dams to elucidate poor survival.

4. Specific Considerations

Drug Route

Several Routes May be Employed
Oral: stomach tube, capsule preferable to diet

Dose

At least two dosage levels

High and lower dose should be subtoxic (no anorexia, sedation or other exaggerated pharmacological effects)

Control essential

If dose is embryocidal, study lower dose since nonembryotoxic level may produce anomalies

Species

No specific recommendations

Chick embryo - ancillary data

Number Animals

At least 20 females (rodents)

At least 10 females (rabbits)

APPENDIX G

MUTAGENICITY GLOSSARY (from NRC, 1983)

APPENDIX G. Mutagenicity Glossary (Reproduced from NRC, 1983)

ANEUPLOID An organism or cell whose somatic nuclei do not contain an exact multiple of the haploid number of chromosomes, one or more chromosomes being represented more (or fewer) times than the rest.

BASE-PAIR SUBSTITUTION A point mutation in which one base pair in DNA is replaced by another, such as adenine:thymine guanine:cytosine or adenine:thymine thymine:adenine.

CHROMATID One of the identical longitudinal halves of a chromosome, sharing a common centromere with a sister chromatid; produced by the replication of a chromosome during interphase.

CHROMOSOME A nucleoprotein structure, generally more of less rodlike during nuclear division; a physical structure that bears genes; each species has a characteristic number of chromosomes.

CHROMOSOMAL MUTATION A mutational change that simultaneously affects many genes, in that it involves segments of chromosomes, rather than a single genetic locus. (See also GENE MUTATIONS, POINT MUTATION, and GENOMIC MUTATION).

CROSSING-OVER A process whereby genes are exchanged by breakage and rejoining of homologous chromatids; crossing-over typically is reciprocal and occurs as a regular part of meiosis; it also occurs, but at a lower frequency, in mitosis. (See also MITOTIC CROSSING-OVER).

DAMAGE In the context of this report, the amount of mutational change produced in germ cells. (See also IMPACT).

DELETION The loss of a part of a chromosome, often involving several genes, sometimes only a portion of one gene.

DIPLOID An organism or cell having two complete sets of chromosomes, with each set typically of a different parental origin; the chromosome number twice that typically present in gametes. (See also HAPLOID and POLYPLOID)

DNA CROSS-LINKS Chemical linkages between the two strands of DNA, for instance by bifunctional adducts.

DNA DAMAGE Any modification of DNA that alters its coding properties or its normal function in replication or transcription.

DOMINANT Pertaining to the member of a pair of alleles that expresses itself in heterozygotes to the exclusion of the other member of the pair; the trait produced by a dominant allele. (See also RECESSIVE)

DOSE Amount of material reaching the target, such as the number of adducts per nucleotide. Used loosely as equivalent to "exposure".

DUPLICATION A chromosomal aberration in which a segment of the chromosome is repeated.

EUKARYOTIC Pertaining to cells or organisms that have membrane-bound, structurally discrete cell nuclei and cell organelles; the cell type of animals, plants, and all other cellular organisms except bacteria and blue-green algae. (See also PROKARYOTIC)

EXCISION REPAIR The enzymatic removal from DNA of a polynucleotide segment that includes DNA damage (such as single-strand breaks and damaged bases) followed by resynthesis and rejoining of the DNA.

EXPOSURE Amount of material ingested, inhaled, or otherwise received by an organism. (See also DOSE)

FIDELITY The biochemical concept that describes the accuracy of the enzymatic copying of DNA or RNA.

FORWARD MUTATION Mutation at any site in a nonmutant gene giving rise to a mutant allele of that gene.

FRAMESHIFT MUTATION A gene mutation that occurs by the addition or deletion of one or a few base pairs and causes a shift in the reading frame of the genetic code, thereby altering the message encoded by all DNA base pairs that are read after the point of the mutation.

GAMETE A mature germ cell (i.e., a sperm or an egg) possessing a haploid chromosome set and capable of initiating formation of a new organism by fusion with another gamete.

