COMMONWEALTH OF MASSACHUSETTS
DEPARTMENT OF ENVIRONMENTAL PROTECTION

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

VOLUME I

1 Winter Street
Boston, Massachusetts 02108

February 1990

Abstract

The Chemical Health Effects Assessment Methodology (CHEM) and the Method to Derive Allowable Ambient Limits (AAL) represents a two step process, which composes the health basis of the Air Toxics Program, developed by the Massachusetts Department of Environmental Protection. Using valid epidemiological, clinical, and experimental data from primary sources and peer-reviewed secondary sources, CHEM systematically identifies and evaluates the following potential adverse health effects of chemical substances: acute/chronic toxicity, carcinogenicity, mutagenicity, and developmental/reproductive toxicity. The method to derive AALs establishes ambient air limits for specific chemical substances based on the health data provided by CHEM; the health data are incorporated in one of two ways: through a series of adjustment and uncertainty factors applied to selected occupational limits to provide protection to the general public against continuous exposure, and to account for gaps and inadequacies in the data; or, through the use of quantitative cancer risk assessment when there are adequate quantitative data on carcinogenicity. The selection of the AAL is based on the most sensitive effect. The Department believes that CHEM and AAL offers a viable tool for protecting public health and decreasing risk from effects of exposure to toxic air pollutants.

Acknowledgements

This document is a publication of the Massachusetts Department of Environmental Protection. Ken Hagg, Deputy Commissioner, Department of Environmental Protection, is acknowledged for his leadership in directing the Department to pursue the issue of health effects of toxic chemicals in ambient air. The CHEM and AAL methodologies were conceived by Carol Rowan West, Donna Bishop, Halina Brown, and Dan Guth of the Department's Office of Research and Standards. The principal author is Donna Bishop. Contributions from James Neely and Lori Bellew, Division of Air Quality Control, are gratefully acknowledged. Diane Manganaro, Office of Research and Standards, served as final editor and supervised final production of the report. Word processing was provided by Marina Andrade, Office of Research and Standards and Helena McLoughlin, Commissioners' Office. Recognition is given to other members of the Department, members of the Advisory Committee on Air Toxics, and members of the External Review Groups for their assistance in the overall development and implementation of the methodologies. In particular, the Department wishes to thank Dr. Edmund Crouch, Energy & Environmental Policy Center, Harvard University, and Dr. David Clayson, Toxicology Research Division, Health Protection Branch, Health and Welfare Canada, for their invaluable contributions to the development and refinement of the methodologies, and their patience in providing comments for numerous drafts over the past four years.

Preface

The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits has changed considerably since the draft version published in the Peer Review document of June, 1985. As described in Part I, the changes resulted from Department consideration of comments received on the draft, and an extensive in-house review of the proposed methodology. This effort involved updating the toxicological data on the 100 chemicals evaluated, assessing the protectiveness of the draft AALs using currently accepted methods of risk assessment, and reexamining the scientific concepts embodied in the draft methodology. As a result of this review, the Department determined that the previous proposal did not fully address the Department's goal of protecting public health. The changes incorporated in the present methodology provide for greater flexibility in selecting and using the best scientific data in deriving AALs, and more precisely addressing differing types of effects and differing types of data. Some of the changes and additions include assessment of available pharmacokinetic data, consideration of non-positive data, separate assessment of threshold and nonthreshold effects, and use of quantitative cancer risk assessment in the derivation of AALs for those chemicals having adequate quantitative cancer potency data (see Appendix D). These changes reflect the Department's commitment to utilizing the best available scientific approach in evaluating the health effects of chemicals and developing health-based ambient air limits.

In the past, the Department proposed to derive allowable ambient limits by applying a series of adjustment and uncertainty factors to selected occupational limits. Thus, while specific factors were applied on a case-by-case basis, the procedure itself was standardized and applied to all chemicals, including those associated with nonthreshold effects (i.e.,

carcinogenicity, mutagenicity). However, because of the variability in occupational limits, chemical potency values, and types of effects among chemicals, the approach relying on uniform uncertainty factors was found to be inadequate to compensate for that variability in the case of nonthreshold effects for some compounds. Based on EPA calculations of potency and unit risk, the proposed AALs for carcinogens were shown to be associated with variable levels of excess lifetime cancer risk, most of which were unacceptably high (defined as greater than 1×10^{-5}). Since the same uncertainty factors were used for both threshold and nonthreshold effects, and since carcinogenic potency was not directly factored into the AAL derivation procedure, AALs were not equally protective against threshold and nonthreshold effects, and were not always adequately or consistently protective for carcinogens. The methodology now proposed addresses those limitations by distinguishing threshold from nonthreshold effects, incorporating cancer potency data where available, and selecting the final AAL on the basis of the most sensitive effect.

Executive Summary

The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL) represents a two step process which makes up the health basis of the Massachusetts Air Toxics Program. The Massachusetts Department of Environmental Protection (DEP) is the state regulatory agency responsible for developing, administering, and enforcing programs which regulate air, surface water and groundwater, wetlands and waterways, and solid and hazardous waste. DEP is responsible for developing the air toxics program, the primary objective of which is to protect public health.

CHEM is designed to systematically identify and evaluate the potential adverse health effects of chemical substances. The method to derive AALs establishes chemical-specific ambient air limits based on the health data provided by CHEM; health-based limits are derived by applying a series of adjustment and uncertainty factors to selected occupational limits or by directly using carcinogenic potency. The rationale behind each component of the two methodologies is presented in this document.

In CHEM, chemicals are evaluated for acute/chronic toxicity, carcinogenicity, mutagenicity, and developmental/reproductive toxicity, using valid epidemiological, clinical and experimental data from primary literature and peer-reviewed secondary sources. A letter-code "score" is produced in each health effects category for each chemical. Over one hundred chemicals have been evaluated in order to develop and test CHEM. The respective health effects scores are provided in this document, as well as the AALs derived for each chemical.

The CHEM/AAL procedure begins with selection of the "most appropriate occupational limit" (MAOL), the occupational level which provides the best protection against the greatest number of

documented acute and chronic health effects. The MAOL is used in two ways: as a factor in scoring acute and chronic toxicity, and as a starting point in deriving AALs. In selecting the MAOL, an evaluation is made of the occupational limits and corresponding health data for specific chemicals as published by the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygenists, Inc. (ACGIH), and the Occupational Safety and Health Administration (OSHA), and the most health-oriented limit is chosen. In the future, the Department may use EPA or similarly derived inhalation Reference Dose values when these become available, rather than occupational limits.

In the acute and chronic toxicity category, all adverse health effects from short-term and long-term exposures to chemicals are considered, including neurotoxicity, allergenicity, immunosuppression, and all cellular, organic, systemic, glandular, behavioral, and other toxic effects or conditions. Carcinogenicity, mutagenicity, and developmental/reproductive toxicity are evaluated separately. Scoring is based on both the numerical value of the MAOL selected (high or low) and the severity of the effects documented. By using both components for scoring, the acute/chronic toxicity assessment is able to differentiate chemicals which have similar occupational limits but very different effects.

CHEM uses both quantitative and qualitative evidence to assess carcinogenicity. Data published by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and the Carcinogen Assessment Group (CAG) of EPA provide information on studies in humans and animals, as well as potency data. Thus, scoring is based on weight-of-evidence as well as unit risk estimation, when available. Weight-of-evidence categories have been adapted from the EPA classification scheme, and unit risk is calculated using NTP or CAG data. By combining

weight-of-evidence with relative potency values, the scoring procedure incorporates the full spectrum of information, and avoids discarding valuable data. This method distinguishes chemicals representing progressively greater hazard potential for humans, and thus also avoids underrating a potential carcinogen which has been less studied, or overrating an animal carcinogen which may be less significant to humans at typical environmental exposure levels.

The mutagenicity assessment in CHEM evaluates a range of genotoxic endpoints of potential significance to humans, such as point and gene mutations, structural or numerical chromosome aberrations, other genotoxic effects, cellular transformation, and abnormal sperm morphology. The assessment relies on results from a battery of long-term and short-term mutagenicity screening assays, each of which has been extensively reviewed by EPA's Gene-Tox and other groups. The tests are divided into three groups, reflecting overall relevance to assessing hazards to humans. A score for each chemical is derived by weighing a number of variables, including the number and type of endpoints measured, the number and type of species represented, the significance of positives and non-positives reported, the relevance of specific tests for predicting effects in humans, the classification of each test result, and overall pattern presented. The mutagenicity score is basically descriptive, representing a relative weight-of-evidence classification, since quantitative data are generally unavailable.

Developmental and reproductive toxicity covers all effects on male and female reproductive functions, as well as effects in the developing embryo or fetus, resulting from chemical exposure. It includes teratogenicity, embryo- and fetal toxicity, postnatal and perinatal developmental toxicity, and reproductive toxicity. Effects in this category are evaluated using the primary science literature. Each study is assessed for validity and reliability

on the basis of criteria developed by the U.S. Environmental Protection Agency (EPA), the U.S. Food and Drug Administration (FDA), and the Interagency Regulatory Liaison Group (IRLG), and classified by the Department as "adequate", "supportive", or "inadequate", for scoring. Three parameters are used for scoring of developmental and reproductive toxicity: weight-of-evidence, low-observed-effect-level (LOEL), and risk ratio. Scoring reflects a balance between the qualitative and quantitative evidence, such that weight-of-evidence, LOEL, and risk ratio are factored together and assessed on the basis of a scoring matrix. This system provides the flexibility of a case-by-case analysis and the consistency of a standardized approach.

The Method to Derive Allowable Ambient Limits (AAL) can be divided into three stages. The first stage is the threshold effects evaluation. The MAOL selected through CHEM is adjusted to provide protection for the general public (including children and high risk groups) against continuous exposure. Uncertainty factors are provided to account for gaps and inadequacies in the data with which the MAOL was set, as well as any threshold effects not accounted for in the MAOL (acute, chronic, developmental, and reproductive toxicity). A relative source contribution factor of 20% is also included to account for exposures to given contaminants from sources other than air. This results in a Threshold Effects Exposure Limit (TEL) which is a concentration which is protective of public health from threshold effects. In the second stage, the non-threshold effects are considered, including positive and non-positive evidence of carcinogenicity and mutagenicity. A Non-threshold Effects Exposure Limit (NTEL) is derived using either uncertainty factors or carcinogenic potency, depending on the availability of quantitative dose-response data. In the third and final stage, the lowest of the values derived (TEL or NTEL) is chosen as the Allowable Ambient Limit. This insures that the value selected for the AAL is protective against the most sensitive effect.

Where carcinogenicity is the most sensitive effect, and there are adequate quantitative data to derive a cancer unit risk, the AAL is set to correspond to an excess lifetime risk of developing cancer of one chance in 1,000,000 ($1x10^{-6}$). However, because it is the Department's policy to limit exposure to carcinogens to the extent feasible, the Department will strive to achieve exposures representing risks of less than one in a million wherever feasible.

The Department believes that, within a reasonable margin of error, CHEM and AAL offer a viable tool for protecting public health and decreasing risk from the effects of exposure to toxic air pollutants. Accordingly, the Division of Air Quality Control, which is responsible for implementing the Department's air programs, plans to employ the AALs in the permitting, compliance, and enforcement components of the Commonwealth's air program in general, and the air toxics program in particular.

Table of Contents

VOLUME I

LIST OF TABLES

List of Tables, continued

List of Tables, continued

VOLUME I (cont.)

VOLUME II

List of Figures

VOLUME II

LIST OF APPENDICES

VOLUME II

PART I. INTRODUCTION

A. Background

The Massachusetts Department of Environmental Protection (the Department) is the state regulatory agency responsible for developing, administering, and enforcing programs which regulate air, surface water and groundwater, wetlands and waterways, and solid and hazardous waste. Within DEP, the Office of Research and Standards has the responsibility to protect public health and environmental quality by defining acceptable human exposure levels to toxic substances and providing information and guidance to the Department on a broad range of environmental and public health issues. The primary objective of the Department in developing an Air Toxics Program is to protect public health.

In the past, the Department has addressed issues concerning air toxics on a case-by-case basis. However, because of an increasing number of such cases, and because the United States Environmental Protection Agency (EPA) has been slow to set emission standards under section 112 of the Clean Air Act, the Department felt it necessary to develop a comprehensive state program. Developing the health basis of the program involved designing a process to systematically evaluate the health effects of diverse chemical substances, and deriving allowable ambient air limits on the basis of the health data. This two-step process ensures a consistently applied health-based toxics policy statewide.

Many other states have recognized the need to develop programs as well, especially for air toxics problems which may be more local in scope. However, this situation places states in the position of having to develop the technical bases for their air toxics programs, where historically the EPA has provided this information. Accordingly, the Department's Division of Air

Quality Control and Office of Research and Standards worked together to develop the policies and scientific basis of the public health components of the program, in conjunction with a broadly constructed Advisory Committee on Air Toxics. Two products of this effort, the Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits (CHEM/AAL), are presented in this document.

Developing an air toxics program requires collaboration among specialists from many disciplines, including scientific, technical, planning, research, legal, administrative, and data management personnel. The needs and perspectives of regulatory, industrial, and public constituencies must be considered and integrated. Goals must be established, resources identified, and policies elucidated. Thus, it is a time-consuming process which demands the cooperation and investment of many people.

With the Office of Research and Standards, the Division of Air Quality Control initiated this collaborative process by establishing an Advisory Committee on Air Toxics (see Appendix A), composed of scientists, environmentalists, public health professionals, industry representatives, and academicians, in order to bring maximum expertise and diversity to the complex process of program development. Subcommittees were formed to provide guidance in specific areas, including definitions, methods of listing and evaluating chemical compounds, and development of allowable ambient limits. Open meetings were held regularly between December of 1982 and September of 1986, widely attended by Committee members and many others. In addition, proceedings of the meetings were mailed to over 200 interested individuals across the country.

Prior to development of the methodologies described in this document, health assessment and regulatory schemes used or proposed by other governmental or scientific groups were

carefully reviewed. Elements of many of these schemes have been incorporated into CHEM and AAL. The methodologies described in Parts II and III of this document seek to combine the best components of existing systems with an innovative and scientifically credible approach to air toxics. Thus, CHEM/AAL is designed to fit the unique needs and policies of the Department.

With respect to legal authority, the Department is empowered to "prevent the occurrence of conditions of air pollution where such do not exist and to facilitate the abatement of conditions of air pollution, where and when such occur. They [the regulations] are designed to attain, preserve, and conserve the highest possible quality of the ambient air compatible with needs of society." (M.G.L. c.111 142B and 142J, and in 310 CMR 6.00, 7.00, and 8.00). In this context the Department's primary air quality goal is to "protect the public health and welfare from any air contaminant causing known or potentially injurious effects." The Department believes that the system outlined in this document (referred to as "the Massachusetts system") represents an important step toward accomplishing that goal.

As indicated, the Department began working on the methodologies in 1982. Since that time, various approaches to evaluating health effects and setting ambient exposure limits have been proposed and discussed. In May of 1984 a preliminary document briefly describing CHEM was sent out for national peer review. In response to comments and questions generated by the review a number of changes were introduced into the system, and a second, comprehensive document describing both CHEM and AAL was published for peer review in June, 1985. The second national peer review group included all reviewers submitting comments on the 1984 draft as well as members of the Advisory Committee on Air Toxics and experts recommended by Committee members to serve on the second peer review panel. The names of all those who

responded to the request for comments on both the 1984 and 1985 peer review documents are listed in Appendix B of this document.

On the basis of comments received and an extensive in-house review of the proposed methodologies, the Department has worked since 1985 to modify and refine the system. The current document has evolved from that process and represents substantial progress toward establishing a consistent scientific methodology for evaluating the health effects of airborne contaminants and developing ambient exposure limits protective of the public health. Past reviewers will recognize the addition of several important components and significant changes to the system since the 1985 Peer Review Draft. The Department believes that the changes and refinements represent the best possible blend of current scientific knowledge and sound regulatory policy toward the management of risk in a complex environment.

B. Scope and Contents

In designing an air toxics program, two major components can be identified: program development and program implementation. The purpose of this document is to describe the health basis of the program, its goals, scope, and assumptions, and the method to derive Allowable Ambient Limits (AALs). Because the Department felt strongly that development of the program's health basis should not be influenced by technological, economic, and enforcement concerns, the ambient numbers generated are health-based only, and were developed without regard to production volume, exposure level, or regulatory implication. Similarly, economic and control technology issues are neither discussed nor considered here. An active, in-house effort is underway to identify and resolve the many implementation and enforcement issues. Thus, while the Department acknowledges the importance of implementation considerations, these factors have not influenced the health-based aspects of the program. The

scope of the present work is therefore limited to a discussion of CHEM and the Methodology to Derive AALs.

The Chemical Health Effects Assessment Methodology (CHEM) represents a set of procedures for identifying and evaluating the potential adverse health effects of chemical contaminants. In CHEM, chemicals are evaluated for acute/chronic toxicity, carcinogenicity, mutagenicity, and developmental/reproductive toxicity. Within each of these four health effects categories, chemicals are "scored" using letter codes to reflect degree of hazard. Thus, CHEM is designed to produce a letter score (A-E or F) in each health effects category for each chemical, and a comprehensive health effects database which will be used to determine AALs. Over one hundred chemicals have been evaluated in order to develop and test CHEM, and their respective scores are provided in Table II-35. Specific health effects categories are fully described in Part II.

The second part of the Massachusetts system is the Method to Derive Allowable Ambient Limits (AALs). For the majority of chemicals, the health data gathered in CHEM are incorporated in the AAL derivation method through a series of adjustment and uncertainty factors applied to selected occupational limits. When adequate quantitative data on carcinogenicity exist, and the comprehensive health effects evaluation shows carcinogenicity to be the most sensitive effect, quantitative risk assessment procedures are used to generate AALs. A detailed explanation of these methods appears in Part III of this document, including the types and uses of uncertainty factors. Table III-6 shows the AALs derived for the 105 chemicals evaluated to date.

A glossary of acronyms used throughout the text is included in Appendix C. Appendix D contains a detailed description of the procedures used to quantify cancer risks, and chemical-specific cancer risk assessments are provided in Appendix E. Appendix F

contains a mutagenicity glossary; Appendix G contains the U.S. Food and Drug Administration (FDA) Guidelines for evaluating reproductive studies; Appendix H provides the U.S. FDA guidelines for conducting Structure-Activity Relationship analysis; and Appendix I contains a discussion of uncertainty factors for use in setting allowable exposure limits.

C. Policy Decisions

The potential adverse health effects related to the discharge of toxic air pollutants have been of long-time concern to the Department. Moreover, the public has become increasingly aware and concerned about exposure to chemical emissions. In a society which attempts to recognize and balance the hazard of a particular activity with the benefit derived from that activity, regulatory agencies are placed in the position of identifying the point at which that balance is achieved. Such a position theoretically allows the regulator to evaluate all the issues and, accordingly, to determine what poses an unreasonable risk and what does not. Unfortunately, reality affords no such clear-cut decision points.

The issues involved in developing an air toxics program are complicated, in part, by the sheer number of chemicals in commercial use and the wide range of toxic properties they exhibit. In addition, mixed exposures, cumulative exposures, latency periods, medical uncertainties, and insufficient databases further complicate decision-making, particularly in establishing a cause and effect relationship between exposure and illness. Nevertheless, the inevitable uncertainties do not relieve the regulator of the responsibility to protect public health. As Supreme Court Justice Thurgood Marshall wrote in the 1980 benzene case, "Frequently no clear causal link can be established between the regulated substance and the harm to be averted. Risks of harm are often uncertain, but inaction has

considerable costs of its own." (448 U.S. 607, L.Ed. 2d 1010, p. 2904.)

Given the need to act on air toxics problems in spite of the uncertainties involved, the Department has encouraged public involvement throughout the process of program development, in order to gather as much information and varying opinion as possible. If new information emerges to suggest the need for changes, particular decisions can be reviewed and revised accordingly. The Department's objective in designing the CHEM and AAL procedures is to be consistent and scientifically valid yet feasible with respect to available staff resources for conducting health evaluations of chemicals and responding to regulatory mandates.

The system presented in this document represents more than five years of effort. As indicated, many issues are not purely scientific, and cannot be resolved on a purely scientific basis. Instead, in utilizing available data or setting regulatory priorities, it is science policy, and risk management, which guide final decision-making. For example, there is no one "right" way to assess carcinogenicity, or to develop ambient exposure limits, yet public health protection requires that both be accomplished despite the uncertainties and ambiguities involved. Thus, the necessary decisions can rarely be based solely on fact, but reflect a combination of scientific information, professional judgement, and risk management, based on the goals and objectives of the agency. The term "risk management", as used here, refers to the process of balancing scientific and other data to establish public policy and set regulatory goals.

In the course of developing and using the methodologies described in Parts II and III of this document it was necessary to make decisions on a number of issues. Some of these policy

decisions are described below.

1. Choice of Chemicals to Evaluate

As indicated, the Department has evaluated over 100 chemicals to date, and has developed a corresponding AAL for each. The chemicals were not chosen on the basis of hazard, but rather as a representative sample, in order to develop and test the proposed Massachusetts system. Selection of chemicals was based upon the following criteria:

- o A wide range of chemical and physical properties.
- o Diversity of health effects.
- o Known and suspect carcinogens, as well as chemicals not known to have carcinogenic properties.
- o Chemicals with and without occupational limits.

Once the various program components have been reviewed and completed, and the regulatory program is underway, work will begin in the assessment of the next group of chemicals. The criteria for selecting these chemicals have not been determined as yet, but could be influenced by factors such as toxicity, production volume, and/or public requests.

2. A Standardized Approach

Available monitoring data for several United States cities indicate that urban air typically contains a wide variety of organic and inorganic compounds, many of them having evidence of carcinogenicity, teratogenicity, or other types of toxicity (Singh et al., 1982; Lioy and Daisey, 1983; USEPA, 1984; Lioy and Daisey, 1986). Information about the potentially harmful effects of these substances varies from scarce to extensive; moreover, little is known about the health impacts resulting from long-term exposure

to mixtures of chemicals. Any program aimed at preventing adverse health effects due to exposure to toxic air contaminants must therefore be designed to address a large number of substances, and to account for uncertainties in the data.

Many states have responded to the need for such a program by establishing allowable ambient limits for chemicals of concern to those states. Due to constraints both of resources and of available scientific data, several states have chosen to adopt a generic method for deriving acceptable ambient concentrations, usually produced by dividing an occupational exposure limit by a safety factor (e.g., Texas Air Control Board, New York Department of Environmental Conservation, Michigan Department of Natural Resources, Vermont Agency for Environmental Conservation).

In contrast, EPA has approached the regulation of hazardous air pollutants on a chemical-by-chemical basis, conducting exhaustive reviews of all known toxicological and exposure data, and resulting in some cases, in the establishment of a National Emission Standard for Hazardous Air Pollutants (NESHAP) which corresponds to a level at which no "unreasonable" health risks to the public are expected. However, EPA activities in this area have produced only six emission standards for hazardous air pollutants (beryllium, vinyl chloride, mercury, asbestos, benzene, and radionuclides) in the 18 years since passage of the Clean Air Act (section 112).

Because the Department is concerned about the immediacy and seriousness of the air pollution problem, as well as the need to allocate Departmental resources judiciously, it has chosen an intermediate approach, one which effectively incorporates both credible science policy and efficient

regulatory action. The Massachusetts system involves a case-by-case health assessment of each chemical, and a standardized approach to the derivation of AALs, including a maximum allowable excess lifetime cancer risk of one chance in one million or less. It is intended that implementation of the air toxics program will result in protection to the public, consistency in decision-making, and clarification to industry of future regulatory requirements.