GENE CONVERSION An unequal exchange of genetic markers during recombination that results in limited homozygosity in chromosomal regions that were previously heteroallelic. (See also MITOTIC GENE CONVERSION)

GENE MUTATION Mutation due to a molecular change in a gene, as opposed to a large chromosomal mutation; includes point mutations and intragenic deletions, (see also GENOMIC MUTATION)

GENOME A complete set of chromosomes or of chromosomal genes.

GENOMIC MUTATION A change in the number of chromosomes in the genome that does not alter the structure or arrangement of genes in the chromosomes. (See also ANEUPLOIDY, POLYPLOIDY, CHROMOSOMAL MUTATION, GENE MUTATION, and POINT MUTATION)

GENOTOXICITY The capacity to cause an adverse effect on a genetic system, including mutagenesis and other indicators of genetic damage.

GENOTYPE The genetic constitution of a organism; the specific genes possessed by an organism. (See also PHENOTYPE)

HAPLOID An organism or cell having a single complete set of chromosomes; the chromosome number of typical gametes; monoploid. (See also DIPLOID and POLYPLOID)

HERITABILITY A concept that quantifies the proportional contributions of genotype and environment to some trait; broadly, the proportion of the phenotypic variance in a population that is attributable to genetic differences among individuals in the population; narrowly, the proportion of the phenotypic variance proportion of phenotypic deviation from the population mean than is transmitted to the next generation).

HERITABLE TRANSLOCATION A stable rearrangement of the position of chromosomal segments that leads to successful chromosomal replication.

HETEROZYGOTE An organism whose chromosomes bear unlike alleles of a given gene; heterozygotes produce gametes of more than one kind with respect to a particular locus. (See also HOMOZYGOTE)

HGPRT Hypozanthine-guanine phosphoribosyl transferase (also called HGPRT); an enzyme involved in the utilization of the purine bases hypozanthine and guanine in mammalian cells (there are related enzymes in submammalian species); mutants that lack HGPRT resistent to the toxic effects of the guanine analogues 8-azaguanine and 6-thioguanine, which can therefore be used to select HGPRT mutants and form

the basis of several mutation-detection systems.

HOMOZYGOTE An organism whose chromosomes bear identical alleles of a given allelic pair or series; homozygotes produce gametes of only one kind with respect to the given locus. (See also HETEROZYGOTE)

IMPACT Medical and social effects on future generations of genetic damage in the current generation. (See also DAMAGE)

INSERTION SEQUENCE One of several short (e.g., IS1 in E. coli is about 800 base pairs long) segments of DNA that are able to insert into a variety of places in a chromosome; best characterized in bacteria, insertion sequences are involved in several types of genetic instability. (See also TRANSPOSON)

INVERSION Reversal of the order of a segment of DNA in a given chromosome.

LOCUS The position that a particular gene occupies in a chromosome.

MEIOSIS The process by which a eukaryotic cell nucleus (in which the DNA has been replicated only once) undergoes two coordinated divisions that yield four cells, each having ploidy half that of the original cell; in higher animals, meiosis provides for the production of haploid sperms or eggs from diploid spermatocytes or oocytes. (See also MITOSIS)

MENDELIAN Pertaining to the principles of dominance, segregation of alleles, and independent assortment of alleles, as initially discovered by Gregor Mendel.

METABOLIC ACTIVATION The metabolic conversion of a promutagen into a mutagen--an aspect of toxification, the possibility that a chemical may undergo toxification in vivo procides the rationale for using S-9 mixtures or other metabolic activation systems with many in vitro genetic-toxicity tests.

METAPHASE The stage of nuclear division in which the chromosomes are highly condensed and in the equatorial plane of the spindle before centromere separation; the stage of mitosis at which chromosomal morphology is optimal for cytogenetic analysis.

MICRONUCLEUS A nucleus, separate from and additional to the main nucleus of a cell, produced during telophase of mitosis or meiosis by lagging chromosomes or

chromosomal structural changes; the smaller of the two nuclei that occur in the cells of ciliate protozoans.