3. Assessment of Risks

Risk assessment is defined and used in different ways by different groups, but the term "risk assessment" generally refers to a collection of procedures designed to evaluate and quantify the risks associated with exposure to a given hazard. These procedures are used by regulatory agencies and others to define risks to individuals and/or populations, and to generate the data which can be used to make regulatory decisions. For example, this information can be used to set regulatory priorities, or to set standards for ambient exposures.

Risk assessment can involve any or all of a number of steps, depending on the needs and objectives of the user. As employed by the EPA, risk assessment incorporates evaluation of chemical hazard and of population exposure. In this context, hazard is defined as "the inherent toxicity of a substance for some toxic endpoint," and exposure refers to "the amount of the substance that people come in contact with." (OSTP, 1984). Exposure assessment also involves identifying populations at risk and numbers of people affected. Risk is then characterized by coupling the results of the exposure and hazard assessments, using the following steps:

- Evaluate qualitative evidence - identify the adverse effects that a given substance is capable of causing in animals or humans.

- Estimate dose-response relationship at low doses.

- Estimate human exposure to the chemicals, and the distribution of exposures likely to be encountered in the population.

- Combine exposure assessment with dose-response relationship assessment in order to generate an estimate of risk.

Thus, risk assessment is the process of estimating the incidence of an adverse health effect in a given population under certain exposure conditions. In the case of cancer, it provides an estimate of the risk of excess cancer incidence in exposed individuals or populations.

As indicated, risk assessment can involve various steps, and can be used in a number of ways. In determining which steps to use and how to conduct the assessment, it is important to identify how the results will be utilized and what the goals of the agency or group are. In this context, the question arises as to whether allowable levels of human exposure to toxic substances should be determined by the dose-response and toxicity data alone, or whether an evaluation of the number of people exposed should also be included. In other words, should decisions about whether and how much to regulate a substance be based on its inherent hazard, or on the number of people exposed to it (population risk), or on a combination of both?

These are policy issues, subject to the risk management

objectives of the particular agency. In decisions of this sort agency needs and mandates are likely to differ from state to state and at varying levels of government. Specific issues are often localized, and a serious concern in one geographical area may not represent a significant threat on a national scale, or in another region. In prioritizing regulatory activities and working to manage environmental risks at the federal level, exposure assessment is often emphasized as a means to evaluate the scope of any given problem. For example, the Food and Drug Administration (FDA) relies on exposure assessment in setting priorities for regulating direct food and color additives (USFDA, 1982). Each chemical is assigned to one of three Minimum Testing Levels depending on the number of people exposed as well as perceived toxicity, based on chemical structure analysis. The minimum amount of toxicity testing required by the agency is directly related to the size of the population exposed.

EPA uses a similar approach in setting regulatory priorities under section 112 of the Clean Air Act (NESHAP), relying on assessments of individual and population risk to determine whether risks from exposure to a chemical are sufficiently significant on a national level to warrant federal action. In these cases, chemicals are ranked according to their toxicological properties as well as levels of human exposure. Decisions may be based on individual risks, total population risks, or both. Acrylonitrile provides a recent example. EPA has determined that it may pose a threat to public health, but because overall exposures on a national scale appear to be low, it fails to meet the "significance" test for federal action under section 112.

The Department has chosen a different procedure, and

does not use population exposure assessment as a "trigger" or significance test for action. If a chemical of concern in Massachusetts were not regulated on the federal level, and the Department relied on population exposure assessments to identify and define significant health concerns, no safety net would exist to protect populations which did not meet an arbitrarily defined size. Individuals belonging to a large exposed group would then receive greater individual protection than those belonging to a small exposed group. Establishment of a more stringent approach when larger numbers of people are exposed than when the exposed group is small is unacceptable to the Department. Therefore, the Massachusetts system uses hazard assessment only, and does not use the number of exposed individuals as a criterion for regulatory action on toxic air contaminants. However, the Department may include exposure indices such as production volume, or numbers of persons exposed when selecting chemicals for AAL development or in the process of prioritizing regulatory activities.

4. Policy on Carcinogens in CHEM

In the past, the Department chose not to use quantitative cancer risk assessment in deriving exposure limits for identified carcinogens, due mainly to the uncertainties involved in defining carcinogens for regulatory purposes, and estimating low-level human exposure risks from high-dose animal studies. Previous drafts of this document outlined the Department's rationale for this position, and described a proposed procedure for deriving allowable ambient limits for all chemicals (threshold and non-threshold) by applying a series of adjustment and uncertainty factors to a selected occupational limit for each chemical. However, as a result of comments received during the peer review process, and an extensive in-house

review of the proposed methodologies, the Department concluded that the approach described was neither feasible for all chemicals, nor sufficiently protective of public health. Specifically, in re-calculating the unit risks for carcinogens on the basis of the more complete and up-to-date bioassay data now available, and using this information to evaluate the excess lifetime cancer risks associated with the previously proposed AALs, the Department found the associated cancer risks for a number of chemicals to be unacceptably high. In the course of investigating the underlying reasons for the inconsistent or variable risk levels provided by the previous system, the Department concluded that a single safety factor approach for threshold and non-threshold effects was inadequate for some chemicals, and explored ways to overcome the limitations described.

On the basis of this effort, and after careful consideration of all the strengths and limitations of various options, the Department decided to use quantitative risk assessment in the derivation of AALs where there is adequate evidence of carcinogenicity. In this context, the Department has worked closely with the Massachusetts Department of Public Health to develop consistent policies and procedures for identifying and evaluating carcinogens in the Commonwealth. The methods and criteria employed are detailed in Appendix D. An uncertainty factor approach similar to that described in the 1985 Draft document has been developed for chemicals lacking adequate quantitative data on carcinogenicity. This methodology is described in detail in Part III, Section D of this document.

The approach to carcinogens adopted incorporates the following points:

a. Chemicals are not classified simply as carcinogens or

non-carcinogens and regulated as such. Rather, evidence for both threshold and nonthreshold effects are evaluated, and the AAL is derived on the basis of all known or potential adverse effects. Chemicals lacking adequate quantitative data on carcinogenicity are not automatically relegated to a "non-carcinogenic" category. Each chemical is evaluated for potential nonthreshold effects on the basis of the weight-of-evidence for carcinogenicity and mutagenicity, including positive and non-positive evidence, as well as structure-activity relationship analysis. In this way, a chemical which has not been tested for carcinogenicity is not assumed to have zero cancer risk, and all chemicals are provided the same level of review. Most importantly, by developing an alternative methodology for assessing nonthreshold effects for chemicals having only qualitative evidence of carcinogenicity and/or mutagenicity, the Department can provide a more complete analysis of risks which are not otherwise quantifiable.

b. While all positive evidence of carcinogenicity may be used to define and/or classify carcinogens, not all bioassays producing positive results are biologically or methodologically appropriate for use in estimating quantitative cancer risks for humans. Because some tumor types or sites, routes of exposure, species, or test methods may be of questionable value in predicting human risk, the Department reviews bioassays on a case-by-case basis to determine eligibility for cancer risk assessment (see Appendix D). Any relevant information may be used in the evaluation, including pharmacokinetic data and non-positive assay results. Tumor types/sites and species to be used are always decided on a case-by-case basis, and the Department

does not use unit risks calculated by EPA or other agencies without first assessing the adequacy and relevance of the data. The specific criteria for selecting appropriate data are provided in Appendix D.

c. Selection of the final AAL is based on the most sensitive effect, whether threshold or non-threshold, and not necessarily carcinogenicity in every case. Thus the AAL is designed to provide protection against a wide range of adverse health effects, rather than assuming that carcinogenicity will always be the effect of greatest significance or that weak carcinogens (or non-carcinogens) are also non-toxic on other counts.

The Department acknowledges the uncertainties inherent in the risk assessment process, and the difficulties involved in defining "reasonable", "acceptable", or "negligible" risk. In the absence of low-dose human data, reliable estimates of risks to humans depend upon accurate estimations of potency from the raw dose-response data, reliable procedures for extrapolating from high-dose to low-dose and from animals to humans, valid study protocols, and accurate experimental exposure analyses. Despite the uncertainties involved in each step of the risk assessment process however, low-dose risks for non-threshold effects must be estimated as scientifically as possible, and the Department's decision is to use quantitative cancer risk data in deriving allowable ambient exposure limits for humans. In this context the Department has developed a methodology for estimating cancer risk using the most complete, up-to-date information and scientifically acceptable procedures currently available. The methodology presented in Appendix D describes an approach to evaluating risk which can be used to generate AALs in a scientifically credible and consistent way. The approach described is

consistent with the approach adopted by the Massachusetts Department of Public Health (Mass. DPH, 1988, Draft Carcinogen Policy).

The Department believes that the best way to adequately address concerns about non-threshold effects and cancer risk, and to make uniform the degree of protection afforded by individual AALs, is to define a maximum allowable risk level and to utilize accepted methods for calculating exposure limits based on estimated risk. While this reflects a change in Department policy from previous drafts, the Department believes that the approach described here represents the most responsible and technically valid public policy currently available to the regulatory community.

The maximum allowable risk identified for this purpose corresponds to an excess lifetime risk of developing cancer as a result of lifetime (70-year) exposure to specific contaminants of not more than one chance in a million (10^{-6}). This means that an individual exposed to a chemical at a specified level for a 70-year lifetime would have at most, one chance in a million of contracting cancer as a result of that exposure. The risk level is used as follows: where adequate quantitative data to calculate potency are available, and carcinogenicity is identified as the most sensitive effect, AALs are set to correspond to a maximum allowable risk of one in 1,000,000 ($1x10^{-6}$). However, while human risks are estimated conservatively, the Department believes that risks to the public should be minimized as much as possible. Therefore, the Department will work with the regulated community to reduce emissions and corresponding risks below $1x10^{-6}$ to the extent feasible. The AALs for identified carcinogens are provided in Table III - 6. It should be noted that where carcinogenicity is <u>not</u> the most sensitive effect, and the TEL is lower than the

NTEL, the AAL will naturally correspond to a risk of less than $1x10^{-6}$ (i.e., epichlorohydrin, toluene diisocyanate). Implementation issues and methods will be discussed at length in future implementation documents.

5. Consideration of Risk

The Department recognizes that any risks associated with chemical exposure are of concern to the public, and must be addressed. Unfortunately, individual risks can rarely be quantified with precision, even for exposures to single chemicals. Nevertheless, the Department acknowledges the importance of such issues. The Department further recognizes, however, that any regulatory approach is likely to involve at least some degree of risk to at least some members of the population. Even a total ban on all commercially produced toxic compounds would not eliminate risk, since many potentially hazardous substances are ubiquitous, naturally occurring, or produced as a result of various common activities.

It is clear that no regulatory program can provide zero risk. It is also clear that the Massachusetts system does not attempt zero risk. As described earlier, risk assessment can provide only imprecise estimates of hazard potential, and the present state of knowledge cannot provide for determination of specific no-adverse-effect levels for humans in most cases. Nevertheless, the Department recognizes its responsibility to protect public health, despite scientific uncertainty. The system outlined in Parts II and III of this document is designed to produce ambient air limits which the Department considers protective. The extent to which that goal is achieved depends a great deal on the amount of information available for a given chemical, and the types of effects associated

with that chemical. The system addresses data gaps through the use of safety or uncertainty factors, in order to protect against the potential effects of chemicals which have not been adequately tested as yet. The assumption is that the margin of error or uncertainty is narrower for well-studied chemicals, and wider when information is scarce. However, it should be emphasized that AALs reflect conservative assumptions about potential human risks, but cannot eliminate all risks for all effects. Regardless of the method used, no system can do away with uncertainty, and no program can provide zero risk. When a chemical has been well-studied, and exhibits only effects which are generally believed to have a threshold, the AAL is likely to provide a margin of safety with respect to those effects, and therefore little or no risk for those effects. In contrast, carcinogens and mutagens are assumed to pose some level of risk, even at very low doses, since there is a considerable body of scientific opinion that there is usually no demonstrable threshold for these effects (Albert et al., 1977; Hooper et al., 1979; NAS, 1983). Therefore, risk can be minimized but not removed. Although it is impossible to quantify individual risks precisely, the Department believes that the system outlined in this document produces AALs which effectively minimize these risks while maintaining a practical regulatory approach to air toxics.

6. Selection of Averaging Time

Controlling emissions of toxic contaminants is critical to the protection of public health, and the selection of appropriate averaging times is critical to controlling emissions. The Department has designated two averaging times to protect the public against threshold and nonthreshold effects, including an annually averaged AAL, and a 24-hour ceiling limit corresponding to the TEL

(threshold Effects Exposure Limit). Shorter averaging times or ceiling limits may be established in the future on a chemical-by-chemical basis as warranted.

Most chemicals exhibit a range of effects over a range of doses, and sometimes very different types of effects even at a single dose or exposure level. Thus it is important to account not only for overt short-term toxicity as well as less readily observable chronic effects, but also for differing types and mechanisms of toxicity within the same dose range. The use of two averaging times, one short-term and one longer-term, is one approach which has been advocated for addressing both acute and chronic effects. Differing effects within the same dose range can best be addressed by narrowing the range of exposures and limiting allowable concentration peaks. This assures that thresholds will not be exceeded. The Department believes this conservatism is appropriate, particularly since long-term effect and non-effect levels are derived without considering daily fluctuations in dose.

Thus, the Department has designated dual averaging times for all chemicals for two reasons: first, to limit exposure peaks which may trigger threshold effects such as teratogenicity or nervous system effects, and second, to maintain allowable risk levels for nonthreshold effects such as carcinogenicity. The purpose is to achieve exposure concentrations as close as possible to the AAL and TEL in order to protect public health against all adverse effects. For chemicals also associated with acute effects where a 24-hour averaging period may not provide adequate protection against peaks and fluctuations, the Department will also designate a short-term exposure limit (such as one-hour) to narrow the allowable exposure range within acceptable limits. This is consistent with National Ambient Air

Quality Standards (NAAQS), such as for sulfur dioxide. The methods for establishing such short-term exposure limits have not yet been developed by the Department.

7. Designation of Compliance Location

The Department has designated the point of maximum concentration at or outside of the source property line as the location for determining compliance with AAL values.

8. Schedule for Updating

DEP will review the toxicological basis for existing AALs at the rate of about 35-40 AALs per year and will revise them if warranted. In this way it is estimated that an individual AAL will undergo review a minimum of every three years. In addition, the Department will continue to develop new AALs as the need for them arises.

The Department will reissue a complete updated list of AALs on an annual basis in January of each year. Any changes or additions to the list which have been made in the preceding year will be reflected in this list.

The DEP Division of Air Quality Control will issue an implementation document describing how the AALs are used by DEP.

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PART II. CHEMICAL HEALTH EFFECTS ASSESSMENT METHODOLOGY (CHEM)

A. Introduction

The purpose of the Chemical Health Effects Assessment Methodology is to identify the range of adverse health effects associated with a given chemical compound. It is designed to evaluate the potential toxicity of a large number of chemicals in a consistent and comprehensive manner, based upon weight-of-evidence, potency, and/or severity of effect. For purposes of assessment and scoring in CHEM, the term "weight-of-evidence" refers to the amount or strength of evidence pointing to a particular health effect. It describes how much data exist, and the degree of confidence that the effects noted are genuinely associated with the chemical being evaluated. "Potency" refers to the magnitude of response at a given dose, and "severity of effect" pertains to the seriousness or health implications of a particular effect. Health effects are divided into four categories: acute and chronic toxicity, carcinogenicity, mutagenicity, and developmental and reproductive toxicity. Health effects data on each chemical are recorded on referenced worksheets for each category, and are updated and maintained as a permanent documentation file. This health effects information is then used to derive allowable ambient limits.

The product of the assessment is a relative hazard score in each health effect category for each chemical. Scores for the more than 100 chemicals evaluated under CHEM are presented in Table II-35. Letter scores are assigned rather than numerical scores in order to emphasize the descriptive and comparative nature of the scores, and to avoid the temptation to add or multiply health effects scores from various categories. All health effects are

considered and accounted for independently, and there is no attempt to balance one type of effect against another. Therefore, a high score in one category cannot be negated by a low score or lack of data in another category. Moreover, by scoring health effects individually, rather than cumulatively, oversights, gaps, or duplications can be minimized, and the system can effectively account for chemicals exerting multiple effects without diluting the significance of any one of those effects. Thus, the resulting scores represent an objective assessment of all the diverse health effects documented by the sources used. Scoring methodologies for each category are detailed in the appropriate sections below, and presented in Tables II-2, II-3, II-9, II-18, II-31 and II-32. In addition, examples are included throughout the text in order to illustrate the practical applications of the concepts presented.

1. Data Sources Used in CHEM

CHEM uses both primary and secondary data for the assessment of chemical-specific health effects. Primary data refers to original experimental studies, as published in peer-reviewed scientific journals (e.g., Journal of the National Cancer Institute, Environmental Health Perspectives, Journal of Environmental Pathology and Toxicology). Secondary sources contain reviews and summaries of the original studies [e.g., International Agency for Research on Cancer (IARC), National Institute for Occupational Safety and Health (NIOSH), the federal Food and Drug Administration (FDA), and Environmental Protection Agency (EPA)]. Depending on the amount of existing data, using primary sources can mean collecting hundreds of articles and evaluating each for its adequacy and validity, while using good secondary sources allows the regulator to rely on the judgement of qualified experts in each field.

Secondary sources are more practical as well, since each may contain scores of studies, reviewed and organized on a consistent basis. Because Department resources are finite, and because the protection of public health requires expeditious regulatory action, the Department has relied on secondary sources wherever possible (i.e., acute/chronic toxicity, carcinogenicity, and mutagenicity). Specific data sources used in each health effects category are listed in Table II-1, and described in the appropriate health effects sections below.

Thus, health effects data are compiled from the original science literature in addition to peer-reviewed secondary sources such as the National Toxicology Program (NTP), the Genetic Toxicology Program (Gene-Tox), IARC, EPA, and NIOSH. Secondary sources were selected on the basis of the following criteria, after extensive Department review:

- Reliability.
- Scientific accuracy.
- Clear, thorough documentation.
- Subject to peer-review, reflecting a consensus of expert opinion.
- Well-known and accepted by the scientific community.
- Current, updated regularly.
- Readily accessible.

Original science literature is evaluated on a case-by-case basis before it can be included in the health assessment. At no time are computerized lists or findings not subject to peer review incorporated into the evaluation. Even when using IARC, NTP, or EPA documents the study findings are reviewed, summarized on worksheets, and

II-1. DATA SOURCES USED IN CHEM

ACUTE/CHRONIC TOXICITY	
o NIOSH	National Institute of Occupational Safety and Health
o ACGIH	American Conference of Governmental Industrial Hygienists
o OSHA	Occupational Safety and. Health Administration
o ATSDR	Agency for Toxic Substances and Disease Registry - (Chemical Profiles)
o EPA IRIS database	Environmental Protection Agency - Integrated Risk Information System
o Other	primary science literature, as needed (e.g. no occupational data)
CARCINOGENICITY	
o IARC	International Agency for Research on Cancer
o NTP	National Toxicology Program
o CAG	Carcinogen Assessment Group (EPA)
o Other	primary science literature, as needed (e.g. new data)
MUTAGENICITY	
o IARC	International Agency for Research on Cancer
o GENE-TOX	EPA's Genetic Toxicology Program
o Other	primary science literature, as needed

continued . . .

TABLE II-1. DATA SOURCES USED IN CHEM, continued

DEVELOPMENTAL/REPRODUCTIVE TOXICITY
o Primary science literature consulted in all cases o Bibliographic references to literature obtained from: IARC (International Agency for Research on Cancer) EPA (Water Quality Criteria Documents, Health Assessment Documents, IRIS) Shepard's Catalog of Teratogenic Agents CESARS (Michigan's Chemical Effects Search and Retrieval System) Index Medicus RTECS (NIOSH's Registry of Toxic Effects of Chemical Substances) NIOSH, ACGIH, OSHA Library reference sources, current toxicology journals Computerized databases such as the National Library of Medicine (NLM), Toxline, etc.

referenced in all cases. Details about the selection of data sources and criteria employed by the Department in evaluating the quality and adequacy of primary literature are provided in each health effects section.

CHEM utilizes all valid toxicity data documented by the sources listed, encompassing qualitative and quantitative evidence, animal and human evidence, and positive and non-positive evidence, in order to develop a comprehensive evaluation of potential health hazards to diverse populations. The methods and assumptions underlying the uses of various types of evidence are discussed below.

a. Use of Qualitative and Quantitative Data

CHEM uses both qualitative and quantitative data in assessing hazard potential. Specific methods are detailed under individual health effects sections. In general, however, both weight-of-evidence and potency are factored into the assessments wherever the availability of data permits.

Qualitative assessment, a component of scoring in all four health effects categories, is used to distinguish chemicals having greater or lesser evidence for a particular effect, and to distinguish more severe from less severe effects (e.g., systemic toxic effects versus irritant effects, irreversible as opposed to potentially reversible effects). Quantitative data are then factored into the assessment in order to distinguish degree of hazard. Thus, each score reflects both the degree of confidence that the effect noted can be causally associated with exposure, and the severity of that effect, as well as the magnitude of the response at given dose levels (the lowest dose at which observable responses are elicited).

For example, chemical X may be a potent irritant, but compared to chemical Y which causes irreversible liver damage, chemical X will receive a lower score for acute/chronic toxicity. Further, if both chemical X and chemical Y demonstrate teratogenic effects in laboratory animals, it will be important to know that chemical X has been shown to do so only at very high levels, while chemical Y exerts that effect at exposure levels typical of those in the ambient air. In this case the qualitative data are used to describe the potential teratogenicity of each chemical, and the quantitative data serve to distinguish relative degrees of hazard. This allows CHEM to account for all documented health effects, while focusing concern on those chemicals and effects most likely to have an adverse impact on public health.

b. Use of Animal and Human Data

Wherever possible, CHEM uses human data from clinical, epidemiological, and occupational literature to directly assess human toxicity. With the exception of acute and chronic toxicity, however, much of the hazard evaluation relies on animal evidence, since quantitative human evidence is rarely available. In addition to the problems of mixed exposures and long latency periods, epidemiological studies have often lacked the power to adequately determine risk, particularly for common effects, or in small populations. In discussing the limitations of epidemiological studies, NAS gives the following example:

> "...if 20% of all pregnant women...used a chemical that caused stillbirths in 5% of the women, the resulting increase in stillbirths would be 1% (0.20 x 0.05 = 0.01), and it is likely that it would not even be noticed. If 5% of all pregnant women used a chemical that caused a delayed effect in 20% of their offspring,

> this also would probably escape notice. Even if the chemical caused a 10% increase in a most common form of cancer in the offspring of the 5% of women (e.g., cancer of the colon, which would mean an increase of 200 deaths per year), the effect would very likely go undetected." (NAS, 1977, p. 30)

Incidence in the control population and the size of both control and exposed populations will affect the magnitude of the response rate needed to demonstrate risk. It is also true that relatively rare events are much more easily detected and do not require the same degree of statistical sensitivity that more common responses or higher existing ("background") incidence will require to be detectable.

Aside from the problems of statistical power, a number of other factors must be considered in designing and interpreting epidemiological studies, particularly where the results are equivocal or non-positive:

- Difficulty characterizing exposure - accounting for all routes of entry, as well as the magnitude, duration, and frequency of exposure.

- Difficulty quantifying specific doses received - e.g., mixed or multiple exposures.

- Difficulty identifying and characterizing exposed versus control groups - occupational and other groups are heterogeneous with respect to age, sex, health, exposure history, etc. Also, levels of exposure to any given chemical may vary across so broad a range as to make "group" distinctions meaningless. Even applying "low-moderate-high" exposure level classifications is arbitrary, and may mask significant differences or

similarities among exposed groups. Furthermore, in the case of ubiquitous chemicals, it may be impossible to identify an unexposed control group. Lastly, group classifications may be inaccurate, due to faulty or incomplete records, recall bias on the part of exposed individuals, or inadequate monitoring data. The net effect of any one of the above factors may be to obscure real differences in outcome between exposed and unexposed groups or individuals.

- Difficulty detecting response - variable latency periods, individual differences, small changes in common effects, inadequate biological monitoring or poor follow-up can complicate detection of effects in humans. Hospital records or death certificates may be incorrect or misleading, reporting procedures may not be standardized, and some significant effects may not be readily observable. In other cases, effects of exposure may be attributed to other causes, and not measured.

- Difficulty in designing an adequate study - e.g., controlling for important variables such as age, race, smoking habits, nutritional status, socio-economic status, prior exposure history, gender, health, pregnancy, etc.; ruling out bias; identifying and accounting for any confounding variables which will lead to misclassification or mismeasurement of responses; assuring adequate population size and statistical power.

Thus, while valid epidemiological studies represent the best source of data, and while use of human data obviates the need for uncertain dose and species extrapolations, it is important to note the limitations and difficulties

involved in detecting human responses to environmental or occupational contaminants in currently available studies. This is not to say that epidemiological studies should not be emphasized or given more weight, only that negative results in epidemiological studies must be viewed with caution. The Department recognizes that animal studies are no more than a surrogate for adequate epidemiology, and recognizes that more and better studies in humans should be undertaken. When these are available, the Department will use EPA and IRLG (1979) criteria to evaluate the adequacy of such studies.

Since most assessments of toxicity currently rely on experimental studies in animals, it is important to recognize how interspecies differences may affect those assessments. Animal models cannot provide precise indications of human response. In an extensive discussion of the subject, NAS concludes that if anything, animal data are likely to under-estimate the hazard to human populations, based on the following (NAS, 1977, pp. 31-34):

- Differences in size - in larger animals, substances are distributed and metabolized more slowly, and tend to persist longer; the number of susceptible cells is larger; the ratio of cardiac output per minute to blood volume is greater; the life-span is longer. "This is consistent with data obtained in studies of anticancer drugs, which showed that - on a milligram-per-kilogram basis - a mouse required 12 times as much drug to respond as did man, a rat 6 times as much, and a dog and a monkey 2-3 times as much." (NAS, 1977, p.32)

- Differences in population characteristics - human populations are genetically and otherwise heterogeneous, while laboratory animals are healthy,

inbred, and subject only to controlled, specific exposures. Moreover, the number of exposed humans who must be protected is substantially higher than the number of experimental animals which can be tested.

- Environmental differences - nutritional and environmental factors such as stress, light, temperature, ionizing radiation, etc., can affect response to pollutants. While synergism can rarely be accounted for in the laboratory, synergistic effects are an ever-present danger for humans, who are exposed to overwhelming numbers and types of substances.

- Pharmacokinetic differences - differences in absorption, metabolism, excretion, and reabsorption. The data suggest that in general, larger mammals tend to bind substances more extensively and to metabolize and excrete xenobiotics more slowly than smaller mammals.

Thus, as NAS concludes, "These observations suggest that small animals that are routinely used for toxicity testing are often more resistant than man to toxic compounds. This implies that small animal systems are likely to produce many false-negative results, and has important implications for establishing safety factors or using `conservative' techniques for extrapolation." (NAS, 1977, p. 32)

While human evidence provides the verification and understanding necessary to precise assessments of human risk, animal data have traditionally been relied upon for identifying potential hazards to human populations (Clayson et al., 1983; NCAB, 1983; IARC, 1982). The goal of CHEM is to provide a descriptive evaluation of the range of health

effects associated with each chemical, and animal data are used in that context.

c. Use of Positive and Non-positive (Null) Data

CHEM relies primarily on positive data, since CHEM`s purpose is to evaluate hazard rather than establish non-effects. Furthermore, the focus of the Massachusetts system is to develop allowable ambient air levels for chemicals on the basis of the adverse health effects which they can induce. Therefore, identification of "non-carcinogens", "non-mutagens", or "non-teratogens" is not relevant in CHEM.

Most scientists agree that non-positive (null) data reflect specific testing and exposure conditions and cannot be used to provide assurance of safety, or to prove non-effect (OSTP, 1984; IARC, 1982). Since test protocols, laboratory techniques, species sensitivity, and study strengths and weaknesses vary from one experimental situation to the next, and because these variations can influence outcome, non-positive results in one test can not cancel out positive results in another (USEPA, 1984a; USEPA, 1984b; NCAB, 1977). Thus, positive results in a well-designed study provide a stronger basis for assessment and should not be overridden. On the other hand, several non-positives from replicated studies looking at identical endpoints would cast doubt on a single positive result for the same endpoint and procedure. All of the data, including any human evidence, must be evaluated in order to appropriately interpret conflicting experimental results. Clearly, the same criteria and degree of stringency should apply to the evaluation of both positive and non-positive results.

An illustration of why non-positive results must be interpreted cautiously with respect to human outcomes is provided by NAS in a discussion of carcinogenic potential:

> "...failure to observe positive responses does not guarantee that the probability of response is actually zero. From a statistical viewpoint, zero responders out of a population of size N is consistent at the 5% significance level with an actual response probability between zero and approximately 3/N (e.g., when N = 100 and zero responders are observed, the true probability of response may be as high as 3%)." (NAS, 1977, pp. 42-43).

> "For example, even if no tumors are obtained in an assay of 100 animals, this means only that at a 95% confidence level, the true incidence of cancer in this group of animals is less than 3%. Even if we were to carry out the formidable task of using 1,000 animals for assay and no tumors appeared, we could only be 95% sure that the true incidence was less than 0.3%. Obviously, 0.3% is a very high risk for a large human population." (NAS, 1977, p.54).

The Department's approach to evaluating non-positive data in carcinogenic, mutagenic, and developmental/ reproductive toxicity studies is described in detail under each health effect category. Briefly, for carcinogenicity, the upper confidence limit of potency is calculated for all adequate bioassay data, and both positive and non-positive results are recorded and evaluated. For mutagenicity, non-positive results are considered when there are no positives, or when there are conflicting results in tests measuring the same endpoint in the same species. For developmental/reproductive toxicity, as in acute and chronic toxicity, non-positive results are evaluated and weighed within the context of all the available data, but do not contribute directly to the score. Both positive and non-positive results are recorded on the worksheets for each chemical, and non-positive results are carefully distinguished from positive results. Non-positive data <u>do</u>

play a significant role in the derivation of AALs, as described in Part III of this document.

2. Uncertainties in the Data

Uncertainty is an inevitable component of toxicological assessment, particularly as it applies to human populations. The Department recognizes the inherent difficulties encountered in dose, route, and species extrapolations of experimental data. Additional sources of uncertainty, and the ways in which these issues are addressed in CHEM are discussed below.

a. Threshold

In discussing the complexities surrounding dose-response and interpretation of experimental test results, the NAS states:

> "The most common expressed objection to regulatory decisions based on carcinogenesis observed in animal experiments is that the high dosage to which animals are exposed have no relevance in assessment of human risks. It is, therefore, important to clarify this crucial issue. Practical considerations in the design of experimental model systems require that the number of animals used in experiments on long-term exposure to toxic materials will always be small, compared with the size of the human populations similarly at risk. To obtain statistically valid results from such small groups of animals requires the use of relatively large doses so that effects will occur frequently enough to be detected. For example, an incidence as low as 0.01% would represent 20,000 people in a total population of 200 million and would be considered unacceptably high, even if benefits were sizable. To detect such a low incidence in experimental animals directly would require hundreds of thousands of animals. For this reason, we have no choice but to give large doses to relatively small experimental groups and then to use biologically reasonable models in extrapolating the results to estimate risk at low doses. Several methods of making such calculations have been considered and

> used, but we think that the best method available to us today is to assume that there is no threshold and that the incidence of tumors is directly proportional to dose." (NAS, 1977, p. 55).

Relying on models developed by Crump et al. (1976) and others (Armitage and Doll, 1961; NCAB, 1983), EPA generally assumes non-threshold and linearity of response for carcinogenicity in extrapolating high-dose experimental results to estimate low-dose risks for humans, (OSTP, 1984; USEPA, 1984a). Likewise, CHEM assumes at least some carcinogenic response at low doses. The response is assumed to be proportional to dose and is estimated on the basis of upper confidence intervals on the data. The specific carcinogenic response predicted will also be mediated by the model chosen, exposure duration, and mechanism of action (Crump and Howe, 1984). Mutagens are also considered to be without a threshold for effects. For developmental/reproductive toxicity and acute/chronic toxicity, CHEM does assume a threshold and evaluations are based on environmentally- relevant dose levels.

b. Dose-Response Data

The Department recognizes that "exposure level" does not necessarily reflect "dose level" in either experimental or natural settings, and that the term "exposure-response" is sometimes preferred, in order to emphasize the distinction. However, for purposes of simplicity, "dose-response" will be used throughout this document.

In CHEM, dose-response data are incorporated into the health effects assessment wherever possible. Details are provided under individual effects categories (Part II sections C-F), and summarized briefly here. CHEM uses dose-response data in the following ways:

- Estimating carcinogenic potency, wherever data permit (see section D).
- Developing a "risk-ratio" for developmental toxicants (see section F).
- Excluding threshold effects occurring only at doses or concentrations well above anticipated levels of human exposure (sections C and F).
- Establishing degree of toxicity (sections C, D, F).
- Assessing test protocols, and adequacy of data.
- Confirming experimental results.

Dose-response information is considered by the sources used in CHEM (IARC, NTP, EPA, Gene-Tox, etc.) and is, therefore, an integral part of each health effects assessment. As a descriptive tool, it helps to demonstrate cause and effect, and thus provides greater confidence in study results. Dose-response data are not used in CHEM to establish "no effect" levels for humans, but valid dose-response data are used to calculate doses corresponding to specific levels of risk, used in the derivation of AALs. Thus, dose-response data are used to develop allowable ambient limits (AALs), and are also used to develop scores for acute/chronic toxicity, carcinogenicity, and developmental/reproductive toxicity. Dose-response is not currently factored into the mutagenicity assessment because sufficient data are not yet available.

Example for Dose-Response

The ways in which dose-response data are used in CHEM can be illustrated in the case of formaldehyde:

- Acute/Chronic Toxicity: Dose is used to evaluate the relevance of a particular effect, and to exclude those effects occurring only at levels substantially above the occupational limits, and therefore well over

typical environmental levels. Moreover, quantitative toxicity data are used by NIOSH, ACGIH, and OSHA to calculate the recommended occupational limits. In the case of formaldehyde, acute toxicity data resulting from high-level exposures (>10 ppm) are not considered in the assessment, since exposures of that magnitude are not relevant to ambient exposure levels. In selecting the "most appropriate occupational limit" and assigning a severity score (see Part II, sections B and C), only effects at or below 2 ppm are of concern. The 1 ppm occupational limit selected as the MAOL (ACGIH) is based primarily on acute and chronic respiratory effects in humans and animals (observed at exposure concentrations even less than 1 ppm).

- Carcinogenicity: Quantitative dose-response data provide a basis for determining the carcinogenic potency and unit risk associated with formaldehyde exposure in inhalation studies with rats (CIIT, 1981). The unit risk estimate is used in conjunction with the weight-of-evidence classification (IARC, 1982; CAG, 1979; Kerns et al., 1983; Siegel et al., 1983) to produce a score for carcinogenicity (see Part II, section D). The unit risk is used to derive the final AAL (see Part III, Section D).

- Mutagenicity: Dose-response data are considered by Gene-Tox in the assessment of mutagens. When Gene-Tox indicates that a dose-response relationship was observed in a particular study, this fact is noted on the mutagenicity worksheets. However, mutagenic potency, as such, is not factored into the scoring mechanism for CHEM, since there are no generally agreed upon methods as yet for assessing overall mutagenic potency in short-term tests. Dose-response is

therefore not a factor in scoring for mutagenicity in CHEM (see part II, Section E).

o Developmental/Reproductive Toxicity: Dose-response data serve two purposes in the assessment of developmental and reproductive toxicity. First, the quantitative data are used to calculate a "risk-ratio" for each chemical (developmental toxicity only) in order to distinguish progressively stronger developmental toxicants, (see Part II, section F). Second, dose is used to characterize degree of hazard, such that effects occurring at low doses are given greater weight than those occurring at higher levels. In addition, effects found only at very high levels (>500 mg/kg) are excluded from review altogether (see Part II section F). Formaldehyde is identified in CHEM as a reproductive toxicant for males. The evidence is based on replicated studies in animals. Dose-response curves are unavailable, however, because in each study, statistically significant results were produced only at the highest dose used. This is considered a limitation, and decreases confidence in the results. For this reason, the score is flagged by an asterisk to indicate that more data need to be developed. If dose-response data had been available, the lowest statistically significant effect level would have been used for scoring. When the database on formaldehyde improves, and dose-response relationships are established, the score can be refined and the asterisk removed.

c. Route of Exposure

The Department acknowledges that experimental procedures should duplicate expected human exposure

conditions as closely as possible in order to minimize the uncertainties associated with extrapolation. Unfortunately, however, much of the available database pertains to routes of exposure other than inhalation. Some of the reasons for this include:

- Volatile organics, which are of interest toxicologically, are difficult to confine to the exposure area in such a way as to assure specific, uniform, and continuous exposure.

- Gavage and injection are frequently preferred as a means to quantify dose, since exposure via feed or inhalation may not assure uniform uptake or guarantee that precise doses can be ascertained.

- Other exposure conditions may be easier to accomplish, less expensive, and less difficult to replicate.

The Department recognizes that the "first pass effect" is a relevant and significant toxicological consideration, and that differing routes of administration may produce differing patterns of metabolism, distribution or excretion. Unfortunately, route of exposure comparisons by dose and species do not exist for many chemicals of regulatory interest. However, comparative toxicology does provide many examples of pharmacokinetic similarities. Based on various principles of toxicology and pharmacokinetic studies, extrapolation from one route of exposure to another is an acceptable practice and must often be used by regulatory agencies when data from specific exposure routes are unavailable.

For example, few carcinogenicity studies in experimental animals have been carried out using inhalation,

and while NTP relies primarily on gavage studies to assess carcinogenicity, the EPA nevertheless uses the data to develop cancer risk assessments for ambient air exposures. A case in point is carbon tetrachloride: the EPA Carcinogen Assessment Group (CAG) estimated lifetime excess cancer risk for exposure to carbon tetrachloride via air and water on the basis of a gavage study in male mice (NCI, 1976). In order to estimate the risk from inhalation corresponding to a concentration of 1 ug/m^3 of carbon tetrachloride in air, the equivalent human dose was calculated assuming an air intake of 20 m^3/day and a 40% absorption rate. This example illustrates an approach to extrapolating from one route of exposure to another, in order to estimate risks associated with air exposures for humans.

Inhalation data do figure more prominently in developmental toxicity studies but, for the reasons listed above, other routes are still more common. Only in acute/chronic toxicity, where CHEM relies on occupational data, is there a significant database for inhalation. Even so, epidemiological and case studies can be difficult to judge since precise inhalation doses for human exposures are rarely known.

Thus, if a health assessment is to be carried out at all, CHEM must rely on data derived from various exposure situations. Since the goal of CHEM is to identify the range of potential health effects associated with each chemical, rather than to develop a specific no-observed adverse effect level (NOAEL), it is appropriate to examine and use all valid data documented by the sources selected. Naturally however, valid human data will be used wherever possible, and inhalation data from human or animal studies are preferred over data from other routes of exposure.

Example of Route of Exposure

A common experience with route of exposure variations can be seen with the chemical epichlorohydrin:

- Acute/chronic toxicity: Occupational limits have been derived primarily on the basis of inhalation data for humans and animals, in order to protect against respiratory, liver, and kidney effects. Acute data were also derived from inhalation studies (rats). Unlike some chemicals, epichlorohydrin was expected to be associated primarily with respiratory effects, so more toxicity testing has been carried out using the inhalation route.

- Carcinogenicity: Animal studies have been carried out via oral, inhalation, subcutaneous, intraperitoneal, and skin application routes, each of which consistently demonstrated evidence of carcinogenic activity. In developing potency and unit risk data, CAG (1983) has selected the oral (rat) data as the most reliable for their assessment, and quantitative component used for scoring in CHEM is based upon that figure (unit risk estimate = 1.2×10^{-6}).

- Mutagenicity: Specific protocols are required for each species and endpoint tested. Route of exposure considerations are not relevant here.

- Developmental/Reproductive Toxicity: Experimental studies on epichlorohydrin used in CHEM are limited to oral routes of administration. In replicated tests, epichlorohydrin has consistently produced reproductive toxicity in laboratory animals (i.e., sterility). The influence of different routes of exposure on reproductive toxicity

findings was evaluated and discussed by NIOSH in the Criteria Document on Epichlorohydrin (1976). The NIOSH committee concluded that reproductive effects occurring after oral exposures would likely be the same following inhalation exposure since several systemic effects have been observed after both dermal and inhalation exposures. The NIOSH committee used the oral data on epichlorohydrin in setting the occupational limit for air. This supports the concept that exposure via one route may be applicable to the assessment of exposure via another route.

d. Individual Variations

As discussed in an earlier section, individual differences with regard to pharmacokinetics, genetic make-up, lifestyle, environment, medical and immunological status, etc. will act to influence disease process and exposure outcome. In addition, the variable exposures and the heterogeneity of human populations as compared to experimental animal populations make extrapolation difficult. Sensitive subgroups within the population further complicate assessment. Nevertheless, it is the regulators' responsibility to predict for, and protect, highly sensitive populations, as well as groups showing more average responses.

The Department recognizes the uncertainties associated with predicting individual response or calculating allowable ambient limits which will be protective of all individuals within the population. Due to the lack of information in this area it is impossible to estimate the effect of all genetic and environmental differences in human populations, yet these variations must be considered in developing AALs. The Department believes, therefore, that the most prudent

approach to AAL derivation and public health protection is to evaluate valid data from various sources, select the best data for assessment purposes, and apply safety or uncertainty factors to account for specific areas of uncertainty. (Details of this approach are provided in Part III of this document.) Since the aim of the air toxics program is to protect a large and diverse population from the adverse effects of air contamination, and since available scientific data do not permit precise quantification of hazards for either individuals or specific high risk groups, CHEM reflects the Department's attempt to balance judgment and fact, measurement and estimation, within the bounds of acceptable scientific principles.

Example for Individual Variations

Hydrogen sulfide is known to be a systemic toxicant acting primarily through the respiratory system to cause effects such as headache, dizziness, gastrointestinal distress, fatigue, irritability, insomnia, and loss of sense of smell. It is also an irritant, causing corneal damage, conjunctivitis, keratitis, nose and throat irritation, and pulmonary edema. At higher exposure levels it can cause respiratory paralysis, asphyxia, and death. Eye effects for workers are variously reported from 4 ppm - 20 ppm, indicating a range of susceptibilities to irritant effects. In addition, ACGIH reports the possibility of brain damage at low levels, and also cites a case report of polyneuritis and encephalopathy resulting from a one-day occupational exposure. Since variability is encountered among healthy adult workers, it is reasonable to assume that asthmatics, children, the non-inured, and other more sensitive populations will exhibit greater variability and greater susceptibility to the effects of exposure. Unfortunately, however, there are no data to quantify exposure-response or

atypical reactions in non-working populations. Therefore, the best available option is to account for exposure differences and sensitive populations through the use of uncertainty factors designed specifically for that purpose. It is assumed in this case that the traditional uncertainty factor applied to account for intra-species variability (a factor of 10) will be adequate to protect the more susceptible groups within the population. (see Part III, sections B and E).

e. Lack of Data

Gaps in the data present another problem for regulators. CHEM accounts for this in a number of ways, depending on the nature of the specific problem. First, CHEM utilizes data from a variety of sources, including human and animal, in vivo and in vitro, based on the best available studies. This minimizes the chance that relevant data will be overlooked. Second, when important data gaps do exist, as noted in CHEM, the method to derive allowable ambient limits does not overlook this fact and instead accounts for the missing data by applying uncertainty factors.

When carcinogenicity or mutagenicity data are lacking, the AAL derivation procedure relies upon structure activity relationship (SAR) analysis to estimate the potential toxicity of the chemical and the likelihood that it may exhibit properties and effects similar to chemicals of known toxicity having a comparable structure (NCAB, 1983; USEPA, 1984a; OSTP, 1984). Also, when the occupational data used to derive AALs are inadequate, and no long-term exposure data for humans exist, an uncertainty factor for inadequate toxicity data can be applied in the AAL derivation procedure. Details are provided in Part III, section B.

When occupational limits have not been developed for a chemical of interest, other scientific literature and data sources will be reviewed, and toxicity assessed. The method for accomplishing this task has not been developed as yet.

f. Mixtures/Multiple Exposures

Mixtures

The Department recognizes the problem of mixed and multiple exposures and the attendant health risks. Where reliable studies have been conducted on specific mixtures, or chemicals and their isomers can be effectively grouped for purposes of assessment (e.g., PCBs, certain solvents, asbestos fibers), the effects can be evaluated. For the most part, however, CHEM provides a chemical-specific assessment of adverse health effects and does not assess interactive exposures or multiples of risk. This issue will be addressed in the future, as part of an overall implementation plan. Currently, when the DEP Office of Research and Standards is asked to evaluate the risk posed by mixtures of contaminants (e.g., hazardous materials sites), total risk for the mixture is assessed using published EPA procedures (51 FR 34014, US EPA, 1986 a). Department policy regarding mixtures and total allowable risk is to sum estimated lifetime cancer risks for identified carcinogens and derive a "Hazard Index" to assess the risk of threshold effects for a given mixture of contaminants. Hazard Indices are calculated for groups of chemicals which share the same or similar mechanisms of action by dividing the exposure concentration for each chemical over the Threshold Effects Exposure Limit (TEL) (see Part III.B.) for that chemical and then summing the ratios obtained, as shown below:

Hazard Index = EC_1/TEL_1, + EC_2/TEL_2 + ... EC_i/TEL_i

where:

EC = Ambient exposure concentration to substance 1, plus substance 2, etc (modeled or detected)

TEL = Threshold effects exposure limit for substance 1,2, etc.

Hazard indices are calculated in this way for each group of like compounds. The total hazard index is then compared to a value of one, and total excess lifetime cancer risk is compared to a maximum allowable risk level of one in one hundred thousand (1×10^{-5}) for the mixture. This is consistent with policies described in the Massachusetts contingency Plan (MCP), and supporting documents for evaluating risks associated with hazardous materials sites. (Readers familiar with the MCP will note that in that context, the hazard index is compared to a value of 0.2 rather than one. A value of one is used in this case because the TEL already incorporates the relative source contribution factor of 20% (see below), whereas the RFD and ADI values used for evaluating exposures involving other environmental media generally have this 20% factor applied later. Thus, the values are identical, and are only expressed differently).

g. Interactive Effects

Again the Department acknowledges that toxicity can be influenced by a variety of factors, including synergism and other interactive effects of mixed exposures. Adverse effects can be mitigated or exacerbated depending on individual characteristics and chemical properties. This is evidenced in the case of cancer promoters and co-carcinogens

in drug interactions, smoking and asbestos exposure, alcohol consumption and carbon tetrachloride exposure. However, since it is not currently possible to account for individual exposure patterns or to quantify the effects of interactive exposures on a consistent basis, the AAL methodology does not attempt to address this issue. With the exception of a few clear-cut examples listed above, the regulator can neither anticipate all potential exposure scenarios, nor attempt to regulate on that basis, since the possibilities are endless. Rather, like other regulatory programs, the Massachusetts system focuses on individual chemicals and attempts to identify the range of possible health effects associated with each.