MITOSIS The process by which the nucleus of a eukaryotic cell (in which the DNA has been replicated) divides, providing for the exact division of the cell to produce two daughter cells of the same policy as the original cell. (See also MEIOSIS)

MITOTIC CROSSING-OVER Somatic crossing-over; crossing-over during mitosis of somatic cells or other cells (e.g., yeasts) with a ploidy higher than haploid, leading to the segregation of heterozygous alleles.

MITOTIC GENE CONVERSION Nonreciprocal recombination occurring in mitosis.

MITOTIC RECOMBINATION Mitotic crossing-over and mitotic gene conversion.

MUTAGEN An agent that causes mutation.

MUTANT An organism that possesses an alteration in its DNA that makes its genetic function or structure different from that of a corresponding wild-type organism.

MUTATION LOAD The decrease in fitness of the average genotype due to the accumulation of deleterious mutation.

NONDISJUNCTION The failure of homologous chromosomes to separate at anaphase I of meiosis; the failure of chromatids to separate at anaphase of mitosis or at anaphase II of meiosis.

NUCLEOTIDE The monomeric unit of polynucleotide polymers known as nucleic acids; consists of three components--a ribose or a 2-deoxyribose sugar, a pyrimidine or purine base, and a phosphate group--each of which exists as a phosphate ester of the N-glycoside of the nitrogenous base.

PENETRANCE The frequency with which a gene or gene combination manifests itself in the phenotype of the carriers; penetrance depends on genotype and environment.

PHENOCOPYA phenotypic variation due to environmental influences that mimics the expression of a genotype other than its own.

PHENOTYPE The detectable expression of the interaction of

genotype and environment; the characteristics of an organism. (See also GENOTYPE)

PHENOTYPIC EXPRESSION TIME The time required for the manifestation (expression) of a new mutation, presumably including the time required for the fixation of a premutational lesion in DNA as a mutation and for the dilution of the wild-type gene product in the cell.

PLOIDY Refers to the number os sets of chromosomes in a cell or organism--1 set in monoploids (haploids), 2 in diploids, 3 in triploids, 4 in tetraploids, etc.

POINT MUTATION A mutation affecting only one or a few DNA base pairs in a gene. See also CHROMOSOMAL MUTATION, GENE MUTATION, and GENOMIC MUTATION)

POLYPLOID An organism or cell having more than two complete sets of chromosomes, e.g., triploid, tetraploid. (See also DIPLOID and HAPLOID)

PROKARYOTIC Pertaining to cells or organisms (i.e., bacteria and blue-green algae) that do not have membrane-bound cell muclei and cell organelles. (See also EUKARYOTIC)

PROMOTER In carcinogenesis: A chemical that increases the carcinogenic activity of other agents that initiate carcinogenesis. In genetics: A region of DNA that is the initial binding site for the enzyme (RNA polymerase) that will transcribe a gene into RNA.

PROMUTAGEN A chemical that is not mutagenic itself, but can be metabolically converted into a mutagen.

RECESSIVE Pertaining to the member of a pair of genes that fails to express itself in heterozygotes in the presence of its dominant allele; pertaining to the trait produced by a recessive gene; recessive genes ordinarily express themselves only in the homozygous state. (See also DOMINANT)

RECIPROCAL TRANSLOCATION An exchange of segments between two non-homologous chromosomes.

RECOMBINATION Formation of a new association of genes (or DNA sequences) of different parental origins; recombination in eukaryotes typically occurs by the independent assortment of genes on different chromosomes in meiosis and by crossing-over or genes on different chromosomes in meiosis and by

crossing-over or gene conversion; in modern usage,"recombination" is sometimes restricted to situations in which new linkage relationships are established in chromosomes (i.e., to crossing-over and gene conversion), rather than including independent assortment; in recombinant-DNA technology, different isolated DNA sequences are joined in the laboratory under experimental conditions. (See also MITOTIC RECOMBINATION)

REPLICATION The formation of replicas from a model or template; applies to the synthesis of new DNA from preexisting DNA; the process by which genes (hereditary material; DNA) duplicate themselves.