As previously noted, the relative source contribution factor of 20% is conventially applied by EPA and other regulatory agencies (including the Massachusetts DEP) in the assessment of threshold-type health risks. The CHEM and AAL methodology incorporates this factor in the TEL to account for exposures through multiple routes. This factor allots twenty percent of the exposures from a particular chemical to inhalation exposures. The relative source contribution factor has not conventially been applied in the evaluation of nonthreshold effects. However, conceptually there is no difference between estimating relative exposures to carcinogens and noncarcinogens. It is noted that exposure to carcinogens as to noncarcinogens can be through a variety of exposure routes. Thus, whereas the Department does not currently apply the 20% factor to the NTEL, it recognizes that this is an inconsistency. The Department will consider use of this factor for nonthreshold effects evaluation as a longer term project.

h. Multiple Effects

The purpose of categorizing effects and establishing individual scores for each health effect category is to distinguish chemicals having the potential to produce more than one type of effect, and to weigh the significance of each effect in an objective way. The toxicity of each chemical, within each health effect category, is assessed independently of other effects in the other categories. The advantage of this method is that both the quality of the data and the severity of the effect are assessed, and the results achieve the significance merited without overlap or diminution of emphasis in any one category.

3. Confronting Uncertainties in the Data

The foregoing discussion highlights the areas of uncertainty which complicate toxicological assessment and slow regulatory progress. Scientific uncertainties notwithstanding, however, the need to protect public health from exposure to toxic air pollutants make further delays in regulatory action unacceptable, even in the face of unresolved questions. As Clifford Grobstein (1983) states in an editorial,

> "in general terms, therefore, when working in the policy mode, scientists must recognize that the declared purpose is an important determinant of the necessary level of certainty. In all cases, it is essential to communicate accurately what the level of certainty is, as well as how it can be improved. But if science is to be used as constructively as it must be, the rigid criteria of fundamental science are often inappropriate. What often is needed is the best available advice for a complex decision arena. Soundly assessed and accurately communicated, the current state of knowledge can be a most important guide, even though not fully complete and not yet wrapped up in the golden trappings of complete certainty. We would be remiss to withhold what can be useful because it is not perfect."

In a presentation before the National Coalition on Disease Prevention and Environmental Health, Douglas M. Costle, then Administrator of the EPA, characterized regulatory responsibility as follows:

> "Given the potential for long-term damage, it seems to be the case for a policy that emphasizes protecting health where the scientific evidence is inconclusive should be irrefutable...We do need to improve our scientific understanding of the links between pollution and health -- especially in the case of toxic chemicals, many of which didn't exist a generation ago. But we cannot delay writing sensible balanced rules governing these substances. We know enough to do that... We must say, in candor, that there are limits to what science can tell us about this relationship; but that the more serious limitation is an inability to see the suffering that lies behind the dry projections of injury that science does permit us to make; and that, if this failure of vision can be overcome, the need for firm and farsighted environmental regulation will be very plain to see." (Costle, 1980)

Thus, in the area of regulating potentially toxic substances in the environment, "pure" science is only one facet of the process, and science policy provides the link between the hard data and the need to make decisions regarding public health. The term "science policy" denotes management issues that are grounded in scientific analysis, but for which technical data are insufficient to support an unequivocal scientific conclusion. For example, there is no scientific way to tell if a community regards a certain level of risk "acceptable". Such decisions involve social, economic, political, and health considerations, as well as scientific input.

Given the need to address the issue of air toxics, the Department takes the view that a prudent approach to the reduction of human health risks is to utilize valid scientific principles and the best available data to

evaluate the potential toxicity of each chemical, while tolerating the inevitable uncertainties involved, and allocating resources wisely. CHEM reflects an attempt to combine science fact with reasonable science policy, and to balance qualitative and quantitative components in a way which maximizes the strengths and advantages of each.

4. Summary

In summary, CHEM represents a standardized approach to a chemical-specific toxicity evaluation, utilizing valid epidemiological, clinical and experimental data from primary sources and peer-reviewed secondary sources, and is designed to produce a toxicity score in each of the four health effects categories. CHEM does not provide quantitative measures of biological exposure and interaction. It does provide a health-based mechanism for scoring toxic effects on a relative scale, and it provides the database for deriving allowable ambient air limits. Assessment and scoring procedures for each category are described in detail in the following sections.

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B. The "Most Appropriate Occupational Limit" (MAOL)

1. Introduction

The Massachusetts system uses occupational literature in two ways: as a database for assessing the acute and chronic toxicity of chemicals under consideration, and as a means to select a beginning number to use in deriving preliminary human exposure limits for chemicals having threshold effects. Details on the assessment and scoring of acute and chronic toxicity are provided in Part II, section C. The AAL derivation method is described in Part III.

The selection of the "most appropriate occupational limit" (MAOL) is a critical step in the Massachusetts system because it affects both the health effect score for acute and chronic toxicity in CHEM, and potential AALs. In this context, MAOL is defined as the occupational limit which provides the best protection against the greatest number of documented health effects. The selection criteria have been prioritized as follows:

a. The degree of protection afforded by the occupational limit.

b. Relevance of the occupational limit to documented health effects.

c. Adequacy and comprehensiveness of the toxicity data;

d. Limitations in the occupational level, as reported by the occupational sources themselves

e. The importance (severity) of the health effects accounted for

f. How recently reviewed, toxicologically current

g. Relevance to long-term chronic effects

Selection of the MAOL is based on comparisons of the toxicity data evaluated and used by NIOSH, ACGIH, and OSHA, and the occupational limits developed by each. If one occupational limit is higher than another, and health effects are reported at or below the higher limit, the lower limit will be selected as the MAOL. To the extent that specific, reported, threshold effects are associated with a given occupational limit, the choice of a lower limit where available is fairly straightforward and objective, and relates to criteria a, b, and c above. Thus, the MAOL is that occupational limit which comes closest to the lowest observed adverse effect level for specific effects reported by the sources, without exceeding it. When the decision is not so straightforward and cannot be clearly related to specific effect levels, criteria "d" and "e" become most important, and over-all hazard is considered. Other factors such as thoroughness of database, and the factors involved in "c" are also included in the selection. When occupational limits do not differ numerically, and one agency must be chosen over another, criteria "f" and "g" are used.

All data pertaining to selection of the MAOL, including health bases, effects not accounted for, effects below the occupational limit, and criteria used/rationale behind each choice, are documented on worksheets designed for this category. A sample worksheet is provided at the end of this chapter.

2. Background Information

Recommended or permissible levels of human exposure to industrial chemicals are set by the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists, Inc. (ACGIH), and the Occupational Safety and Health Administration (OSHA). NIOSH is specifically authorized to "recommend occupational standards to the appropriate regulatory body" (i.e. OSHA) and to "conduct such research and experimental programs as...are necessary for the development of criteria for new and improved occupational safety and health standards." (NIOSH/OSHA, 1981). In addition to commenting on OSHA's standards, NIOSH has also developed comprehensive Criteria Documents for approximately 100 of the chemicals regulated by OSHA.

Independently of the federal government, ACGIH reviews the scientific and industrial hygiene literature, and establishes a recommended threshold limit value (TLV) for each chemical under consideration. ACGIH has reviewed virtually all chemicals regulated by OSHA, in addition to some unregulated chemicals. ACGIH's TLV Committee is composed of experts from the fields of toxicology, engineering, industrial hygiene, analytical chemistry, and medicine. Committee members provide the documentation, which is updated and published annually. While only OSHA limits carry regulatory weight, many groups and industries have voluntarily adopted the generally more stringent and more toxicologically current recommendations of NIOSH and ACGIH.

Occupational limits (generically referring to the exposure limits set by NIOSH, ACGIH, OSHA) generally

represent time-weighted average concentrations of airborne substances to which a worker can be exposed during defined work-periods, and under specified work conditions, throughout a working lifetime. NIOSH recommendations are based on a 10-hour day, 40-hour week; ACGIH TLVs and OSHA standards pertain to an 8-hour day, 40-hour work week. Short-term exposure limits and ceiling values are evaluated and set on case-by-case bases.

For the same chemical, NIOSH, ACGIH, and OSHA frequently set different limits (see Rowan et al., 1984 for a discussion comparing these differences). NIOSH-recommended limits are often, but not consistently, lower than those set by OSHA and ACGIH. Differing recommendations are influenced by a variety of factors, including different agency mandates, cancer policies, and multi-dimensional approaches to controlling exposures for workers. An example of differing perspectives can be seen in the respective definitions and assessment procedures for regulating carcinogens.

First, the number of substances regulated as carcinogens differ among the agencies. ACGIH has assigned TLVs for 34 carcinogens and has identified another 19 carcinogens for which TLVs are not assigned due to insufficient data on environmental conditions (ACGIH, 1987). NIOSH considers 33 chemicals as potential carcinogens, and recommended standards were set for all 33 (NIOSH, 1981). OSHA has established workplace standards for 17 substances identified as carcinogens (NIOSH/OSHA, 1981).

Secondly, varying procedures are utilized by the three groups. For example, ACGIH has developed a standardized cancer assessment procedure for chemicals based upon the available evidence, taking into account certain appropriate

experimental parameters for animal data (ACGIH, 1980). In contrast to ACGIH procedures is the case-by-case approach by which NIOSH evaluates workplace carcinogens, or OSHA's policy of categorizing chemicals depending on the degree of evidence for carcinogenicity (OSHA, 1981). Inconsistencies in the criteria for classifying carcinogens have led to differences in identifying chemical carcinogens and in allowable levels of worker exposure to these substances.

Due to the vast number of chemicals that are emitted into the air, the lack of federal guidance for most of those chemicals, and limited resources at the state level to develop individual air quality standards, states often use occupational limits in their air toxics programs to establish acceptable exposures to the general public. A common procedure is to use ACGIH TLVs, reduced by some safety factor to protect sensitive groups exposed beyond a 40-hour workweek.

However, before using occupational limits to derive allowable ambient limits for the general public, it is important to understand the strengths and limitations of occupational limits and their intended use. Occupational limits represent permissible exposures for healthy adult workers in controlled settings. Each assumes a recovery period during which exposure will be zero, as follows: OSHA standards and ACGIH limits allow a recovery period of 16 hours between daily exposures and 64 hours on weekends. NIOSH limits allow 14 hours between workdays and 86 hours on weekends. Workers are assumed to be between 18 and 65 years of age, and to represent a relatively healthier subset of the general population.

In addition to significant differences between working and non-working (e.g. old, young, infirm) populations,

occupational settings offer different control opportunities. Occupational exposure limits can be achieved in a number of ways, including reducing environmental exposures (air and/or skin exposures), using personal protective devices, medical surveillance programs, use permit systems, technology-based controls, and product substitution or prohibition. Thus, the techniques available in occupational settings to provide worker protection significantly differ from the techniques which are available to regulatory agencies to protect the general population, since many of these options are not feasible for ambient exposures to large populations.

Finally, occupational limits were not designed for use by, or to be protective of, the general public (ACGIH, 1986). Multiple or continuous exposures, and populations including children, the elderly, the chronically ill, and the hypersensitive are not accounted for.

Even in the occupational setting, all workers are not protected against all health-related effects. In fact, of the more than 100 chemicals evaluated by the Department to date, more than half are reported by the sources themselves to have specific adverse acute or chronic effects below the occupational limits. Given differing occupational limits then, and the varying degrees of protection afforded by each, it is essential that each occupational limit be thoroughly evaluated as to its health basis, rationale, adequacy, and relevance for setting ambient exposure levels.

Despite the fact that occupationally derived exposure limits are not directly applicable to environmental settings, there are, nevertheless, significant advantages to using the documentation and recommended limits provided by NIOSH, ACGIH, and OSHA. First, these comprise the largest

available body of knowledge pertaining to the effects of airborne contamination for human populations, based on years of experience. Second, the documentation has been prepared by qualified committees that evaluate data from many sources. The documentation is peer-reviewed, thorough, and updated regularly. Third, reports include the range of effects and effect levels, experimental as well as field data, an overall toxicity evaluation, and the reasoning behind each recommendation. Areas of disagreement among the three agencies, conflicting evidence, gaps in the data, and limitations in recommended levels are explicitly discussed by the occupational agencies. This allows for the objective comparison of differing recommendations.

3. Selection and Use of the MAOL

In order to illustrate the MAOL selection process, aniline is presented as a representative case. Aniline is a systemic toxicant which affects the ability of the blood to carry oxygen. The OSHA standard for aniline is 5 ppm, and NIOSH has not proposed any change (NIOSH/OSHA, 1981). However, ACGIH recommends a 2 ppm TLV, based on a different interpretation of the health data reported, and a greater emphasis on chronic effects (ACGIH, 1986). Both NIOSH and ACGIH report blood and nervous system effects, as well as high rates of skin absorption. NIOSH lists the short-term exposure effects as methemoglobinemia and oxygen deficiency with symptoms such as headache, weakness, irritability, drowsiness, and shortness of breath. Long-term exposure effects include the above, plus paleness, insomnia, decreased appetite, and anemia. Both agencies report methemoglobin formation at levels as low as 5-7 ppm. ACGIH stresses the number of fatalities and cases of chronic poisoning associated with aniline, and reports the presence of liver atrophy and cirrhosis in at least one case of fatal

overexposure. The TLV Committee cites the work of two researchers demonstrating effects at 5 ppm, one of whom recommends an occupational limit of 1 ppm. ACGIH points out that the current OSHA standard was derived from older data, and allows no margin of safety. ACGIH recommends a limit of 2 ppm.

The Department chose the MAOL of 2 ppm based on (1) presence of effects at the NIOSH/OSHA level of 5 ppm, (2) the potential for chronic poisoning, and (3) the seriousness of the effects noted. As ACGIH points out, the OSHA/NIOSH limit of 5 ppm provides no margin of safety even for the healthy worker exposed intermittently. Both NIOSH and ACGIH emphasize the fact that even a small amount absorbed from clothing can cause intoxication. Moreover, the sensitivity of the general population to anoxia and related effects of aniline exposure suggest a conservative approach, particularly since ambient exposures are likely to occur in the presence of carbon monoxide and other asphyxiants.

The lower occupational limit is selected in order to begin with a number which accounts for chronic toxicity, and which is below levels of reported effects. Since the carcinogenicity of aniline is reported elsewhere and will be accounted for by the scoring system for carcinogenicity, it is not necessary to account for it here. Thus, the use of the 2 ppm limit for aniline is "most appropriate" for the following reasons:

- Lack of margin of safety at 5 ppm
- Aniline's acute and chronic toxicity
- Magnitude of effects
- Relatively large number of people likely to be sensitive to the effects

- Ubiquitous nature of other anoxia-producing chemicals

As indicated, the MAOL is used in two ways: in CHEM, as a basis for assessing and scoring the acute and chronic toxicity of chemical compounds; in the AAL derivation method, as the starting point for developing health-based ambient exposure limits for chemicals associated with threshold effects.

Use of the MAOL approach serves two purposes: First, it provides a mechanism for assessing differing occupational limits, and allows for objective selection based on standardized criteria. Second, it allows the Department to review all of the data presented by NIOSH, ACGIH, and OSHA, and to choose the most health-oriented limit rather than being arbitrarily restricted to one agency's recommendations. This case-by-case analysis of each occupational limit provides a basis for interpreting conflicting data or conflicting recommendations, insight into how and why each limit was recommended, and a less arbitrary, more objective mechanism for choosing among differing values.

Occupational limits are set by NIOSH, ACGIH, and OSHA (not by the Department). A problem involved in using occupational limits to set allowable ambient limits is the fact that some occupational limits are less adequate than others. Chemicals representing similar degrees of hazard may not have similar MAOLs. In the case of 1,3-butadiene for example, the occupational limit recommended by NIOSH, ACGIH and OSHA has been 1000 ppm. ACGIH has now adopted a 10 ppm TLV, and the MAOL has changed accordingly. However, until the new TLV was set, none of the occupational limits

could really be characterized as "appropriate" since exposure levels even lower than 1000 ppm (625 ppm) produced tumors in animals in carcinogenicity studies (NTP, 1984). The Department acknowledges this problem, and will develop an alternative procedure using other data sources in these cases, rather than rely on obviously outdated and toxicologically inadequate occupational limits, when such deficits cannot be sufficiently addressed by the use of safety or uncertainty factors in deriving the AAL. The procedure used will be the same as when no occupational limits exist for a compound.

When no occupational limit exists for a chemical of concern, the Department will use other toxicity literature and establish an alternative process (e.g., inhalation Reference Dose). The Department is currently working on developing the procedure to be used. When an occupational limit recommended by NIOSH, ACGIH or OSHA is changed by one of those agencies, the Department will review the data and recommendation in order to determine whether a change in the MAOL or AAL is warranted. It should be noted that when inhalation reference doses (RfD) become routinely available, the Department will refer to these in deriving AALs, and may not use occupational limits for this purpose.

4. Summary

The "most appropriate occupational limit" (MAOL), defined as the level which provides the best protection against the greatest number of documented acute and chronic health effects, represents a critical component of the Massachusetts system. As outlined, the MAOL serves two purposes: first, as a factor in scoring acute and chronic toxicity, and second, as the starting point in deriving AALs for some chemicals. In beginning with the MAOL, the

Department seeks to provide a sound health basis for evaluating toxicity and deriving exposure limits for threshold chemicals.

5. References for MAOL

American Conference for Governmental Industrial Hygienists (ACGIH). 1986. Documentation of the Threshold Limit Values. Fifth Edition. ACGIH, Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists (ACGIH). 1987. Threshold limit values and biological exposure indices for 1987-1988. ACGIH, Cincinnati, Ohio.

Bierma, T. 1982. The use of occupational exposure standards to estimate safe ambient concentrations for air pollutants: A comparative study. Illinois Environmental Protection Agency. Springfield, Illinois.

National Institute for Occupational Safety and Health (NIOSH). 1984. U.S. Department of Health and Human Services. 1,3-Butadiene. NIOSH Current Intelligence Bulletin, 2/9/84. DHHS Publication No. 84-105.

National Institute for Occupational Safety and Health/Occupational Safety and Health Administration (NIOSH/OSHA). 1981. Occupational Health Guidelines for Chemicals, vol. I and II. U.S. Department of Health and Human Services. U.S. DHHS Pub. No. 81-123.

National Toxicology Program (NTP) 1984. Toxicology and Carcinogenesis Studies of 1,3,-Butadiene in B6C3F_1 Mice. U.S. Department of Health and Human Services. Technical Report Series No. 288. NIH Publication No. 84-2544.

Occupational Safety and Health Administration (OSHA). 1980. OSHA regulations on identification, classification, and regulation of potential occupational carcinogens. Occupational Safety and Health Reporter. Sec. 1990. 106(b)(1) Washington, D.C.: The Bureau of National Affairs: 41:7301-7318.

Occupational Safety and Health Administration (OSHA). 1981. OSHA regulations on identification, classification, and regulation of potential occupational carcinogens. Code of Federal Regulations. Sec. 1990. 103: 33-50.

Rowan, C.A., W.M. Connolly, and H.S. Brown. 1984. Evaluating the use of occupational standards for controlling toxic air pollutants. J. Environ. Sci. Health B19(7): 618-648.

6. Most Appropriate Occupational Limit (MAOL) Worksheet

The purpose of this worksheet is to document how and why each MAOL was chosen by the Department. The worksheet includes any health effects data reported by NIOSH, ACGIH, and OSHA in support of their respective recommendations, as well as the reasoning behind the Department's decision to select one occupational limit rather than another. The worksheet presents the data in a way which allows straightforward comparison among all three occupational agencies. However, except in the case of a proposed change (e.g., lead), OSHA does not provide documentation for its published standards, and the general industry standard (OSHA, 1978) is, therefore, the only information from OSHA which is provided on the worksheets (see Part II, sections B and C).

At the top of each worksheet the following information is given: Chemical name, CAS code, date worksheet was completed by Department, MAOL chosen, and originating agency. The worksheet is then divided into seven columns, with headings as explained below.

Occupational Limit: Under each agency name the occupational limit is listed. All values represent time-weighted averages unless otherwise noted (e.g., "50ppm, 5-minute ceiling").

Health Effects/Basis for Limit: Effects reported by each agency and considered in the derivation of the occupational limit are listed by major effect categories (e.g., irritant, systemic toxicant, carcinogen, etc.). The effects listed are summarized from those listed in more detail in the acute/chronic toxicity worksheets.

Effects At or Below the Occupational Limit: Any effects reported by the occupational agency which occur at or below the recommended occupational limit are listed, as well as the levels at which those effects are observed. This information is used by the Department to judge the degree of protection afforded by each occupational limit, and to select the MAOL.

Additional Data: This column is used to record any additional toxicological information or comments provided by the occupational agencies, to facilitate selection of the MAOL.

Effects Not Accounted For: Any effects identified in the assessments for carcinogenicity, mutagenicity, or developmental/ reproductive toxicity which were not accounted for in the occupational limit are recorded, as well as any acute or chronic effects not covered by the occupational limit. This information is used by the Department when assigning the Threshold Effects Uncertainty Factor for Effects Not Accounted for in the MAOL. The data are collected primarily through CHEM, and not from the occupational agencies, and are listed after all assessments are completed. Carcinogenicity, and mutagenicity are not considered when selecting the MAOL.

Basis for Decision: This column is used to record which criteria were applied in the Department's decision to select one occupational limit as "most appropriate".

References: The documentation provided by each occupational agency is referenced briefly. Complete references are included following the MAOL section of the text (Part II, section B).

SELECTION OF MAOL WORKSHEET

FOR:
CAS CODE:
DATE:
MAOL CHOSEN:

OCCUPATIONAL LIMITS	HEALTH EFFECTS/BASIS FOR LIMITS	EFFECTS AT OR BELOW OCCUPATIONAL LIMIT	ADDITIONAL DATA	EFFECTS NOT ACCOUNTED FOR	BASIS FOR THE DEPARTMENT'S DECISION	REFERENCES
NIOSH:						
ACGIH:						
OSHA:						

C. Acute and Chronic Toxicity

1. Introduction

Adverse health effects are defined in CHEM as effects that occur with intermittent or continued exposure and that result in impairment of functional capacity (as determined by anatomical, physiological, biochemical, or behavioral parameters), or in a decrement of the ability to compensate for additional stress, or enhance the susceptibility of the organism to disease or other deleterious effects.

In CHEM, acute toxicity is defined as the occurrence of adverse health effects which develop within a reasonably short period of time after exposure to a single dose or multiple doses of a substance. Chronic toxicity is defined as the occurrence of adverse health effects that develop and persist over time after exposure to a single dose or multiple doses of a substance. It should be noted that the category of acute and chronic toxicity covers all adverse health effects not considered under carcinogenicity, mutagenicity, or developmental/reproductive toxicity. It includes neurotoxicity, allergenicity, immunosuppression, and all cellular, organic, systemic, glandular, behavioral, or other toxic effects or conditions. The steps involved in evaluating chemicals for acute and chronic toxicity include compiling a wide range of health data from the occupational literature, selecting the occupational limit which offers the greatest protection, determining the severity of effects associated with the chemical, and deriving the final score.

2. Data Base

All of the toxicity information reported by NIOSH and ACGIH in support of their respective occupational limits is

recorded on standardized worksheets (a sample worksheet is provided at the end of this chapter). As described in the previous section, background documentation provided by these groups represents a comprehensive and valuable source of toxicity data, particularly in relation to human inhalation exposures. Existing OSHA standards are recorded as well, but unless these have been recently reviewed or revised, the background data for OSHA standards are not factored into the health assessment. OSHA standards are excluded because, with few exceptions, they were simply adopted from the early American National Standards Institute (ANSI) or ACGIH guidelines, and do not reflect current toxicological information. For example, the current 3 ppm OSHA standard for formaldehyde was adopted from the 1967 ANSI guideline #Z37.16, based on the chemical's irritant characteristics only. Since that time, formaldehyde has been shown to be carcinogenic, mutagenic, and teratogenic in experimental animals, and both NIOSH and ACGIH have recommended lower occupational limits on those bases.

The worksheets for acute and chronic toxicity provide a comprehensive profile of the toxic effects documented by NIOSH and ACGIH. Limitations in the data, effects not accounted for, and the rationale behind each limit are also recorded. The data and recommendations provided by each source are not elaborated upon by the Department in the worksheets. The worksheets are used to record only the information and judgements of the sources themselves. Both human and animal data are included and are carefully distinguished from one another. A sample worksheet is provided at the end of this chapter.

3. Scoring Procedure

Scoring for acute and chronic toxicity is based on

qualitative and quantitative indices of toxicity. The quantitative component is reflected in the numerical value of the MAOL, and the qualitative component is represented by an evaluation of the severity or seriousness of those effects associated with exposure to the chemical. Tables II-2 and II-3 present the scoring system for acute and chronic toxicity (gases and particulates), using both the severity factor assigned and the numerical value of the MAOL. The selection of the severity factor is described below.

Based on the acute and chronic health effects documented in the MAOL, a rating factor of 1, 2, or 3 is assigned, representing the severity of those effects, as well as potential reversibility. Evidence of carcinogenicity, mutagenicity, developmental, and reproductive toxicity are not considered in assigning the severity factor since they are evaluated separately (see sections D, E, and F, respectively). In addition, only those effects occurring at levels relevant to the occupational limit are included in the assessment and scoring. Severity factors are assigned as follows:

one point:	Mild or transient irritant effects (e.g. runny nose, eye irritation, headache, coughing).
two points:	Moderate to severe irritant effects; mild to moderate transient systemic effects; effects generally considered to be reversible (e.g. bronchitis; anoxia; incoordination; fatigue; dizziness)
three points:	Irreversible pulmonary effects; serious systemic effects; chronic or persistent effects; cumulative effects, or effects involving multiple sites or organ systems (e.g., emphysema,

TABLE II-2. SCORING MATRIX FOR ACUTE AND CHRONIC TOXICITY (GASES)

Methodology: Combine "Most Appropriate Occupational Limit" (MAOL) with Severity Factor (1-3) to obtain score code (A-E)

MAOL (ppm)	Severity Factor 3	2	1
≤ 2	A	B	C
3 - 24	B	B	C
25 - 100	B	C	D
> 100	C	D	E

TABLE II-3. SCORING MATRIX FOR ACUTE AND CHRONIC TOXICITY (PARTICULATES)

Methodology: Combine "Most Appropriate Occupational Limit" (MAOL) with Severity Factor (1-3) to obtain score code (A-E)

MAOL (mg/m^3)	Severity Factor 3	2	1
≤ 0.25	A	B	C
0.25 - 1	B	B	C
2 - 5	B	C	D
> 5	C	D	E

three points (cont.):	epilepsy, cirrhosis, peripheral nerve damage, liver or kidney effects).

Table II-4 shows the acute and chronic health effects associated with 10 sample chemicals, as well as the severity factor selected for each. Table II-5 presents the toxicity scores for all chemicals evaluated to date.

In using the MAOL as one of two components in scoring for acute/chronic toxicity, CHEM assumes that the MAOL will bear some relationship to the dose levels noted for the acute and/or chronic effects described.

This means that generally speaking, CHEM assumes that lower occupational limits will be associated with chemicals producing toxic effects at lower concentrations, while higher occupational limits will reflect less hazard. However, because effects occurring at the same level may not necessarily represent the same degree of toxicity, severity of effect is also incorporated into the scoring mechanism.

For example, both chloroform and methyl acrylate have MAOLs of 10 ppm, but chloroform receives a score of `B' for acute and chronic toxicity, while methyl acrylate receives a score of 'C'. The difference in scores is a reflection of the difference in the type and severity of effects associated with each chemical. Chloroform is hepatotoxic and fetotoxic, and also exhibits cardiac, central nervous system, and kidney effects; whereas methyl acrylate acts primarily as a local irritant (eyes, nose, throat, lungs). Thus, Chloroform receives a 3-point "severity of effect" classification based on the chronic and potentially irreversible effects documented, and methyl acrylate receives 1 point for its transient irritant effects.

TABLE II-4. SEVERITY FACTORS ASSIGNED TO TEN SAMPLE CHEMICALS

CHEMICAL	ACUTE AND CHRONIC HEALTH EFFECTS*	SEVERITY FACTOR
Ammonia	acute: irritant (skin, eyes, respiratory tract) chronic: respiratory tract irritation, damage; can affect cerebral energy metabolism	2
Benzene	acute: CNS depressant, irritant, narcotic chronic: blood changes, chronic poisoning myelotoxicant	3
1,3-Butadiene	acute: irritant (skin, eyes, nose, throat) chronic: liver effects in experimental animals, none reported in humans	1
Dichloromethane	acute: irritant (skin, eyes, respiratory tract) e.g. COHb formation, angina symptoms, liver, kidney, CNS effects chronic: liver, kidney, CNS effects	3
Epichlorohydrin	acute: irritant (skin, eyes, respiratory tract) severe; e.g., pneumonitis, lung edema; cyanosis, nausea, vomiting, abdominal pain chronic: liver, kidney, lung damage; sensitization	3
Formaldehyde	acute: irritant (skin, eyes, respiratory tract) chronic: allergic dermatitis, eye damage, pneumonitis, pulmonary edema with residual cardiac impairment, sensitization	2

continued . . .

TABLE II-4. SEVERITY FACTORS ASSIGNED FOR TEN SAMPLE CHEMICALS, continued

CHEMICAL	ACUTE AND CHRONIC HEALTH EFFECTS*	SEVERITY FACTOR
Hydrogen Sulfide	acute: irritant (eyes, nose, throat); also edema, asphyxia; headache,dizziness, fatigue, upset stomach,irritability, insomnia, loss of sense of smell chronic: polyneuritis, brain damage, cumulative or chronic irritant effects	2
Methyl Methacrylate	acute: irritant (skin, eyes, nose, throat); e.g. drowsiness chronic: skin irritation	1
Propyl Alcohol	acute: mild irritant (skin, eyes, nose, throat) chronic; none noted	1
Tetrachloro-ethylene	acute: irritant (eyes, nose, throat); e.g., headache, nausea, drowsiness, dizziness, incoordination; liver effects, cardiac effects chronic: skin irritation, liver and kidney damage, neuropathy, CNS effects, cardiac effects	3

* As reported by NIOSH and ACGIH.

TABLE II-5. RESULTS OF SCORING FOR ACUTE AND CHRONIC TOXICITY

continued

CHEMICAL NAME	MOST APPROPRIATE OCCUPATIONAL LEVEL (MAOL)[1]		SOURCE OF MAOL[2]	SEVERITY FACTOR[3]	TOXICITY SCORE[4]
	mg/m^3	ppm			
Acetaldehyde		100	A	1	D
Acetone		250	N	1	E
Acrylonitrile		2	A	3	A
Ammonia		25	A	2	C
Aniline		2	A	3	A
Asbestos		0.1 fibers/cm^3	N	3	A
Benzene		1	N	3	A
Benzyl Chloride		1	A	2	B
Beryllium	0.0005		N	3	A
1,3-Butadiene		10	A	1	C
n-Butyl Alcohol		50	A	2	C
Cadmium	0.01		A	3	A
Calcium Chromate	0.001		N	3	A
Carbon Tetrachloride		5	A	3	B
Chlordane	0.5		A	3	A
Chlorine		0.5	A	2	B
Chlorobenzene		75	A	2	C
Chloroethane		1000	A	1	E
Chloroform		10	A	3	B
Chloroprene		1	N	3	A
Chromic Acid	0.001		N	3	A
Chromium (metal)	0.5		A	2	B
Chromium (VI) compounds	0.001		N	3	A
p-Cresol		2	N	2	B
Cyclohexane		300	A	1	E
o-Dichloro-benzene		50	A	2	C
p-Dichloro-benzene		75	A	2	C
1,2-Dichloro-ethane		10	A	3	B
1,2-Dichloro-ethylene		200	A	1	E
Dichloromethane		50	A	3	B
1,2-Dichloro-propane		75	A	3	B
Diethylamine		10	A	2	B
Di(2-ethylhexyl) phthalate	5	0.3	A	3	A
Dimethyl-formamide		10	A	2	B
1,4-Dioxane		25	A	3	B

continued . . .

TABLE II-5. RESULTS OF SCORING FOR ACUTE AND CHRONIC TOXICITY, continued

CHEMICAL NAME	MOST APPROPRIATE OCCUPATIONAL LEVEL (MAOL)[1] mg/m^3	ppm	SOURCE OF MAOL[2]	SEVERITY FACTOR[3]	TOXICITY SCORE[4]
Diphenyl (biphenyl)		0.2	A	3	A
Diphenylamine	10	1.4	A	3	A
Epichlorohydrin		0.5	N	3	A
Ethanol		1000	A	3	C
Ethyl Acetate		400	A	1	E
Ethyl Acrylate		5	A	2	B
Ethyl Benzene		100	A	1	D
Ethylene Glycol		50	A	2	D
Ethyl Ether		400	A	2	D
Fluoride	2.5		A	3	B
Formaldehyde		1	A	2	B
Heptachlor	0.5		A	3	B
Hexachlorocyclo-pentadiene		0.01	A	3	A
Hexachloroethane		1	A	2	B
Hexachlorophene	No Occupational Limit		-	-	-
2-Hexanone	4	0.98	N	2	B
Hydrazine		0.1	A	3	A
Hydrogen Chloride	5		A	2	B
Hydrogen Fluoride	2.5		A	3	B
Hydrogen Sulfide		10	A	2	B
Isoamyl Acetate	100		A	1	D
Isobutyl Acetate		150	A	1	E
Isobutyl Alcohol	50	2.5	N	1	D
Isopropyl Acetate		250	A	1	E
Lead		0.05	0	3	A
Lead Subacetate		0.05	0	3	A
Lindane		0.04	A	3	A
Maleic Anhydride		0.25	A	2	B
Methanol		200	A	3	C
2-Methoxy-ethanol		5	A	3	B
Methyl Acrylate		10	A	1	C
Methyl Bromide		5	A	3	B
Methyl ethyl ketone		200	A	3	C
Methyl isobutyl ketone		50	A	3	B

continued .

TABLE II-5. RESULTS OF SCORING FOR ACUTE AND CHRONIC TOXICITY, continued

CHEMICAL NAME	MOST APPROPRIATE OCCUPATIONAL LEVEL (MAOL)[1] mg/m^3 ppm	SOURCE OF MAOL[2]	SEVERITY FACTOR[3]	TOXICITY SCORE[4]
Methyl Methacrylate	100	A	1	D
Mirex	No Occupational Limit	-	-	-
Naphthalene	10	A	2	B
Nickel	1	A	3	B
Nickel Oxide	1	A	3	B
Nitrobenzene	1	A	2	B
Pentachloro-phenol	0.05	A	3	A
Phenol	5	A	3	B
Phosphoric Acid	1 -	A	2	B
Phthalic Anhydride	1	A	2	B
PCBs	0.001	N	3	A
Propyl Alcohol	200	A	1	E
Propylene Oxide	20	A	2	B
Resorcinol	10	A	1	C
Selenium	0.2	A	3	A
Selenium Sulfide	0.2	A	3	A
Styrene	50	N	3	B
Sulfuric Acid	1	A	2	B
1,1,2,2-Tetra-chloro-1,2-di-fluoroethane	500	A	2	D
1,1,2,2-Tetra-chloroethane	1	A	3	A
Tetrachloro-ethylene	50	A	3	B
Tetrahydrofuran	200	A	2	D
Toluene	100	A	2	C
Toluene diiso-cyanate	0.005	A	3	A
o-Toluidine	2	A	. 2	B
1,1,1-Trichloro-ethane	350	A	2	D
1,1,2-Trichloro-ethane	10 .	A	3	B
Trichloro-ethylene	25	N	3	B
2,4,6-Trichloro-phenol	No Occupational Limit	-	-	-
Triethylamine	10	A	2	B

continued

TABLE II-5. RESULTS OF SCORING FOR ACUTE AND CHRONIC TOXICITY, continued

CHEMICAL NAME	MOST APPROPRIATE OCCUPATIONAL LEVEL (MAOL)[1] mg/m^3	ppm	SOURCE OF MAOL[2]	SEVERITY FACTOR[3]	TOXICITY SCORE[4]
Vanadium	1		N	2	B
Vanadium pentoxide		0.05	A	2	B
Vinyl Acetate		4	N	2	B
Vinyl Chloride		5	A	3	B
Vinylidene Chloride		5	A	2	B
Xylenes		100	A	2	C

1) Occupational limits are usually expressed in parts per million (ppm) for gases and in mg/m for particulates.

2) Abbreviations used: A - ACGIH; N - NIOSH; 0 - OSHA.

3) See p. 90.

4) Assigned according to matrix, Tables II-2 amd II-3.

Since scores are based on the MAOL as well as severity of effect, new occupational data or changing occupational limits could result in a change of score.

Toxicity updates and revised occupational recommendations published by OSHA, NIOSH, and ACGIH will therefore be reviewed periodically, so that worksheets and scores will reflect the best current information on each chemical. New data bearing on acute or chronic toxicity from sources other than NIOSH, ACGIH, and OSHA will be evaluated for validity and relevance on a case-by-case basis and may be used to supplement the occupational data if warranted. Cases where this would be necessary might include the discovery of a previously unknown or unaccounted for, but serious health effect, or the availability of human evidence where only animal data existed when the occupational limit was developed. Such information would affect only the background documentation and severity of effect component of scoring, and not the MAOL itself (unless the occupational limits themselves are changed as well).

When no occupational limit has been developed for an air contaminant identified in Massachusetts the Department will still have the responsibility to develop an allowable ambient limit. The Department is working on the procedures to be used in that case. The current plan is to use EPA inhalation Reference Doses when these become available.

4. Summary

Acute/chronic toxicity is one of the four health effects categories used in CHEM. All adverse health effects are included in this category with the exception of carcinogenicity, mutagenicity, and developmental/reproductive toxicity, which are evaluated

separately.

CHEM relies primarily on occupational literature to assess acute and chronic toxicity. Documentation for occupational limits set by NIOSH, ACGIH, and OSHA is used to compile health data and to derive a score for each chemical. Scoring is based both on the MAOL selected and the severity of the effects documented. Thus, a chemical with a low MAOL and/or severe health effects (e.g., chronic liver damage) receives a higher score than a chemical with a high MAOL and/or less serious health effects (e.g., local irritation). By using both components for scoring, the acute/chronic toxicity assessment is able to differentiate chemicals which have similar occupational limits but very different effects, and thus, is sensitive to the relative hazard posed by each chemical.

5. References for Acute and Chronic Toxicity

American Conference for Governmental Industrial Hygienists (ACGIH). 1986. Documentation of the Threshold Limit Values. Fifth Edition. ACGIH, Cincinnati, Ohio.

American National Standards Institute (ANSI). 1967. U.S.A. Standard for Acceptable Concentrations of Formaldehyde. ANSI Standard Z37.16 - 1967.

National Institute for Occupational Safety and Health (NIOSH). U.S. Department of Health, Education and Welfare. 1980. Criteria for a recommended standard....occupational exposure to hydrogen sulfide. Washington, D.C.

National Institute for Occupational Safety and Health (NIOSH). 1984. U.S. Department of Health and Human Services. 1,3-Butadiene. NIOSH Current Intelligence Bulletin, 2/9/84. DHHS Publication No. 84-105.

National Institute for Occupational Safety and Health/Occupational Safety and Health Administration (NIOSH/OSHA). 1981. Occupational Health Guidelines for Chemicals Vol. I and II. U.S. Department of Health and Human Services. U.S. DHHS Pub. No. 81 - 123.

6. Acute and Chronic Toxicity Worksheets

As described, the scoring procedure incorporates a matrix system in which both the occupational levels and the assigned severity factor are considered (Table II-3). Inclusion of the severity factor is important because it enables the system to differentiate between various types of effects among chemicals having similar occupational levels, and is responsive to the rationale behind a given recommendation. For example, one level may be low because of its local irritant qualities, while another may have been set at a similar level to protect against hematopoietic effects or liver damage. Standardized worksheets have been designed to summarize the toxicity information provided by the occupational sources as completely as possible. Worksheet headings are described below. All data are for humans, unless otherwise noted. Thus animal and human data are clearly distinguished. Animal species are identified whenever they have been identified by the source. All data on worksheets are summarized directly from the sources referenced, frequently including quoted material. All comments are those of the data sources.

Column 1 - Occupational Group: NIOSH, ACGIH, OSHA. The groups are divided into three sections, and data from each source are recorded.

Column 2 - Occupational Level: The occupational levels recommended by NIOSH, ACGIH and OSHA are recorded.

Column 3 - Principal Action: This section describes the nature of predominant effects, abbreviated as follows:

I	=	irritant	Ter	=	teratogen
C	=	carcinogen	R	=	reproductive effects
T	=	systemic toxin	M	=	mutagen

Column 4 - Toxicity: LD_{50}s, and upper limits of toxicity or lethality are recorded in this column for both animals and humans, as available.

Columns 5-13 - Health Effects: Health effects are subdivided by anatomical site of action, including skin, eyes, respiratory tract (RT), liver and kidney, and nervous system. A miscellaneous category ("other") is included for less common effects such as hematopoietic effects, or information about effects described in another subdivision when additional space or description is needed. Carcinogenic, mutagenic, developmental and reproductive effects are noted as well, but evaluated separately. NIOSH data are recorded in the same format in which they are reported - they are divided into short-term and long-term exposures. Health effects are noted by a check mark (%) under the appropriate column and are briefly summarized. ACGIH data, if already documented in the NIOSH section, will be indicated: "same as NIOSH". Effects which differ from those reported by NIOSH are appropriately recorded in the ACGIH section.

Columns 14-15 - Data: These columns describe the lowest effect levels reported for various effects, and characterize the data used as human (H) or animal (A), arranged in order of predominance. Finally, the adequacy of the data is noted, toxicity information based primarily on acute or high

level exposures (as opposed to chronic exposures at lower levels) is noted, and/or when the evaluation is based on very little data.

Column 16 - Comments: This section is provided in order to record additional information, including the rationale behind the recommended level, limitations in the level, or other comments by the source.

ACUTE/CHRONIC TOXICITY WORKSHEET

FOR:
CAS CODE:
DATE:

SEVERITY FACTOR:
MAOL:
SCORE:

OCCUPATIONAL LIMITS

	NIOSH	ACGIH
PRINCIPAL ACTION		
TOXICITY		

II. HEALTH EFFECTS

	SHORT-TIME EXPOSURE	LONG TERM EFFECTS	COMBINED SHORT AND LONG TERM EXPOSURES
SKIN			
EYES			
RESPIRATORY TRACT			
LIVER & KIDNEY			
NERVOUS SYSTEM			
OTHER			
CARCINOGEN MUTAGEN			
DEVELOPMENTAL REPRODUCTIVE			

DATA

LOWEST EFFECT LEVEL REPORTED			
ANIMAL OR HUMAN			
COMMENTS			
REFERENCES			

D. Carcinogenicity

1. Introduction

A carcinogen is defined in CHEM as any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant primary neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental species. Also included is any substance which is metabolized into one or more carcinogens. "Benign" neoplasms are included when they are observed in conjunction with malignant lesions, when they are classified as an earlier stage of malignancy, or when malignancy cannot be definitively ruled out (NCAB, 1977; USEPA, 1984e). Metabolites are included in the definition so that carcinogenic hazards can be fully addressed, including those posed by co-carcinogens and pro-carcinogens (chemicals which are activated in the metabolic process). Short-term mutagenicity screening assays are not utilized in the assessment of carcinogenicity since they are evaluated separately in the mutagenicity section.

As noted earlier, definitions have been developed to be used within the context of CHEM. However, it should be emphasized that expert working groups (e.g., IARC, EPA, NTP) review the data submitted by qualified pathologists in order to classify tumors. Since the Department is in no way involved in this process, and instead relies on the judgement of the pathologists or groups cited, tumors are actually identified and classified according to the expressed opinions of the sources cited and not the Department. Any areas of disagreement or uncertainty among the sources used are documented and referenced in CHEM. When new data become available which have not yet been

reviewed by IARC, EPA-CAG, or NTP, the Department will evaluate these on a case-by-case basis, as described in sub-section 2 below.

The purpose of the carcinogenicity assessment is to evaluate the relative carcinogenic hazard or degree of concern for carcinogenicity associated with a given chemical, represented by a letter score (A-F, ND) for each chemical. Whenever possible, direct human evidence is utilized in the assessment of carcinogenic hazard for humans. However, conclusive human evidence exists for very few chemicals and when it does not exist, the scoring methodology employs a combination of qualitative and quantitative information from animal studies.

Qualitative information provides an indication of the overall certainty that a chemical is linked to a carcinogenic response. The Department generally relies on information from IARC, EPA, NTP, and others for such judgements and the evidence is used to assign each chemical to a weight-of-evidence category as described below. The weight-of-evidence is used as a major component in scoring.

Quantitative information provides an estimation of the magnitude of the risk which results from exposure to a chemical. The risk is expressed as a unit risk value representing the excess lifetime cancer risk which results from continuous lifetime human exposure to 1 ug/m^3 of a chemical. Unit risk values used have been calculated by the Department, by the Carcinogen Assessment Group (CAG) of the EPA, or by other agencies. The Department will rely primarily on the CAG for quantitative assessments and will review other sources when available. When no unit risk values are available from other sources, or the Department does not agree with those values available, the Department

will calculate the unit risk value. The methods used by the Department to calculate unit risks are outlined below and described in detail in Appendix D.

2. Data Sources

As indicated in Table II-1, CHEM relies primarily on the following data sources in evaluating carcinogenicity:

IARC (International Agency for Research on Cancer, World Health Organization) - "IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans", published by the Ad Hoc Working Groups - all volumes and supplements. The available data (human and animal) are reviewed and evaluated, and a weight-of-evidence category is assigned for each chemical by the Working Group.

NTP (National Toxicology Program, of the U.S. Department of Health and Human Services) - In July of 1981, the Carcinogenesis Bioassay Testing Program of the National Cancer Institute (NCI) was transferred to the National Institute of Environmental Health Sciences (NIEHS). NTP provides detailed reports of carcinogenicity bioassays in experimental animals.

CAG (Carcinogen Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, U.S. EPA) - The CAG assigns a weight-of-evidence classification to each chemical from both human and animal data, and calculates unit risk values for purposes of cancer risk assessment (Anderson, 1985). The CAG serves as the primary source of unit risk values to the Department.

Other

- o Quantitative and qualitative carcinogenicity assessments conducted by other EPA offices (e.g., Office of Toxic Substances), other state agencies (e.g., California DHS), or private parties (e.g., Gold et al.) will be reviewed when they are available.

- o Primary science literature is reviewed and may be used to assess carcinogenicity when data are unavailable from the sources listed above, or when new evidence is published. Primary literature sources may be used in both the quantitative and qualitative assessments. In this case, the Department uses established protocols to judge the validity and reliability of the data and studies used. These protocols have been thoroughly described elsewhere (USEPA, 1983a; USEPA, 1983b; USEPA, 1984e; USFDA, 1982; IRLG, 1979; NTP, 1984; OSTP, 1984; Clayson et al., 1983; Feron et al., 1980; Mantel, 1980), and are detailed in Appendix D.