REVERSE MUTATION Mutation that restores the wild-type phenotype or gene function in a mutant; may occur either by restoration of the original DNA sequence (back mutation) or by indirect compensation for the original mutation (suppression).

S-9 A metabolic activation mixture that is used with many vitro genetic-toxicity tests to provide for the conversion of promutagens into mutagens; the enzymatic activities of an S-9 mixture are those of a post-mitochondrial supernatant (i.e., microsomal and cytosolic enzymes) derived from a mammalian liver homogenate; the expression "S-9" originally referred to supernatant from centrifugation at 9,000 rpm.

SENSITIVITY The proportion of human mutagens that are positive in the system being evaluated. In this report, because there is no way to measure human mutagenesis, "sensitivity" means the capacity of the test to detect small increases in the mutation rate.

SEX CHROMOSOME One of a pair of chromosomes that are morphologically dissimilar in one of the two sexes and that are involved in the determination of sex; in mammals, the sex chromosomes are designated the X and Y chromosomes, and females have two X chromosomes and males have one X and one Y chromosome.

SEX-LINKED Pertaining to a genetic trait that exhibits a pattern of inheritance indicating that it is determined by a sex chromosome, particularly the X chromosome; pertaining to a gene that is on the X chromosome.

SISTER CHROMATID EXCHANGE The exchange of segments between the two chromatids of chromosome.

SOMATIC CELL One of the two cell types (the other being a germ

cell) of a multicellular diploid organism; it contains a diploid number of chromosomes and is involved in all functions of the organism except fertilization.

THYMIDINE KINASE (TK) An enzyme involved in the utilization of the mucleoside tymidine (which ultimately becomes part of the structure of DNA); catalyzes the phosphorylation of thymidine to thymidine monophosphate; mutants that lack TK are resistant to the toxic effects of several thymidine analogues, including bromodeoxyuridine and trifluorothymidine; selection of these drug-resistant mutants provides the basis of several mutation-detection systems, most notably in mammalian cells.

TOXICANT Any substance that, through its chemical action, causes adverse effects in living organisms.

TOXIFICATION The metabolic conversion of a substance into another substance that has greater toxicity; sometimes occurs as a consequence of processes that are usually associated with detoxification. (See also METABOLIC ACTIVATION)

TRANSITION MUTATION A base-pair substitution mutation in which the purine:pyrimidine base-pair orientation is preserved, as in adenin;thymine guanine:cytosine.

TRANSLOCATION The shift of a portion of a chromosome to another part of the same chromosome or to a different chromosome. (See also RECIPROCAL TRANSLOCATION)

UNSCHEDULED DNA SYNTHESIS (UDS) DNA synthesis that occurs at a stage in the cell cycle other than S; incorporation of precursors (e.g., tritiated thymidine into DNA in the absence of semiconservative replication; a manifestation of genetic repair, whose occurrence has been used as an indicator of induced DNA damage.

VALIDATION The process by which the consistency of a particular test is determined; the concordance of results of a test in question and previously established tests for a representative sample of chemicals is evaluated.

XENOBIOTIC Pertaining to a substance that is foreign to the normal constitution of an organism.

Source: National Research Council (NRC).1983. Identifying And Estimating the Genetic Impact of Chemical

Mutagens.Washington, D.C.National Academy ofScience Press. Selected entries from Glossary pp.237-251.

APPENDIX H

TOXICOLOGICAL PRINCIPLES FOR THE SAFETY ASSESSMENT OF DIRECT FOOD ADDITIVES AND COLOR ADDITIVES USED IN FOOD,

U.S. FOOD AND DRUG ADMINISTRATION (1982)

Chemical Structure Category System

Introduction:

The purpose of grouping food additives into chemical structure classes is to estimate the potential toxicity of the additives on the basis of their chemical structures. The structure classes will subsequently be used for assignment to Levels of Concern. Additives will be assigned to one of three structural classes (A, B, C) based on their structural similarities to known toxicants. This assignment initially involves determining the chemical structures of the additives' functional groups and comparing these structures with substances of known toxicity.