3. Evaluating Carcinogenicity

In CHEM, the evaluation of carcinogenic hazard involves two components: the qualitative evidence that a given chemical substance is likely to be a human carcinogen, and the quantitative evidence on the inherent potency of the substance. The qualitative and quantitative data are evaluated independently, and then combined to produce an overall score indicating the degree of carcinogenic hazard of the chemical.

a. Qualitative Evidence

The evaluation of carcinogenicity involves the review of a wide array of data, including clinical, occupational,

and epidemiological evidence, as well as bioassays in experimental animals. Conclusive evidence of carcinogenicity from human studies exists for only a few chemicals. Epidemiology has been used for identifying cancer distribution in exposed populations and for detecting increases in the rates of comparatively rare tumor-types. The lack of conclusive epidemiological data demonstrating carcinogenic effects of chemical exposures to many chemicals is a result of the relative insensitivity of epidemiological methods, the difficulty in eliminating confounding effects, and the difficulty in identifying sufficiently large or well-defined study populations (see part II section A). Nevertheless, increased cancer rates, and detection of cancer incidence, even in small populations, are of great concern to the regulatory agencies responsible for protecting public health. Until more human studies are available for chemicals of concern, the Department must rely on estimations of carcinogenic hazard from animal data, despite the uncertainties involved.

The use of animal data in the assessment of human carcinogenicity is widely considered to be a reasonable approach. This interpretation is supported by experimental evidence and by various theories of cancer causation. Almost all known human carcinogens are also carcinogenic in animals when adequately tested (Tomatis, 1979; IARC, 1980) and most chemicals that are carcinogenic in one species are carcinogenic in other species when adequately tested (Tomatis et al., 1978; Purchase, 1980). The theories regarding the mechanisms of chemical carcinogenesis also would predict similarities in the mechanisms in different species (CalDHS, 1985). In the assessment of carcinogenic hazard, the Department will adopt the IARC position that "in the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is

sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk for humans" (IARC, 1979).

Interpretation of animal carcinogenicity tests requires a series of simplifying assumptions. Toxicological data on interspecies differences in absorption, metabolism, distribution, and excretion are rarely available, and are still subject to variations with age, sex, health, individual traits, etc. In addition, carcinogenicity testing is carried out using various routes of exposure, often feed or gavage. Whether and how mechanisms or effects may be influenced by differences in route of exposure, and the "first pass" effect is usually uncertain. The task would be less formidable if, as a result of an animal bioassay, chemicals could be neatly categorized as either carcinogens or non-carcinogens in humans. Unfortunately, this is not the case, and the potential for carcinogenicity is assumed on the basis of positive results in animals. The Department therefore takes the position that, for qualitative interpretation of animal studies, it is reasonable to assume that route-to-route,species-to-species, and high-dose to low-dose extrapolations are valid. The use of these assumptions in the quantitative dose-response assessment of carcinogens is discussed in detail in Appendix D.

CHEM uses weight-of-evidence categories adapted from the EPA (EPA, 1986). Human and animal data are evaluated independently and classified as follows: Sufficient, Limited, Inadequate, No Data, or No Evidence. The criteria for each classification of human and animal data are shown in Table II-6. The overall weight-of-evidence for human carcinogenicity is then based on the combination of the human and animal data. The criteria for classification are listed in Table II-7a. Table II-7b provides the same

TABLE II-6. WEIGHT-OF-EVIDENCE CRITERIA FOR HUMAN AND ANIMAL DATA

Category	Description of Evidence
Human Evidence	
Sufficient	evidence indicates a causal relationship between- the agent and human cancer.
Limited	evidence indicates that a causal relationship is credible, but that alternative explanations, such as chance, bias, or confounding could not be adequately excluded.
Inadequate	(a) there were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding and therefore a causal interpretation is not credible.
No Data	data are not available.
No Evidence	no association between exposure and an increased risk of cancer in well designed and well conducted independent analytical epidemiological studies.
Animal Evidence	
Sufficient	indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset.

continued

TABLE II-6. WEIGHT-OF-EVIDENCE CRITERIA FOR HUMAN AND ANIMAL DATA, continued

Category	Description of Evidence
Animal Evidence(cont.)	
Limited	the data suggest a carcinogenic effect, but are limited because: (a) the studies involve a single species, strain, or experiment and do not meet criteria for sufficient evidence; (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure- to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.
Inadequate	indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of carcinogenic effect.
No Data	data are not available.
No Evidence	there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies indifferent species.

TABLE II-7a. CATEGORIZATION OF OVERALL WEIGHT-OF-EVIDENCE FOR HUMAN CARCINOGENICITY (ADAPTED FROM EPA, 1986)

Category	Description of Evidence
Group A - Human Carcinogen	sufficient evidence from epidemiological studies to support a causal association between exposure to the agent and cancer (Sufficient Human Evidence)
Group B - Probable Human Carcinogen	
B1	limited human evidence and any animal evidence
B2	sufficient animal evidence and no or inadequate human evidence
Group C - Possible Human Carcinogen	limited animal evidence and no or inadequate human evidence '
Group D-Not Classifiable as to Human Carcinogenicity	inadequate animal and human data
Group E - Inconclusive	Available evidence cannot be classified as clearly showing the absence or presence of a carcinogenic effect because of major limitations in qualitative and quantitative data. However, the quantitative data are sufficient to estimate the upper bound of potency at the 95% confidence limit.
Group F - Non-positive	adequate evidence suggesting lack of carcinogenicity from human and animal studies
No Data	Chemical has not been tested, no data available

TABLE II-7b. CHEM ASSIGNMENT OF SUBSTANCES TO CARCINOGENICITY CATEGORY BASED ON WEIGHT-OF-EVIDENCE FROM HUMAN AND ANIMAL STUDIES

Weight of Animal Evidence	Weight of Human Evidence					
	Sufficient	Limited	Inadequate	Inconclusive	Nonpositive	No Data
Sufficient	Group A	Group Bl	Group B2	Group B2	Group B2	Group B2
Limited	Group A	Group Bl	Group C	Group C	Group C	Group C
Inadequate	Group A	Group Bl	Group D	Group D	Group D	Group D
Inconclusive	Group A	Group Bl	Group E	Group E	Group E	Group E
Nonpositive	Group A	*Group Bl or B2	*Group D or F	*Group D or E	Group F	*Group D or F
No Data	Group A	Group Bl	Group D	*Group D or E	*Group D or F	ND

* = case-by-case assessment required

information in a matrix, using all possible combinations of human and animal evidence. The CHEM weight-of-evidence categories are consistent with these adopted by the Massachusetts Department of Public Health, Draft Carcinogen Policy, 1988.

Human evidence is accorded the greatest "weight" in this system, so that chemicals with positive human evidence of carcinogenicity rank higher than those with only animal evidence. Chemicals with Sufficient human evidence are classified in Group A - Carcinogenic to Humans. Likewise, positive results in two or more species of experimental animals are given more weight than positive results in only one species. Chemicals causing cancer in two animal species (Sufficient animal evidence) are classified in Group B - Probable Human Carcinogen, while positive results in only a single animal species without human evidence (Limited animal evidence) place the chemical in Group C - Possible Human Carcinogen. The EPA weight-of-evidence classification is described in detail in the EPA Guidelines for Carcinogen Risk Assessment (EPA, 1986). CHEM weight-of-evidence categories differ from the EPA in that CHEM distinguishes one additional category - Group E - "Inconclusive". Inconclusive evidence refers to studies which suggest a carcinogenic effect but have major qualitative or quantitative limitations and cannot be clearly interpreted. In these cases it may be possible to compute an upper bound unit risk for scoring purposes, but the data cannot be interpreted as clearly showing a carcinogic response. When the data are so limited that no upper bound can be calculated, the chemical is categorized as Group D - Not Classifiable as to Human Carcinogenicity. This is the only distinction between Group D ("Not Classifiable") and Group E ("Inconclusive"). This category, useful for informational purposes, provides an estimate that the potency of the

chemical is less than some value. A case in point is the bioassay for 1,1,1-trichloroethane (NCI, 1977). Because of high mortality from chronic murine pneumonia, the increased incidence of tumors in exposed versus control animals lacked statistical significance. Thus, NTP considered the results insufficient for assessing the carcinogenic potential of 1,1,1-trichloroethane, because the shortened lifespan may have prevented the animals from developing tumors (NCI, 1977).

b. Quantitative Evidence

In addition to describing how likely it is that a substance will cause human cancer, it is important to estimate the magnitude of that effect. Thus CHEM supplements the qualitative assessment with a quantitative assessment of carcinogenic risk. The result of a quantitative dose-response assessment is a measure of the carcinogenic potency or unit risk. The potency is the slope of the dose-response curve (at low doses) and the unit risk is the estimate of the risk due to a defined level of exposure. Carcinogenic potency and unit risk values are obtained from the CAG whenever they are available, or are obtained from other sources, or are calculated by the Department using data from NTP bioassays or from the primary literature. The unit risk values obtained from CAG or derived from NTP data express the lifetime excess cancer risk for humans exposed continuously for a lifetime to 1 ug/m^3 of the chemical in air. Unit risk estimates are then categorized into broad groupings established by the Department for scoring purposes. The groupings are analogous to very high, high, moderate, and low carcinogenic potencies. The ranges of unit risk values established for scoring are:

Unit Risk Range	Potency
o $10^{-3} \leq$ unit risk	Very High
o $10^{-4} \leq$ unit risk $<10^{-3}$	High
o $10^{-6} \leq$ unit risk $<10^{-4}$	Moderate
o unit risk $<10^{-6}$	Low

The Department will rely to the greatest extent possible on the quantitative carcinogenicity assessments published by the EPA-CAG. However, the CAG has performed this analysis for only 55 chemicals to date. The number of chemicals for which there are dose-response assessments available from CAG is small compared with the number of chemicals for which there are adequate data available for calculation of carcinogenic potency. In order to fulfill its objective of using the most current data for health effects assessment, the Department has developed a procedure for quantitative dose-response assessment. This procedure is described in detail in Appendix D.

The Department's procedure was designed to be consistent with the need to perform assessments in a timely manner and to be consistent with the best available current scientific thinking on the subject. The guidelines published by the EPA (1986) and the California Department of Health Services (1985) served as the basis of the Department's procedure.

The calculation of cancer unit risk values is a complex procedure and requires a large number of individual decisions and calculations. The discussion in Appendix D is intended to specify the exact methods that are used by the Department for quantitative dose-response assessment. The rationale and intent on which these procedures are based are also described in the Appendix. The procedures are outlined very briefly here and the reader is referred to Appendix D

for further information. The Department will generally rely on studies from the NTP carcinogenesis bioassay program, but may use other primary sources if necessary.

In order to compensate for the necessarily small study size of experimental animal tests, and thus to provide more adequate statistical power, experimental doses are generally increased by many orders of magnitude over anticipated human exposure levels, usually as close as possible to the animals' maximum tolerated dose (MTD). Since it is not possible to directly measure carcinogenic response at very low doses, either in animal experiments or in epidemiological studies, a number of mathematical models have been developed to extrapolate from high dose to low dose exposures. A major limitation in these models is the fact that their assumptions cannot be tested directly in animals or humans. Different models lead to estimates of risk at low doses which may differ by several orders of magnitude, even though they fit the experimental data equally well (NCAB, 1983a). The model selected is therefore of great significance, both from a scientific and from a regulatory standpoint.

Unfortunately, data pertaining to mechanisms of action, pharmacokinetics, and other biological dynamics are rarely available. Until the mechanisms of carcinogenesis are better understood, no single model can be identified which will be appropriate in all cases, and the regulator must therefore make a judgment on the basis of the best available data and current scientific opinion.

The linearized multistage model is consistent with some epidemiological data, animal studies, and in vitro studies of neoplastic transformation of cells (USEPA, 1980a), and is the model currently used by EPA. The unit risk is

calculated using the linearized multistage model. This model incorporates the assumptions of no threshold and linearity at low doses. Experimental doses are scaled to humans based on surface area. The dose calculation assumes that direct route-to-route, species-to-species, and high-dose to low-dose extrapolation are valid in most cases. Dose-response assessments will be done for tumor sites which show a statistically significant increase in malignant (or combined malignant and benign) tumors, preferably in studies employing at least two dosed groups. Selection of the most appropriate site for dose-response assessment when there is more than one significant site is based on the criteria provided in Appendix D. When a chemical is in weight-of-evidence category Group C - Possible Human Carcinogen, the adequacy of the data for dose-response assessment will also be judged on the basis of the criteria discussed in Appendix D. Where the data produced are judged to be inadequate for dose-response assessment, the unit risk value will be used for scoring but will not be used for quantitative risk assessment. This means that bioassay data exist (e.g., ethyl acrylate), and it is mathematically possible to compute a unit risk value, but the data are considered toxicologically inadequate to derive AALs.

The procedure outlined above will serve as a standard approach to dose-response assessment. An expanded assessment may be performed which could include use of a different model, use of studies from primary literature, or analysis using pharmacokinetic data to define route-, species-, or dose-related effects on carcinogenic potency. An expanded assessment involves a more thorough use of the primary literature and will be done in cases in which data are available and the Department decides that this information is necessary and sufficient.

4. Scoring for Carcinogenicity

Experimental data indicate that carcinogens vary widely in potency. CAG developed a potency index for 53 suspect human carcinogens, demonstrating potency values ranging over 10 orders of magnitude (USEPA, 1984a). Table II-8 shows the unit risk values calculated by EPA for 20 selected compounds, ranging over eight orders of magnitude. A similar range was found in a second study on the relative potency of 10 carcinogenic substances, indicating a potency range of 10 orders of magnitude for chemicals tested by NTP (Zeise, 1984). Because of such variability, a relative potency estimation is used in the methodology to compare the potential cancer risks associated with chronic exposure to identified carcinogens (NCAB, 1983b; NAS, 1983). However, rather than assigning a specific unit risk to a specific score value, ranges of unit risk are used and scores are modified on the basis of weight-of-evidence.

Table II-9 presents the way in which weight-of-evidence and unit risk are combined to produce an overall score for carcinogenicity. It should be noted that the scoring procedure distinguishes between positive data (letter codes A, B, C, and D) and equivocal, non-positive, or inadequate data (E, F, and ND). As shown in Table II-9, the final score for carcinogenicity incorporates both the quantitative and qualitative data, but attaches greater significance to the qualitative evidence. Thus, the weight-of-evidence determines the minimum score.

For example, a chemical classified as a "Probable Human Carcinogen" cannot receive a score lower than 'C', regardless of the unit risk value. This means that when there is compelling evidence of carcinogenicity in animals, human exposure to the chemical warrants concern even if

TABLE II-8. UPPER-BOUND UNIT RISK CALCULATIONS FOR TWENTY SUSPECTED CARCINOGENIC AIR POLLUTANTS*

Chemical	Upper-Bound Unit Risk Estimates**
Acrylonitrile	6.8×10^{-5}
Allyl Chloride	5.5×10^{-8}
Arsenic	3.4×10^{-3}
Benzene	8.1×10^{-6}
Beryllium	2.4×10^{-3}
Diethylnitrosamine (DEN)	1.6×10^{-2}
Dimethylnitrosamine (DMN)	5.4×10^{-3}
Dioxin (2,3,7,8-Tetrachloro-)	1
Ethylene Dibromide	2.7×10^{-4}
Ethylene Dichloride	2.6×10^{-5}
Ethylene Oxide	1.8×10^{-4}
Formaldehyde	1.3×10^{-5}
Manganese	3.5×10^{-4}
Nickel	1.8×10^{-3}
N-Nitroso-N-Ethylurea (NEU)	1.2×10^{-2}
N-Nitroso-N-Methylurea (NRU)	6.7×10^{-1}
Perchloroethylene	4.8×10^{-7}
Trichloroethylene	1.3×10^{-6}
Vinyl Chloride	2.6×10^{-6}
Vinylidene Chloride	5.0×10^{-5}

* From U.S. Environmental Protection Agency, Carcinogen Assessment Group Reports (EPA 1976-1986). These calculations are periodically revised as new data become available.

** Unit risk is excess lifetime risk associated with breathing 1 $\mu g/m^3$ of the chemical in air over a 70-year life-span for a 70 kg person.

TABLE II-9. SCORING MATRIX FOR CARCINOGENICITY

Weight-of Evidence Category	Unit Risk (UR) Estimate	CHEM Letter Code Score
Human Carcinogen (EPA Group A)	Any	A
Probable Human Carcinogen (EPA Group Bl or Group B2)	UR $\geq 1 \times 10^{-4}$	
Possible Human Carcinogen (EPA Group C)	UR $\geq 1 \times 10^{-3}$	
Probable Human Carcinogen (EPA Group Bl)	$1x10^{-4} > UR$	B
Probable Human Carcinogen (EPA Group B2)	$1x10^{-4} > UR \geq 1 x10^{-6}$	
Possible Human Carcinogen (EPA Group C)	$1x10^{-3} > UR \geq 1x10^{-4}$	
Probable Human Carcinogen (EPA Group B2)	$1x10^{-6} > UR$	C
Possible Human Carcinogen (EPA Group C)	$1x10^{-4} > UR \geq 1x10^{-6}$	
Possible Human Carcinogen (EPA Group C)	$1x10^{-6} > UR$	D
Inconclusive (Group E)	Not used for scoring	E
Non-Positive (Group F)	Not used for scoring	F
Inadequate or No data (EPA Group D)	Not available	ND

1. As described in Tables II-6 and ll-7a. Letters in parentheses indicate the EPA letter designation of the weight-of-evidence group. Letters designating EPA weight of-evidence should NOT be confused with letters designating CHEM score shown in the last column.

potency appears to be low. Likewise, when a chemical is classified as a "Human Carcinogen", no consideration is given to potency and the chemical receives a score of 'A'. The scoring system is set up in such a way that the final score is conceptually analogous to an arithmetic product of qualitative weight-of-evidence for carcinogenicity, and a quantitative risk value. The scoring system represents a mixture of two possible approaches to assessing carcinogens; one which emphasizes those chemicals which are associated with higher cancer risk, and the other which ranks highest those most likely to produce cancer in humans. By using this combined approach it is ensured that a chemical which appears hazardous on either count (potency or weight-of-evidence) is not missed.

Thus, as the evidence of carcinogenicity weakens, a higher unit risk value is required for any given score. For example, a substance which is a Probable Human Carcinogen requires a potency value corresponding to a unit risk of 10^{-4} to 10^{-6} to receive a score of 'B'. In order to receive the same score of 'B' a substance considered a Possible Human Carcinogen needs a unit risk value of 10^{-4} or greater. This provides a reasonable balance between qualitative and quantitative evidence, while providing that a less studied chemical will not be overlooked if it has high potency. If quantitative data are unavailable, scoring is based on weight-of-evidence alone, signified by an asterisk (*) following the score.

It should be noted that the EPA uses letters to designate weight-of-evidence categories such that Group A refers to Human Carcinogens, Group B refers to Probable Human Carcinogens, Group C refers to Possible Human Carcinogen, etc. (see Table II-7a). The EPA weight-of-evidence categories are often referred to by

letter designations alone. These should not be confused with the letter scores in CHEM, (e.g., EPA weight-of-evidence "Group B" versus CHEM score `B'). In order to avoid confusion, the Department will refer to the weight-of-evidence classification by the full title, e.g., Probable Human Carcinogen, Possible Human Carcinogen, etc.

5. Results and Discussion

Results of the assessment and ranking of the 105 evaluated substances are shown in Table II-10. The carcinogenicity scores represent overall carcinogenic hazard and can be useful for relative ranking of substances. Of those 105 substances, 53 are classified as "No Data". The remaining 52 are stratified as follows: 3F, 3E, 0D, 11C, 23B and 12A. Thus, among chemicals with at least some positive evidence of carcinogenicity, score B, which could be described as moderately high in hazard, is most commonly represented. No practical distinction is made between individual substances within each category. Instead the relatively greater hazard of one group over the other is emphasized.

An important feature of this system is its utilization of the full range of available data, and its inclusion of both qualitative and quantitative aspects of assessment. Further, the system highlights the uncertainty inherent in evaluating the carcinogenicity of substances. No attempt is made to establish separate categories of carcinogens and "noncarcinogens". Rather, the emphasis is on utilizing and organizing all the available information into hazard categories A through F without overemphasizing either the quantitative or qualitative components of risk assessment. The information obtained through the carcinogenicity assessment is important, because the data generated will be

TABLE II-10. RESULTS OF SCORING FOR CARCINOGENICITY

CHEMICAL NAME	WEIGHT OF EVIDENCE[a]	UNIT RISK[b] $(\mu g/m^3)^{-1}$	SCORE[c]
Acetaldehyde	Probable (B2)	2.2×10^{-6}	B
Acetone	No Data	---------	ND
Acrylonitrile	Human Carcinogen	6.8×10^{-5}	A
Ammonia	No Data		ND
Aniline	Possible	7.09×10^{-6}	C
Asbestos	Human Carcinogen	7.6×10^{-3}	A
Benzene	Human Carcinogen	8.1×10^{-6}	A
Benzyl Chloride	Possible	N.A[e]	C*
Beryllium	Probable (B2)	2.4×10^{-3}	A
1,3-Butadiene	Probable (B2)	2.9×10^{-4}	A
n-Butyl Alcohol	No Data		ND
Cadmium	Probable (Bl)	1.8×10^{-3}	A
Calcium Chromate	Human Carcinogen	$1:2 \times 10^{-2}$	A
Carbon Tetrachloride	Probable (B2)	1.5×10^{-5}	B
Chlordane	Probable (B2)	3.7×10^{-5}	B
Chlorine	No Data		ND
Chlorobenzene	Possible	(5.4×10^{-6})[d]	C
Chloroethane	No Data		ND
Chloroform	Probable (B2)	2.4×10^{-5}	B
Chloroprene	Inadequate		ND
Chromic Acid	Probable (B1)	1.2×10^{-2}	A
Chromium (metal)	Inadequate		ND
Chromium (VI) Compounds	Human Carcinogen	1.2×10^{-2}	A
p-Cresol	No Data		ND
Cyclohexane	No Data		ND
o-Dichlorobenzene	Non Positive		F
p-Dichlorobenzene	Probable (B2)	5.7×10^{-6}	B
1,2-Dichloroethane	Probable (B2)	2.6×10^{-5}	B
1,2-Dichloroethylene	No Data		ND
Dichloromethane	Probable (B2)	4.09×10^{-6}	B
1,2-Dichloropropane	Possible	1.9×10^{-5}	C
Diethylamine	No Data		ND
Di(2-ethylhexyl) - pthalate	Probable (B2)	1.3×10^{-6}	B
Dimethylformamide	No Data		ND
1,4-Dioxane	Probable (B2)	4.11×10^{-6}	B
Diphenyl (biphenyl)	Inadequate		ND
Diphenylamine	Inadequate		ND
Epichlorohydrin	Probable (B2)	1.2×10^{-6}	B
Ethanol	No Data		ND
Ethyl Acetate	No Data		ND
Ethyl Acrylate	Probable (B2)	N.A.[d]	B*
Ethyl Benzene	No Data		ND
Ethylene Glycol	No Data		ND
Ethyl Ether	No Data		ND
Fluoride	Inadequate		ND
Formaldehyde	Probable (B1)	1.3×10^{-5}	B
Heptachlor	Probable (B2)	1.3×10^{-3}	A

continued . . .