Determination of Additive Structures:

The determination of the chemical structures category of an additive should include, where possible, identification of the chemical structure of the additive and any information about known metabolites; predicted metabolites; components of mixtures, such as, fatty acid mixes, components of plant extracts, etc.; and contaminants. For contaminants or secondary components, the quantity in which they are present or predicted should be indicated. Summaries of this information should contain structures, literature references for known metabolites or contaminants, justifications for prediction of metabolism or contamination, and references for contaminant or secondary component content.

Structure Category Assignment Procedures

The structure category assignments are formulated using a qualitative decision tree. After the functional groups of the additive are identified, the decision tree outlined later in this appendix is used to assign the additive to a structure class. Additives with functional groups of high probable toxicity are assigned to category C. Additives of intermediate or unknown probable toxicity are assigned to category B. Additives of low probable toxicity are assigned to category A. With application of the decision tree below, category assignment will be arrived at in a uniform manner. For example, a simple saturated hydrocarbon alcohol like pentanol would be recorded as A, 2. The table and decision tree will enable most assignments to be made; however, there may be cases where the structure is so complex that the decision tree cannot be used. Under these circumstances, structure category assignment can better be made by a structure verification group which may draw upon the complementary expertise of several individuals. If it is known that the functional group of an additive is more or less toxic than the decision tree suggests, then the compound should be assigned to a different category. If a reassignment is made, the change must be justified with referenced literature support.

Structure Category Assignment Verification:

To insure consistency, all structure category assignments will be reviewed by an internal committee on structure-activity relationships. The committee will review only the Structure Category Summary Sheet; therefore, it is essential that all pertinent information and questions concerning the structure assignment of the additive be included on this sheet. Any alterations in category assignment recommended by the verification committee will be discussed with the toxicologist and CSO originally suggesting the structure category change.

Calculation of Adjusted Poundage:

For the purpose of priority ranking, the actual poundage disappearing into the food supply of a food additive may be normalized in order to make a direct comparison of structure type A, B and C materials. This is accomplished by increasing the poundage of a C class additive by a factor of 2 and decreasing the poundage of an A class additive by a factor of 0.5. For mixtures, the percentage of A, B or C components may be adjusted in a similar manner and then summed to give the total adjusted poundage. This adjusted poundage is only a relative figure and will be used only for priority ranking purposes.

Structure Category Assignment

Decision Tree for Food Additive Structure Category Assignment

Tables A, B, and C follow

1. Are 90% (by weight or volume) of the components identifiable for the additive substance(s)?

   If No, then assign additive to Structure Category C.

   If Yes, then continue.

2. If quantification of secondary components or contaminants for an additive is not available, are any of these functional groups contained in Table C?

   If Yes, then assign additive to Structure Group C and calculate the adjusted poundage on this basis.

3. Does 10% (by weight or volume) or more of the total additive mixture, components, and contaminants contain functional groups listed in Table C? For example, an additive is a mixture of 3 components x, y, & z; 90% is x and it is an A structure, component y is 3% of the total mix and it is a C structure, and z is a C structured contaminant accounting for 7% of the total mix. Therefore 10% of the total mix is C structures and thus the additive is given a C assignment; however, the adjusted poundage should be calculated on the basis of the percentages of C or A material present.

   If Yes, then assign additive to Structure Group C.

   If No, then continue.

4. Are any functional groups of known or predicted metabolites of the additive contained in Table C?

   If Yes, then assign additive to Structure Group C.

   If No, then continue.

5. Does 10% or more of the additive mixture (components or contaminants) contain functional groups not listed in Table A?

   If Yes, then assign additive to Structure Group B.

   If No, then continue.

6. Are any functional groups of known or predicted metabolites of the additive not contained in Table A?

   If Yes, then assign additive to Structure Group B.

   If No, then assign additive to Structure Group A.

7. Is there any evidence of bioaccumulation?

   If Yes, then please describe.

Structure Category Assignment

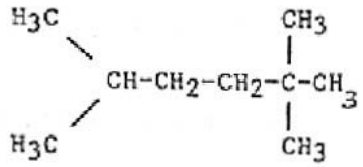
Sub-structure Tables

TABLE A

1. Simple aliphatic, non-cyclic hydrocarbons.

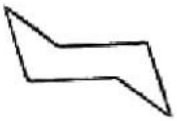
   These compounds should have NO unsaturation, i.e. no aromaticity, no double or triple bonds.

   Example:



2. Mono-cyclic hydrocarbons (alicyclic) up to a total carbon number of C_20. These compounds should have NO unsaturation.

   Example:



3. Fats, fatty acids or their inorganic salts of alkali metals (Na, K) and alkaline-earth metals (Ca, Mg). Both saturated and unsaturated, non-conjugated compounds.

   Carbon length of C_2 to C_30.

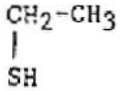
   Example: $CH_3\ (CH_2)_{10}COOH$

   $CH_3(CH_2)_{11}COOH$

4. Simple aliphatic, non-cyclic (saturated) mono-functional alcohols, ketones, aldehydes, acids, esters, ethers, mercaptans, and disulfides of carbon number greater than or equal to C_2 and less than C_30.

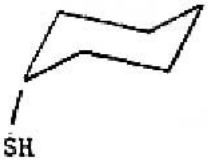
   These compounds should contain only one functional group and NO unsaturation of the carbon chain.

   Example:



5. Mono-cyclic hydrocarbons with mono-functional alcohol, ketone, aldehyde, acid, ester, mercaptan, or disulfide substitution or carbon number greater than 6 and less than 20.

Example:



6. Normal human biochemical constituents of carbohydrate and lipid metabolism excluding perhydrophenanthrenes, terpenes, and elecosadienoates (arachidonic acid percursors and metabolites).

7. Endogenous inorganic salts of alkali metals (Na, K) and earth alkaline-metals (Mg,Ca)

8. Conjugation reaction products of Table A substances.

9. Sugars, Polysaccharides, and their metabolites.

Compounds receiving Structure Category A assignments should be metabolized only to compounds also listed on Table A.

TABLE B

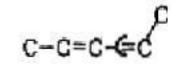
1. Compounds with functional groups not listed in Table A and Table C.

   Example: Methanol, Methylesters, Formates, quaternary amines.

2. Non-conjugated olefins, excluding unsaturated fatty acids and fats.

   Example:

   A.  =B

   B.  ≠B but = C

   C.  ≠B but = C

   D.  =B

3. Any multiple functional group containing structure without features listed in Table C.

4. Inorganic salts of Fe, Cu, Mn, Zn, and Sn.

5. Amino acids, unless containing other functional groups listed in Table C.

6. Benzoic Acid and esters, unless substituted with functional groups listed in Table C.

7. Polypeptides and Proteins.

8. Any compound or mixture of undetermined composition, so long as none of the identified portions contain a Table C entry. At least 90% of any mixture (by weight or volume) should be identified, or else a B is assigned.

TABLE C

R = C or H

1. Structure not covered by Table C but of high probable toxicity.

2. The structure contains: an organic halogen (C–X), not salts.

   X = F, Cl, Br, or I

   Example: CH_3I = C; CHI salts = C

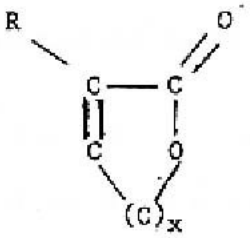
3. Three-membered heterocyclic ring system.

   Example:

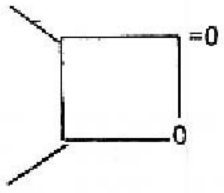
   Epoxides 

   aziridines 

4. α,β- unsturated lactones

   Example: 

5. 4-membered lactone



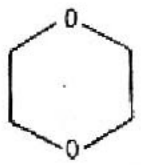
6. (α, β) unsaturated carbonyl function groups (aldehydes, ketones, carboxylic acids, esters), excluding benzoic acid or benzoic ester derivatives.