TABLE II-10. RESULTS OF SCORING FOR CARCINOGENICITY

continued

CHEMICAL NAME	WEIGHT OF EVIDENCE[a]	UNIT RISK[b] ($\mu g/m^3)^{-1}$	SCORE[c]
Hexachlorocyclo-pentadiene	No Data	----------	ND
Hexachloroethane	Possible	4.0×10^{-6}	C
Hexachlorophene	Inadequate	----------	ND
2-Hexanone	No Data	----------	ND
Hydrazine	Probable (B2)	N.A.[e]	B*
Hydrogen Chloride	No Data	----------	ND
Hydrogen Fluoride	No Data	----------	ND
Hydrogen Sulfide	No Data	----------	ND
Isoamyl Acetate	No Data	----------	ND
Isobutyl Acetate	No Data	----------	ND
Isobutyl Alcohol	No Data	----------	ND
Isopropyl Acetate	No Data	----------	ND
Lead	Inadequate	----------	ND
Lead Subacetate	Probable (B2)	N.A.[e]	B*
Lindane	Possible	3.8×10^{-4}	B
Maleic Anhydride	No Data	----------	ND
Methanol	No Data	----------	ND
2-Methoxy-ethanol	Inadequate	----------	ND
Methyl Acrylate	No Data	----------	ND
Methyl Bromide	Inadequate	----------	ND
Methyl ethyl ketone	Inadequate	----------	ND
Methyl isobutyl ketone	Inadequate	----------	ND
Methyl Methacrylate	Non-Positive	----------	F
Mirex	Probable (B2)	N.A.[e]	B*
Naphthalene	Inadequate	----------	ND
Nickel	Possible	N.A.[e]	C*
Nickel Oxide	Probable (Bl)	N.A.[e]	B*
Nitrobenzene	No Data	----------	ND
Pentachlorophenol	Inadequate	----------	ND
Phenol	Inconclusive	----------	E
Phosphoric Acid	No Data	----------	ND
Phthalic Anhydride	Inconclusive	----------	E
PCBs	Probable (B2)	2.2×10^{-3}	A
Propyl Alcohol	No Data	----------	ND
Propylene Oxide	Probable (B2)	6.63×10^{-7}	C
Resorcinoi	No Data	----------	ND
Selenium	Inadequate	----------	ND
Selenium Sulfide	Probable (B2)	2.02×10^{-5}	B
Styrene	Probable (B2)	5.7×10^{-7}	C
Sulfuric Acid	No Data	----------	ND
1,1,2,2-Tetra-chloro-1,2-di-fluoroethane	No Data	----------	ND
1,1,2,2-Tetra-chloroethane	Possible	5.8×10^{-5}	C
Tetrachloroethylene	Probable (B2)	5.52×10^{-5}	B
Tetrahydrofuran	No Data	----------	ND

b. Excess lifetime cancer risk from continuous lifetime

TABLE II-10. RESULTS OF SCORING FOR CARCINOGENICITY,

continued . . .

CHEMICAL NAME	WEIGHT OF EVIDENCE[a]	UNIT RISK[b] ($\mu g/m^3$)	SCORE[c]
Toluene	No Data		ND
Toluene cyanate	Probable (B2)	6.79×10^{-6}	B
o-	Probable (B2)	5.72×10^{-6}	B
1,1,1- ethane	Inconclusive		E
1,1,2- ethane	Possible	1.6×10^{-6}	C
Trichloroe	Probable (B2)	1.63×10^{-6}	B
2,4,6- phenol	Probable (B2)	6.2×10^{-6}	B
Triethylam	No Data		ND
Vanadium	No Data		ND
Vanadium	No Data		ND
Vinyl	Inadequate	2.6×10^{-6}	ND
Vinyl	Human Carcinogen		A
Vinylidene	Possible	5.0×10^{-5}	C
Xylenes	Non-Positive		F

a. As defined in Tables II-6. and ll-7a.

exposure to 1 ug/m of the chemical in air

c. As derived using Table II-9. Asterisk (*) next to score indicates quantitative data not available to the Department.

d. Unit Risk Value used for scoring only and not used for quantitative risk assessment

e. Quantitative data not available to the Department (see Appendix E).

used in deriving allowable ambient limits.

6. Summary

CHEM relies primarily on data and assessments published by IARC, NTP, and CAG, to evaluate carcinogenicity. Experimental animal bioassays provide the majority of data, although human evidence is incorporated wherever possible.

CHEM utilizes both qualitative and quantitative evidence to assess carcinogenicity, and scoring is therefore based on weight-of-evidence as well as unit risk estimations, when available. Weight-of-evidence categories have been adapted from the EPA classification scheme, and unit risk is calculated using NTP data or obtained from CAG. Combining weight-of-evidence with potency values provides several advantages: The scoring procedure permits relative ranking of all chemicals along a continuum ranging in evidence from conclusive data to no data and from higher to lower potency, based on amount and quality of data available, as well as magnitude of effect. In this way the procedure avoids discarding valuable data by incorporating both qualitative and quantitative evidence. Thus, the methodology provides a consistent mechanism for evaluating various types and amounts of data, balancing qualitative and quantitative evidence in a way which maximizes the usefulness of each.

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8. Carcinogenicity Worksheet

The purpose of the carcinogenicity worksheets is to record the qualitative and quantitative data reported by IARC, NTP, CAG, and other sources, which are used for scoring carcinogenicity. The first page is a summary of the qualitative and quantitative results. The second page is used to record assigned weight-of-evidence categories and qualitative results of carcinogenicity studies. The third through the sixth pages are used to record the quantitative data supplied by NTP, CAG, and other sources, and to calculate unit risks.

Page 1 - Non-Threshold Effects Summary

This page summarizes the qualitative and quantitative information. This information is summarized from the following worksheets and there will be one copy of this page per chemical. At the top of the page the chemical name, CAS code, and molecular weight are recorded. The following information is also recorded:

CHEM weight of evidence - weight-of-evidence classification for carcinogenicity and mutagenicity.

Score - The final letter score for carcinogenicity and mutagenicity from CHEM are recorded.

SAR - The result of the structure activity relationship analysis is recorded: positive (+) or non-positive (-). See Appendix H.

Unit Risk - In this space, a "yes" or "no" indicates whether the calculated unit risk value will be used for regulatory

purposes. A "no" indicates that the unit risk, if any, is used only for scoring while a "yes" indicates that the unit risk value will be used for quantitative risk assessment (See appendix D for procedures and rationale used).

Unit Risk Value - Under unit risk value the calculated unit risk value and the source of that value is recorded.

CAG - The unit risk value obtained from CAG and the references are recorded.

DEP - The unit risk value calculated by the DEP and the reference (source) for the study used are recorded. Information on pharmacokinetic and metabolism data (pk/met) used in deriving the unit risk value is also recorded here.

Other - Any unit risk value from other sources that have been reviewed by DEP are recorded.

Rationale - When more than one unit risk value is available, a single value is selected for use and the rationale for this choice is recorded.

Page 2 - Qualitative Evidence Summary

On this page, the information reviewed by the DEP in making it's qualitative assessment of carcinogenicity is recorded. There is one copy of this page per chemical.

IARC: Weight-of-evidence classification for human and animal evidence are provided. The evidence is ranked by IARC as follows:

S = Sufficient evidence of carcinogenicity
L = Limited evidence of carcinogenicity
I = Inadequate evidence

Details of study results and evaluations by IARC summarized under the "Comments" heading. The reference to the IARC documentation is recorded for source.

NTP: Bioassay results in male (M) and female (F) rats and mice (or other species) are recorded as positive (+), non-positive (-), or equivocal (?). Additional details are provided under the "Comments" heading.

The source of the information is recorded and any current activity in the NTP is recorded based on a recent copy of the NTP Quarterly Management Status Report.

CAG: Weight-of-evidence classification and species in which results were observed are recorded.

Other: Information from sources other than those listed above is recorded here.

Page 3 - Potency Value Selection

This page records the selection of the DEP carcinogenic potency value when there are more than one tumor site or study analyzed by the DEP. The criteria for this selection are discussed in Appendix D. The following information is recorded:

- Chemical name and CAS code
- the final potency value and unit risk value
- the citation for the study used
- the species and sex of the animal used

- the route of administration
- survival effects - were there significant dose-related effects on survival (non tumor-related)
- incidence adjusted - was the incidence adjusted for early mortality
- weight effects - were there significant dose-related effects on body weight
- MTD comment - was the high dose close to the the MTD
- q_{1*} - the 95% upper confidence limit on the linear term from the multistage model
- LLE - the factor used to adjust the potency due to less than lifetime exposure is recorded
- final q_{1*} - the adjusted potency is recorded
- the site and type of tumor is recorded
- the concurrent and historical (if available) background tumor incidence at the site selected are recorded
- the occurrence of nonneoplastic pathology of the site selected is briefly described based on the information provided in the bioassay report

Rationale for site and study selection. The reasons for selection of the site and study used to estimate the carcinogenic potency are recorded. The criteria for this decision are discussed in Appendix D.

Pages 4, 5 and 6

These pages record pertinent information used for analysis of the carcinogenicity bioassay. There will be one copy of each of these pages for each study used by DEP to calculate carcinogenic potency. The information recorded is described below:

Page 4 - Bioassay Summary Sheet

Chemical name and CAS code, grade of chemical and identified impurities, route of exposure and the reference for the study are recorded. For each species and sex, the administered dose and the adjusted dose (from worksheet page 6) are recorded. Information about the average body weight at 60 weeks of age and at the end of the study, and survival at the end of the exposure period are recorded. It is noted whether the authors report a significant effect on either body weight or survival.

Exposure information is recorded for use in calculation of adjusted dose. If there are any tumor sites which were statistically significantly increased but were not considered to be biologically significant by the authors, (or biologically significant but not statistically significant) they are recorded with the authors' reasons for their interpretation. Finally, any nonneoplastic pathology at the sites of increased tumors is recorded as reported by the authors.

Page 5 - Bioassay Results

For each site with significantly increased tumors, the following information is recorded:

Species - species and strain of animal
Sex - male and/or female animal
Site - organs where tumors occurred
Tumor - histogenic tumor types as reported
Statistics - results of statistical analysis performed by the authors
NTP result - for NTP studies - the category assigned by NTP

Incidence - tumor incidences in Control, Low, Medium and High dose groups

M stage - model parameters from the multistage model fit to the incidences listed here and the adjusted doses from Page 6.

Page 6 - Dose Adjustment

This page shows the calculation of the adjusted dose from the administered dose or administered exposure concentration. The details of this calculation are discussed in Appendix D, Section F, and the Appendix should be consulted for a description of the terms used on the worksheet.

Non Threshold Effects Summary

Chemical _____ CAS # _____ M.W. _____

CHEM: weight-of-evidence – Carcinogen _____ Score _____

SAR: _____ Mutagen _____ Score _____

Unit risk value Y/N

Unit risk value

CAG: Unit Risk

Source

DEQE: Unit risk

Source

pk/met data used?

Other:

Rationale for selection of unit risk value:

Qualitative Evidence Summary

IARC Human_____ Animal_____

Comment:

Source:

NTP

Comment:

Source:

Current activity:

EPA Group_____ Animal _____ Human _____

Comment:

Source:

Other:

Potency Value Selection

Chemical _____ CAG _____

Potency value

Source: reference _____

species _____ sex _____

route _____

survival effects _____

weight effects _____

MTD comment:

q0_____q1_____q1*_____LLE_____final q1_____

site/tumor _____ dose response _____

background incidence _____

non neoplastic pathol _____

Rationale for site selection:

Rationale for study selection:

BIOASSAY SUMMARY SHEET

Chemical _____

Route _____

Source _____ CAS # _____

	Dose			Body Weight (g)														
	admin.			adjust			60-wk			Terminal				Sig.	Survival				Sig,
	L	M	H	L	M	H	L	M	H	C	L	M	H	Dif.	C	L	M	H	dif.
Rat	M																		
	F																		
Mouse	M																		
	F																		
	M																		
	F																		

exposure information age at 1st dose _____

age at last dose _____

age at sac. _____

Total time dose _____

Sites not considered significant (sig. by statistics):

non neoplastic pathology at site:

BIOASSAY RESULTS

CARCINOGENICITY WORKSHEET

[Sites that were significant]

Species	Sex	Site	Tumor	Statistics	NTP Results	incidence				nstag				
						C	L	M	H	q^o	q1	qa	q3	q^*1

CARCINOGENICITY WORKSHEET

DOSE ASSESSMENT

SURFACE AREA ADJUSTED DOSE ( )	**LIFETIME AVERAGE DOSE ( )**	**WEIGHT ( )**	**TREATMENT CHARACTERISTICS ( )**	**ADMINISTERED DOSE ( )**

E. Mutagenicity

1. Introduction

A mutagen is defined in CHEM as a chemical capable of inducing alterations in the genetic material of either somatic or germinal cells. The term mutation encompasses a broad spectrum of genotoxic events, including mutations affecting one or more nucleotides of DNA, several genes, large segments of chromosomes, or entire chromosomes. (A glossary of mutagenicity terminology is provided in Appendix F.) Mutagenic endpoints of concern include point and gene mutations, structural or numerical chromosome aberrations, other genotoxic effects, cellular transformation, and abnormal sperm morphology. Thus, while experimental data demonstrate a correlation between mutational events and carcinogenicity, the mutagenicity assessment is designed to evaluate a range of genotoxic endpoints of potential significance to humans, and is not merely a substitute for, or an adjunct to, the carcinogenicity assessment. Somatic cell mutation is included in the mutagenicity assessment both as an indicator of relevant mutational events, and because of its role in the etiology of several disease states, including cancer (EPA, 1984; IARC, 1983). As the National Research Council (NRC) of the National Academy of Sciences states,

> "The range of gene-determined deleterious effects is enormous...Every part of the body and every known function are genetically determined. Normal development is a process of coordinated action of many genes. The failure of any one of these is likely to result in some impairment, disease, or...death." (NRC, 1983, p. 28).

It is estimated that at least 10% of all human disease is related to specific genetic states, such as abnormal

composition, arrangement, or dosage of genes and chromosomes (USEPA, 1984). A few of the thousands of diseases with a genetic component include Down and Klinefelter Syndromes, cystic fibrosis, hemophilia, Huntington's disease, phenylketonuria, achondroplasia, Wilm tumor, hypertension, pyloric stenosis, glaucoma, retinoblastoma, muscular dystrophy, several types of cancer, and mental retardation (Koufos et. al., 1984; Knudson, 1971; USEPA, 1984; NRC, 1983). Obviously, these impose a substantial financial and emotional burden on society. Moreover, conspicuous effects such as these comprise but a small proportion of adverse impacts, since many genes have effects that are covert, mild, or cumulative. Because altered mutation rates can affect not only morbidity and mortality in the present, but also the viability of future generations, the identification of chemicals having the potential to produce such effects is a crucial component of the health assessment. Tables II-11 through II-14 illustrate the genetic contribution to selected diseases and conditions. Additional references concerning the diversity and significance of genetically-related disease may be obtained from Hook (1982), Smith (1982), and Carter (1982).

Preserving genetic integrity is of critical importance. As the National Research Council (NRC) emphasizes,

> "All organisms are the products of long evolutionary history during which favorable genes have been preserved and deleterious genes eliminated by natural selection...A random change is much more likely to make things worse than better...[Thus,] the aggregate effect of all mutation is deleterious...in our view, even the current rate of "spontaneous" mutation is not optimal for human welfare; our descendants for the next few centuries, and probably beyond, would be better off if we could find a way to reduce the rate of spontaneous mutation." (NRC, 1983, pp. 43-44).

TABLE II-11. CONCEPTUSES WITH CLINICALLY SIGNIFICANT CYTOGENETIC ABNORMALITY

Gestational stage in completed weeks	Proportion of conceptuses of recognized pregnancies at given stage onwards with clinically significant cytogenic abnormality (%)	Proportion of conceptuses at given stages onward with cytogenetic abnormality whose clinical significance is manifest morphologically at or before livebirth (%)
5	4.59 –4.68	4.55 - 4.59
8	3.74 – 3.84	3.70 - 3.74
12	2.044 – 2.15	2.00 - 2.04
16	0.77 – 0.88	0.73 - 0.77
20	0.41 – 0.52	0.37 - 0.41
28	0.26 – 0.36	0.21 - 0.26
(Livebirth	0.20 – 0.30a	0.15 - 0.20b)

a The lower figure is more appropriate if livebirth XYYs are excluded (the rate is then 0.22%), the upper figure if they are included (the rate is then 0.27%). The ranges given throughout reflect this difference. The actual precision of the estimates are of course much lower than that implied by the ranges given.

b Best estimate is 0.16%. Calculations are made for other gestational stages assuming this range. Note XYYs as well as most other sex chromosome abnormalities in livebirths are excluded in this column.

SOURCE: Hook, 1982

TABLE II-12. MALIGNANCY AND SPECIFIC SOMATIC CYTOGENETIC ABNORMALITY IN AFFECTED TISSUES

Malignancy	Chromosome abnormality
Chronic myelogenous leukemia	22q translocation (ph+)
Meningioma	22 monosomy
Burkitt's lymphoma	14q+ (8q translocation in non-Africans)
Dysgerminoma and gonadoblastoma	XO/XY
Retinoblastoma	llpl3 deletion
Wilm's tumor-aniridia	13ql4 deletion

SOURCE: Hook, 1982

TABLE II-13. PROPORTION OF CHROMOSOME ABNORMALITIES IN SUBFERTILE MEN AND CONTROLS DETECTED IN PERIPHERAL BLOOD STUDIES IN STUDY OF CHANDLEY ET AL., (1975)

	Subfertile (%)	Controls (%)
All cases	2.13	0.45
XXYs	1.00	0.06
All non-XXYs	1.13	0.39
XYY (and mosaic case)	0.25	0.19
Autosomal translocations	0.50	0.13
47, XY, +mar	0.25	0 (0.13 in newborns)
Others	0.13	0.06
N — number of cases	1599	1560

SOURCE: Hook, 1982

TABLE II-14. ESTIMATES OF BIRTH FREQUENCIES OF SOME MORE COMMON RECESSIVE CONDITIONS IN BRITAIN PER 1000 LIVE BIRTHS

Malignancy	Chromosome abnormality	frequency
Metabolism	Cystic fibrosis	0.5
	Phenylketonuria classical	0.1
Nervous system	Neurogenic muscle atrophies	0.1
Red blood cells	Sickle-cell anaemia	0.1
Endocrine glands	Adrenal hyperplasias	0.1
Hearing	Severe congenital deafness	0.2
Sight	Recessive forms of blindness	0.1
Mental retardation (severe)	Non-specific recessive forms	0.5

SOURCE: Carter, 1982

Lacking definitive answers as to the long-term impacts of specific genetic aberrations, the Department believes that all relevant mutagenic endpoints should be considered in the evaluation. Even apparently mild* mutations are significant in terms of total cumulative impact, since the collective burden of individually mild mutations may be substantial. As the NRC states, "If we adopt a system of mutation cost-accounting that equates a small amount of harm to a large number of people with a great amount of harm to a small number of people, mild mutations can have as great consequences as severe ones, or greater" (NRC, 1983, p. 47).

* Mutations which do not show an immediate (one generation) effect on survival or fertility may be characterized as mild, compared to more severe effects such as early embryonic death. For example, recessive mutations are inherited without obvious effect over many generations until they become homozygous, when they become obvious.

Studies in Drosophila show that mild mutations contribute markedly to the total mutational load, outnumbering severe mutations by a factor of ten or more. It is estimated that for every severe human mutation detected by laboratory test systems, 20 or more mildly deleterious mutations may also occur. Mild mutations can remain in the population for generations, progressively weakening each individual until the balance is tipped between survival, and premature death or sterility (NRC, 1983). Thus, it is essential to monitor the genetic impacts of chemical mutagens very carefully.

A range of endpoints in both somatic and germ cells is considered in CHEM. While heritability is obviously of primary significance, the Department believes that all adverse genetic events of potential relevance to humans should be evaluated. Germ cells present limited opportunity

for testing, and the demonstration of mutagenic activity in somatic cells provides an indication of potential germ cell mutagenicity. Somatic cell mutations themselves are of importance, since these may affect the health and viability of the organism.

As the EPA points out, mutagenic effects arise through a variety of mechanisms, and can be detected in a number of ways (USEPA, 1984). In response to comments about the suitability of including cytogenetic endpoints and tests not designed to measure transmissible aberrations, the EPA stated that "Although it is clear that cells that carry such aberrations generally do not reproduce, other related aberrations (i.e., balanced translocations, inversions, small duplications, and deficiencies) are compatible with cell survival in germ cells and can be transmitted. Additionally, there is no evidence indicating that the non-transmissable aberrations occur by mechanisms different from transmissable aberrations" (USEPA, 1984, pp.46315-6). Likewise, the Department believes that the protection of present and future generations is best served by a comprehensive mutagenicity assessment incorporating all genetic and chromosomal endpoints of significance.

2. Data Sources for Mutagenicity Assessment

CHEM relies primarily on short-term and long-term mutagenicity bioassays in experimental species to assess chemicals for mutagenicity, although valid epidemiological evidence will be used to supplement the bioassay data when available. However, even where population monitoring has been carried out (e.g., sperm and body fluid analyses in occupationally-exposed groups), the results are often difficult to interpret or to confirm. This is because exposed human populations are small, yet diverse, and there

are no unique, easily observed mutant phenotypes to serve as markers in human populations.

Given the increasing backlog of untested chemicals, and the likelihood that at least some of these may pose a genetic risk to human populations, it has been necessary to develop practical alternatives to the prohibitively expensive and time-consuming methods of traditional toxicology. Moreover, as the EPA (1984) points out, the very nature of mutagenic effects precludes traditional methods of identification and testing. Specific mutations are relatively rare events, and only a small fraction of the thousands of human genes and conditions are currently useful as markers in estimating mutation rates. Genetic variability, small numbers of offspring, and long generation times further complicate studies in humans. In addition, only dominant mutations, certain sex-linked recessive mutations, and some chromosome aberrations are detectable in the first generation. Most conditions will therefore go unrecognized for many generations. Thus, CHEM relies on experimental data to predict potential genotoxicity in humans. However, work is underway at the Massachusetts Institute of Technology using the mutational spectra found in human blood cells to investigate causes of particular mutations (Thilly, 1985). As it becomes possible to directly measure mutagenic events in human cells, and distinguish spontaneous mutations from chemically-induced genotoxicity, indirect non-human assays may be unnecessary. The Department is interested in these efforts, and will incorporate such data when available.

In using non-human or non-mammalian species for testing, the assumption is that results from valid tests in other biological systems can be extrapolated to humans. This assumption is supported both conceptually and

experimentally by the fact of the virtual universality of DNA as the genetic material, the reproducibility of genetic damage by specific chemicals among various species, and the occurrence of similar types of mutations in human and non-human somatic cells (IARC, 1980; NRC, 1983; USEPA, 1984). As EPA states,

> "Despite species differences in metabolism, DNA repair, and other physiological processes affecting chemical mutagenesis, the virtual universality of DNA as the genetic material and of the genetic code provides a rationale for using various nonhuman test systems to predict the intrinsic mutagenicity of test chemicals. Additional support for the use of nonhuman systems is provided by the observation that chemicals causing genetic effects in one species or test system frequently cause similar effects in other species or systems. There also exists evidence that chemicals can induce genetic damage in somatic cells of exposed humans. For example, high doses of mutagenic chemotherapeutic agents have been shown to cause chromosomal abnormalities, sister chromatid exchange, and quite probably, point mutations in human lymphocytes exposed in vivo. While these results are not in germ cells, they do indicate that it is possible to induce mutagenic events in human cells in vivo. Furthermore, a wide variety of different types of mutations have been observed in humans including numerical chromosome aberrations, translocations, base-pair substitutions, and frame-shift mutations. Although the cause of these mutations is uncertain, it is clear from these observations that the human germ cell DNA is subject to the same types of mutational events that are observed in other species and test systems." (USEPA, 1984, p.46318).