7. Conjugated alkenes/double bonds and aromatic groups, excluding benzoic acid or benzoic ester derivatives,

Example:

C-C=C-C=C

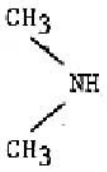
9. 1,4-Dioxane nucleus (six membered cyclic diether)

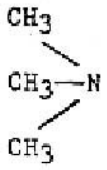


10. Amides and Imines

11. Amines: including primary, secondary and tertiary amines, aromatic amines and heteroaromatic amines, excluding amino acids.

Example: CH_3-NH_2





but not R_4N+ Quaternary amines

12. Nitro groups

$R—NO_2$

13. N-nitroso groups and C-nitroso groups

R-N-NO

14. Nitrilo groups

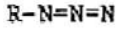
R-CN

15. Diazo-groups and azo-groups

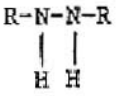
R-N=N R-N=N-R

16. Azoxy groups

17. Azide groups

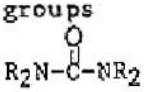


18. Hydrazine groups

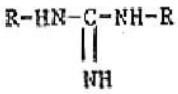


19. Carbamates, thiocarbamides or dithio derivatives

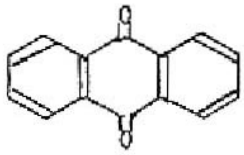
20. Urea groups



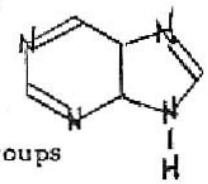
21. Guanidine groups



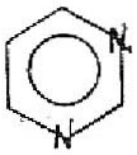
22. Anthraquinone groups



23. Purine groups



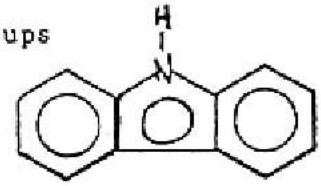
24. Pyrimidine groups



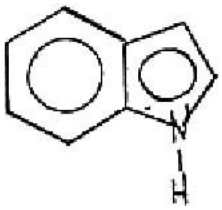
25. Pyrrole groups

26. Pyrazole groups

27. Carbazole groups



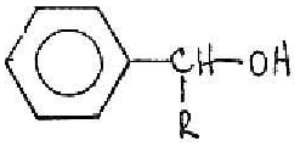
28. Indole groups



29. Imidazole groups

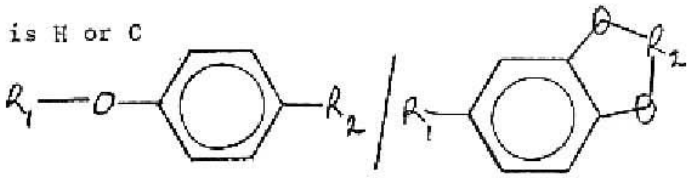
30. Pyrrolidine groups

32. Benzylic alcohols, acids, aldehydes and esters



33. "Salfrole-like" structures

R_1 is H or C

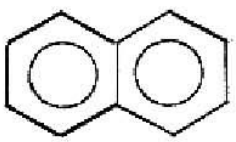


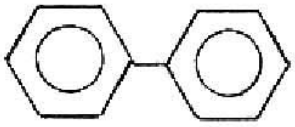
R_2 is C or C=C

34. Polynuclear aromatics (fused)

= Table C-34

≠ Table C-34, but = Table C-7





35. Furan groups

36. Thiazole groups

37. Oxazole groups 

38. Other heterocyclic functional groups.

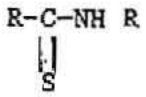
40. Isocyanate groups

R-N=C-O

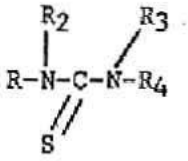
41. Isothiocyanate groups

R-N=C=S

42. Thioamide groups



44. Thiourea groups



45. Thioether groups

R-S-R

46. Sulfamate groups

$R-NH-SO_3$

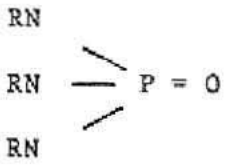
47. Organic Sulfate groups

$R-C-O-SO_2-O-R$

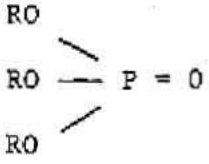
48. Organic sulfonates

$R-C-SO_2-O-R$

49. Phosphoramide groups



50. Phosphoric ester groups



51. Inorganic Salts not covered by Table A or B

52. Organo-metallics other than those mentioned in Table A or B

Structure Category Summary Sheet

Substance Name: _____
(Main Term)

Additive (or mixture components) Structure(s):

Metabolites:

References:

Contaminants:

References

Example Structure Category Summary Sheet
(page 2)

Substance Name: _____

Quantitative Estimates:

Additive = 100%

Parent Additive Substance

Components

Contaminants

References;

Structure Category Assignment:

Comments:

Primary Reviewer _____ date _____

Secondary Reviewer _____ date _____

Verification _____ date _____

APPENDIX I

DR. KENNY CRUMP, 1984: HOW TO UTILIZE INCIDENCE AND/OR SEVERITY-OF-EFFECT DATA IN SETTING ALLOWABLE EXPOSURES

APPENDIX I

PRESENTATION[1]

DR. KENNETH CRUMP: HOW TO UTILIZE INCIDENCE AND/OR SEVERITY-OF-EFFECT DATA IN SETTING ALLOWABLE EXPOSURES

Subissues

1. How to account for severity of effects (acute lethality, cancer, weight loss, changes in blood pressure or plasma enzyme levels, etc.).

2. How to utilize different types of data including: incidence data (number of animals dead or with tumors, etc.); "continuous" data (average levels with standard errors, etc.); limited or graded data (severe, moderate or no liver necrosis, etc.).

Possible Options

1. (Used previously to set water quality criteria.) If carcinogen, extrapolate using linearized multistage model. If not, use the safety factor approach (apply a safety factor to a NOEL, NOAEL OR LOAEL).

   Pro: Minimal data requirements.
   Has been tested and is familiar to most.
   Relatively simple to apply.

   Con: Safety factor approach doesn't fully utilize shape of dose-response curve.

   With safety factor approach, smaller studies tend to yield higher allowable exposures, which is illogical.
   Choice for safety factors is largely judgmental.

   Inconsistences may arise from applying different methods to cancer and non-cancer data.

2. Extrapolate both incidence and continuous data to low doses using mathematical models. Continuous data could be

extrapolated to a dose corresponding to a certain percent change in normal levels or a certain fraction of the standard deviation within a normal population. Extrapolation to different levels could account for differing severity of disease (e.g., extrapolate cancer data to 10^{-5} lifetime risk and weight loss data to 10^{-2}). The smallest allowable exposure obtained from any given health effect could be selected as the standard.

Pro: Accounts for shape of dose-response curve and utilizes all the experimental data.

"Rewards" larger experiments and those with better experimental designs (if confidence intervals are used).

More objective than safety factor approach.

Is not strongly dependent upon choice for mathematical model.

Con: Choice of extrapolation model is judgmental. Has greater data requirements than Option l.

Marginally more costly to implement than Option 1.

3. Use mathematical models to estimate dose corresponding to 10^{1} or some other level in the "observable range", and apply a safety factor reflecting the severity of the health impairment and possibly the nature and extent of the data.

Pro: Accounts for shape of dose-response curve and utilizes all the experimental data.

"Rewards" larger experiments and those with better experimental designs (if confidence intervals are used).

More objective than safety factor approach.

Is not strongly dependent upon choice for mathematical model.

Con: Choice for safety factor is large judgmental.

Has greater data requirements than Option 1.

Marginally more costly to implement than Option 1.

1. Reproduced from USEPA "Approaches to Risk Assessment for Multiple Chemical Exposures". March 1984. EPA-600/9-84-008, pages 76-77.