Moreover, years of testing with thousands of chemicals have demonstrated remarkable consistency among various species in a large number of tests. The data demonstrate that while the sensitivity of a given species or testing methodology may vary with respect to a particular endpoint, the uniformity indicated among the range of biological systems permits a high degree of confidence and predictability for mutagenic response when using a battery

of tests (IARC, 1980; NRC, 1983; USEPA, 1984). Tables II-15 and II-16 show the results of some comparative testing between mouse and Drosophila carried out by NRC. Metabolic differences or differences in the transportation efficiency of reactive metabolites between tissue of production and, for example, germ cell DNA, could explain differences between fruit fly, mouse, and human.

The EPA's Gene-Tox database is the principal data source used in CHEM to assess mutagenicity. Gene-Tox is a peer-reviewed information file produced by the EPA Genetic Toxicology Program. It reports bioassay results for 73 separate tests, and is updated regularly. While the database is relatively new, and many chemicals have yet to be evaluated, it is anticipated that comprehensive analyses of a large number of substances will be available in the near future.

The computer file at the Environmental Mutagen Information Center (EMIC) was generated from 23 independent Work Groups convened in the spring of 1979. These experts on the assay systems they were to evaluate were supplied with complete copies of the publications in their field of expertise. Each group drew up its own criteria for acceptance or rejection of a publication, and they also drew up criteria for classifying results as positive, negative, or equivocal. The cutoff date for publications to be considered for Phase I was early 1979. Papers published since then are being considered now, and reports on this work are expected in the near future.

Both the selection of tests to be used and the evaluation of chemical-specific results represent years of intensive research and collaboration by expert working groups within the Genetic Toxicology Program. The degree of

TABLE II-15. INTERSPECIES COMPARISON IN MUTAGENICITY STUDIES: RESULTS OF TESTS FOR HERITABLE TRANSLOCATIONS IN THE MOUSE FOR 17 CHEMICALS THAT PRODUCED TRANSLOCATIONS OR X-LINKED LETHALS IN DROSOPHILA

CHEMICAL	MOUSE	DROSOPHILA
Cyclophosphamide	+	+
Ethylene oxide	+	+
Ethyl methanesulfonate (EMS)	+	+
Isopropyl methene-sulfonate	+	+
Methyl methane-sulfonate (MMS)	+	+
Mitomycin C	+	+
Nitrogen mustard	+	+
Procarbazine	+	+
TEM	+	+
Tris (I-aziridinyl phosphine oxide) (TEPA)	+	+
Tris (I-aziridinyl phosphine sulfide) (thio-TEPA)	+	+
Aflatoxin B-l	-	+
Cadmium Chloride	-	+
Caffeine	-	+
Captan	-	+
N-Methyl-N' -nitro-N-nitrosoguanidine	-	+

* All treatments were to postspermatogonial stem-cell stages
\+ Significant increase over the controls;
\- No significant increase over controls

Data from Bishop and Kodell (1986), and Lee et al., 1983)
SOURCE: NRC, 1983

TABLE II-16 INTERSPECIES COMPARISONS IN MUTAGENICITY STUDIES: COMPARISON OF THE RESULTS OF 17 CHEMICALS TESTED IN BOTH THE MOUSE-SPECIFIC-LOCUS TEST AND THE DROSPHILA X-LINKED LETHAL TEST

CHEMICAL	MALE MOUSE POSTMEIOTIC CELLS	PREMEIOTIC CELLS	DROSOPHILA POSTMEIOTIC CELLS	PREMEIOTIC CELLS
Ethyl nitrosourea (ENU)	+	+	+	+
Mitomycin C	inc	+	+	+
Procarbazine	+	+	+	+
Triethylene melamine (TEM)	+	+	+	+
Propyl methanesulfonate	inc	+	+	n.t.
Butylated hydroxytoluene (BHT)	inc	-	—	-
Cyclophosphamide	+	n.t.	+	-
Ethyl methanesulfonate (EMS)	+	—	+	+b
Methyl methanesulfonate (MMS)	+	Inc	+	+
Hycanthone methanesulfonate	inc	—	+	-c
Myleran busulfan (Myleran)	inc	—	+	—
Benzopyrene	inc	—	+	-
Methyl nitrosourea (MNU)	+	inc	+	+
Diethyl nitrosamine (DEM)	inc	—	+	+
Sodium bisulfite	Inc	—	n.t.	n.t.
Irradiated wheat	n.t.	-	+	n.t.
Caffeine	n.t.	—	+	n.t.

a. + signifies higher than historical control frequency of 43/801,406 at 5% significance level; inc = inconclusive, which means neither + nor -, and samples evaluated after high exposure range from 911 to over 20,000 offspring; n.t. = not tested; - == induced mutation frequency after high exposure is lower than 4 times the historical control mutation frequency at the 5% significance level.

b. Statistically significant increase (% level) over concurrent control, or significantly greater than 0.5% mutation frequency.

c. Less than a 0.2% Induced frequency (equivalent to spontaneous frequency) with a sample size of 7,000 or more tests at approximately 800 loci per test.

SOURCE: NRC (1983)

effort involved, the stringency of criteria employed by the working groups, and the extensive documentation provided lend a high degree of confidence to the results reported. Until all the chemicals of interest to Massachusetts have been evaluated by Gene-Tox, however, CHEM will use sources such as IARC and primary science literature to supplement the mutagenicity assessments. The criteria outlined by Gene-Tox for evaluation of tests used, as well as results, will be used to assess the validity and relevance of primary data. Use of Gene-Tox data and standards allows for a consistent and reliable approach to the evaluation of potential mutagenicity.

The biological test systems selected by Gene-Tox and utilized in CHEM include humans and other mammals, bacteria, Drosophila, yeasts, molds, and plants. Bioassays are conducted in vivo or in vitro, and with or without metabolic activation; they are collectively designed to assess a variety of endpoints, since the mechanisms of mutagenic activity are expected to vary from one chemical to the next.

3. Selection and "Tiering" of Mutagenicity Tests

In contrast to the other three health effects categories (acute/chronic toxicity, carcinogenicity, developmental/reproductive toxicity), mutagenic effects are ranked on the basis of weight-of-evidence only. This makes it especially important that the tests used are carefully selected.

Test selection involves balancing a number of factors, ranging from the practical to the scientific. As described by NRC (1983) and EPA (1984), these criteria include:

- relevance of endpoint measured to human

populations.

- Anatomical, histological, and/or metabolic similarities to humans, as measured by the metabolic processing of the agent, the structure and chemical nature of the chromosomal target, the processing of DNA damage, the transmission of the mutation, and correspondence of germ cell stages.
- The diversity of phylogenetic groups represented collectively in the test systems.
- The genetic endpoints assayed by the test.
- Sensitivity and specificity of the test.
- Validity.
- Reliability.
- Availability of a large database.
- Variety of classes of chemicals to which the tests have been applied.
- The number of laboratories that have performed the test and the reproducibility of results among laboratories.
- Concordance of results with chemicals previously subjected to other tests.

Of course relevance to humans is the single most important factor, but as the NRC points out, "The tests chosen necessarily represent a compromise: relevance, sensitivity, cost, and other considerations must be balanced against each other" since no one test can meet all criteria. (NRC, 1983, p. 149)

Seventy-five mutagenicity assays are utilized in CHEM. Of these, 73 are currently included in Gene-Tox. Two additional tests, the Dominant Skeletal Mutation Test and the Dominant Cataract Assay have been added for use in CHEM. These were selected on the basis of their predictive value and overall significance to the mutagenicity assessment

(IARC, 1980a and b; USEPA, 1984). A considerable database exists pertaining to the tests selected by Gene-Tox and used in CHEM. A list of the International Commission for the Protection Against Environmental Mutagens and Carcinogens (ICPEMC) and other Gene-Tox reports used in the evaluation of mutagenicity tests appears with the general references at the end of this section. A complete list of Gene-Tox publications may be obtained from TSCA Industry Assistance Office of Toxic Substances, U.S.E.P.A. Table II-17 lists and describes the 75 tests used in the mutagenicity assessment.

Based on the critical reviews published by IARC (1980a and b, 1983), NRC (1983), and Gene-Tox committees, the 75 tests are divided into three groups, representing a tiered approach to evaluate weight-of-evidence. Tests are arranged in such a way as Klinefelter Syndromes, cystic fibrosis, hemophilia, Huntington's disease, phenylketonuria, achondroplasia, Wilm tumor, hypertension, pyloric stenosis, glaucoma, retinoblastoma, muscular dystrophy, several types of cancer, and mental retardation (Koufos et. al., 1984; Knudson, 1971; USEPA, 1984; NRC, 1983). Obviously, these impose a substantial financial and emotional burden on society. Moreover, conspicuous effects such as these comprise but a small proportion of adverse impacts, since many genes have effects that are covert, mild, or cumulative. Because altered mutation rates can affect not only morbidity and mortality in the present, but also the viability of future generations, the identification of chemicals having the potential to produce such effects is a crucial component of the health assessment.

Sixty-eight short-term mutagenicity screening assays are assigned to primary and secondary categories, making up Groups II and III, respectively. Group designation was

again based on the criteria previously outlined, particularly relevance and sensitivity. All endpoints and test organisms are represented in each group, with the exception of plants which are included in Group III only. While all the tests included in Groups II and III are valid, placement in Group II, as opposed to Group III, generally reflects relatively greater confidence in the test, and higher significance with respect to potential effects in humans. As indicated, positive results in Group I tests have more "weight" then those from Group II, and Group II tests have more "weight" than those in Group III. Thus, while two positive results in Group I assays provide "sufficient" evidence of mutagenicity, at least four positive results in Group II or six positives in Group III tests are required for the same designation. Table II-18 presents the mutagenicity scoring system used in CHEM. Since this is a constantly evolving field, selection and tiering of tests will be updated regularly.

Some pairs or groups of assays are virtually identical with respect to organism used and endpoint measured. These are grouped together and, if both are positive, counted as one unit. For example, if a chemical produces positive results in both the WP2 and WPU assays (reverse mutation in E. coli -- see Group II: Primary Short-term Tests on Table II-17), only one positive will be counted for scoring since there is no practical distinction between the two tests/strains used. Such pairs or groups of tests are listed on one line in Table II-17, and separated by a slash (e.g., CY5/CY8). If the results differ, decisions will be made on a case-by-case basis as to whether they cancel one another out. Tests were matched on the basis of a previously published classification scheme (Waters, 1983) and Department judgement.

TABLE II-17. LIST OF MUTAGENICITY TESTS

TEST DESCRIPTION/TYPE	CODES
GROUP I: MAMMALIAN, IN VIVO	
Mouse Specific Locus Test	SLT
Mouse Spot Test	MST
Dominant Skeletal Mutation	"DSM"
Dominant Cataract Assay	"DCA"
Dominant Lethal Test - rodents	DLT
Heritable Translocation Test-rodents	HTT
Micronucleus Test - mouse	MNT
GROUP II: PRIMARY SHORT-TERM TESTS	
Chinese Hamster Lung (V79) cells, all loci	V79
Mouse Lymphoma (L5178Y) cells, TK locus	L51
S. Typhimurium, histidine reversion (Ames Test), (TA 98, TA 110,) TA 1535, TA 1537, TA 1538)	SAL
E. Coli (WP2/WP2 uvra) - reverse mutation	WP2/WPU
Sex-linked Recessive Lethal Test - Drosophila m.	SRL
Host-Mediated Assay Studies	HMA
Mammalian Cytogenics, bone marrow/lymphocyte of leukocyte	CY5/CY8
Mammalian Cytogenics, bone marrow/lymphocyte of leukocyte	CY#/CY%
Mammalian Cytogenics, oocyte, early embryo/male germ cell	CYO/CH9
Mammalian Cytogenics, all mammalian	CY&
Micronucleus Test, lymphocyte	MN7
Micronucleus Test, mammalian cell	MN&
Heritable (reciprocal) Translocation Test - Drosophila	DHT
Sister chromatid Exchange - lymphocyte	SCY
Sister Chromatide Exchange - cells/embryonic lung fibroblasts (Wl-38)/lymphocyte	SCI/SCW/SCL
Sister Chromatid Exchange - in vivo/in/vitro	SC3/SC2
A. Nidulans - cross over studies	ASG
S. Cerevisiae, homozygosis - recombination/gene conversion	YEH/YEC
E. Coli pol A (W3110-P3478) - with S9/without S9	RE2/REI
B. Subtilis rec (H17-M45/17A45T)	REW/REX

continued . . .

TABLE II-17. LIST OF MUTAGENICITY TESTS, continued

TEST DESCRIPTION/TYPE	CODES
GROUP II: PRIMARY SHORT-TERM TESTS, continued	
Human Sperm Morphology	SPH
Cell Transformation Studies - BALV/C-3T3 / C3H/IOTI/2	CTB/CTH
Cell Transformation Studies - mouse prostate	CTM
Cell Transformation Studies - Syrian hamster embryo-clonal/focus assay	CTC/CTF
Cell Transformation Studies - Fischer rat embryo/mouse embryo/Syrian hamster embryo	CTR/CTK/CT7
Cell Transformation Studies - SA7 Fischer rat cells	CTA
GROUP III: SECONDARY SHORT TERM TESTS	
Forward/Reverse Mutation, S. Cerevisiae [YEF/YER]; S. Pombe [YEY/YEZ]	YEF/YER/YEY/YEZ
Forward/Reverse Mutation, A. Nidulans	ASF/ASR
Forward/Reverse Mutation, N. Crassa	NEF/NER
Plant Gene Mutation Studies	PGM
Body Fluid assay - urine	BFU
Aneuploidy studies, whole sex chromosome - loss/loss/gain	DAC/DAP/DAG
Aneuploidy studies, S. Cerevisiae/A. Nidulans/N. Crassa	YEN/ASN/NEN
Micronucleus Test - plants	MNP
Plant Chromosome Studies	PYC
Mammalian Sperm Morphology - mouse/rabbit/rat	SPI/SPR/SPA
Mammalian Sperm Morphology - mouse Fl assay	SPF
Unscheduled DNA Synthesis - human diploid fibroblast	UDH
Unscheduled DNA Synthesis - mouse germ cells	UDT
Unscheduled DNA Synthesis - rat primary hepatocyte	UDP

4. Scoring Scheme

Scoring chemicals for mutagenicity represents a complex task, due to the broad range of effects, test systems and mechanisms of action to be evaluated. Moreover, as IARC points out,

> "Few, if any, mutagens induce only one type of mutational change: rather, most mutagenic agents tend to exhibit a characteristic mutational spectrum which depends upon (i) the nature of the primary DNA alteration,...and (ii) the subsequent secondary effects of DNA repair and replication. The same mutagen may therefore produce different mutational spectra in organisms of different genetic background." (IARC, 1980a).

At the same time, the mutagenic activity of a given chemical may be detectable only in certain species or tests. Because both the endpoint and the mechanism of mutagenic action vary, it is necessary to use a variety of tests in the mutagenicity assessment. The methods preferred by EPA (1984), IARC (1980a), Waters et al. (1983), Gene-Tox, and Weisberger and Williams (1981) employ a battery of tests collectively designed to measure a range of genotoxic endpoints in a number of species. Since each test is limited by the mechanism it is designed to detect, as well as the sensitivity of the species used, a series of bioassays provides a more reliable foundation for identifying potential mutagens. Tests are "tiered" or weighted using the criteria defined in the previous section.

The mutagenicity scoring scheme used in CHEM represents a combination of elements recommended by various assessment committees from IARC (1980a, 1980b), EPA (1980, 1984) and NRC (1983). The method used most closely resembles that outlined by EPA (1984, 1986), but requires a larger number of assays, as well as expanded weight-of-evidence categories

(i.e., EPA uses three categories while CHEM uses five). The Department chose not to adopt any one of the assessment schemes cited above in toto, for the following reasons:

- o No single method accounts for all endpoints of interest.
- o Some methods are geared primarily toward carcinogenicity screening rather than mutagenicity assessment per se (e.g., IARC classification scheme).
- o Many utilize only a few tests, which are not consistently available for the chemicals of concern to the Department (e.g., NRC). If CHEM were to restrict the assessment to results from only five or six tests, most chemicals would remain unclassified since few would have been studied in those specific tests.
- o Most methods seek a yes/no determination of mutagenicity. In contrast, CHEM seeks to evaluate the relevance of the data and to distinguish gradations of confidence and/or potential harm. Since the number and type of results available vary considerably from chemical to chemical, weight-of-evidence categories must be designed to accommodate numerous possible combinations and situations.

Table II-18 shows how the results from tests in Groups I, II, and III are combined and weighted to produce the weight-of-evidence classification scheme. Chemicals are evaluated using this scheme, and each is assigned a letter code score (A-E) reflecting relative degree of hazard. The following factors are considered in deriving the final score:

a. Group designation: Greater weight is given to positive results in a Group I assay than to results in a Group II assay. Similarly, Group II results are given greater weight than those in Group III.

TABLE II-18. SCORING MATRIX FOR MUTAGENICITY IN CHEM

Category	Test Type and Number of Positive Results	Letter Score
Sufficient: Evidence	Group I: Two or More or Group II: Four or More or Group III: Six or More or Group I: One AND Group II: One or Group I: One AND Group III: Two	A A A A A
Substantial Evidence	Group I: One or Group II: Three Group III: Four or Five or Group II: One or Two AND Group III: Three	B B B B
Suggestive Evidence	Group II: One or Two or Group III: Two or Three or Group II: One or Two AND Group III: One or Two	C C C
Limited Evidence	Group III: One	D
Non-Positive	Non-Positive Data	E
No Data	Inadequate Data or Chemical Not Tested	ND

b. Species or organism: Generally speaking, test species have been ranked in order of descending significance as follows: human, other mammal, higher eukaryote, lower eukaryote, prokaryote.

c. Test method: Greater weight is attached to in vivo testing than in vitro testing.

d. Endpoint: The number and variety of endpoints evaluated is considered. Greater confidence is derived from a set of test results which represents a variety of significant endpoints.

e. Species: The number and variety of species used is also important. Greater confidence is placed in assessments which are based on results from diverse species, especially those which include mammals.

f. Correlation between results: As a result of extensive testing, correlations between certain tests have been demonstrated, such that if a chemical is positive (or non-positive) in a given assay, it is likely to be positive (or non-positive) in the other assay as well. Such consistency may indicate similar mechanisms of action and should be noted. Thus, it is important to consider not only the total number of positives and non-positives reported, but also the significance of individual results. This is crucial in scoring, since it would be misleading merely to compare totals of positives and non-positives without regard for predictable correlations among tests. In the case of non-positive or conflicting results, for example, interpretation can be more straightforward if those particular results would have been expected on the basis of mechanism of action.

Judging the significance of individual test results is important in another sense as well, because a positive or non-positive result in one type of test may be less relevant than a positive or non-positive in another test. Each of these factors must be weighed in scoring.

g. Overall pattern of results: In summing up the available data, all of the factors outlined above are considered. Because the assessment involves a battery of tests, it is often possible to identify a trend or pattern among the results, pointing to a particular mechanism of action, or type of hazard posed. After evaluating and weighing individual results, a summary score is assigned on the basis of their collective significance. Thus, scoring reflects an attempt to balance the variables listed in a meaningful way, to account for mechanisms of action, and ultimately to discern an overall pattern - particularly where individual results are conflicting or ambiguous.

The evaluation of mutagenicity involves a great variety of endpoints and biological systems. The evaluation can include hundreds of results or very few, and the number of possible combinations is practically limitless. It is difficult, therefore, to directly compare one chemical with another, since the spectrum of results available for each is likely to be quite different. Moreover, non-positive and equivocal results further complicate classification.

Thus, while Table II-18 presents a fairly simplified and straightforward approach to categorizing the weight-of-evidence, the actual scoring process is considerably more complex than can be illustrated schematically. Clearly, there is a significant amount of

case-by-case judgement involved in arriving at the final score, as the following examples demonstrate.

Examples of Mutagenicity Scoring

Formaldehyde provides an example of a chemical with a comparatively large amount of data, and uniform results. It is positive in a number of biological systems and for a variety of endpoints:

+ SRL (sex-linked recessive lethal, Drosophila)
+ DHT (heritable translocation, Drosophila)
+ YEC (gene conversion, S. cerevisiae)
+ REI (DNA damage, E. coli, without S9)
+ YER (reverse mutation, N. crassa)
+ NER (reverse mutation, N. crassa)

The six positives, four in Group II, and two in Group III would normally provide "sufficient" evidence of mutagenicity. All results are positive, three of four endpoints are represented (gene mutation, chromosomal effects, and "other genotoxic effect" - DNA damage, and gene conversion), and four varieties of test organism are represented. However, formaldehyde is assigned a score code of `B' rather than `A' because no mammalian results are available and the evidence is therefore less than sufficient. It can be no lower than `B' because the spectrum of endpoints and the number of positives provide a consistency which allows confidence in the results.

Carbon tetrachloride presents a very different situation. Only two endpoints are represented, and the results are varied:

-	SAL	(histidine reversion, S. typhimurium - Ames Test)
+	YEH/+ YEC	(recombination/gene conversion, S. cerevisiae)
+	YER	(reverse mutation, S. cerevisiae)
-	SPI	(sperm morphology, mouse)

While carbon tetrachloride is apparently positive for some endpoints and in certain species, only one positive is reported in Group II (YEH and YEC are counted once, and scored as a unit because they are essentially the same) and one in Group III. The non-positives do not cancel out the positives because the endpoints measured are different. In addition, the yeasts are higher phylogenetically than salmonella. The sperm test used a mammal, but is less sensitive than the gene tests, and represents a less conclusive endpoint. Thus, in weighing each of these variables, a "suggestive" weight-of-evidence classification is warranted. The final score for carbon tetrachloride is "C".

5. Interpretation of Non-positive Results

As indicated, mutagenicity assessment involves weighing a range of variables, and no two chemicals are likely to present the same scoring situation. The amount and type of data available for evaluation will vary, as will the constellation of results. Therefore, the scoring system must be flexible enough to accommodate these variables on a case-by-case basis (NAS, 1983).

Interpretation of non-positive results is a problem common to all toxicological assessment (Siemiatycki, 1982). A number of factors will influence experimental outcomes,

and the interpretation of non-positive results must take this into account. These factors include:

- Exposure scenario - duration, frequency, magnitude, and type of exposure; environmental conditions of exposure.
- Dose - actual dose received by germ cell or tissue of concern.
- Pathologic interpretation.
- Statistical interpretation.
- Size of experimental and control groups.
- Chemical properties of substance tested. - e.g., volatile or hydrophobic substances can pose special problems for testing.
- Accuracy of historical and control data.
- Sensitivity and specificity of test method.
- Gender and species' sensitivity to chemical tested.

In addition to the above, accurate interpretation of mutagenicity results also depends upon the adequacy of test protocols used, and the skill of the investigator. Tests must be carefully conducted, according to specific technical protocols. The researcher must be certain that the substance being tested has actually reached the cell, has been administered at the appropriate cell stage, and that the cell remains viable (Sankaranarayanan, 1982). In vivo testing must rule out toxicity, cell death, or sterility, each of which can mask mutagenic potential. As compared to the other health effects categories in CHEM, mutagenicity testing involves a wider variety of test organisms, endpoints, and mechanisms of action. Tests are conducted using in vivo and in vitro methods, mammals and non-mammals, and seek to detect internal and external, cellular or

morphological changes in various cells of both males and females. A chemical may produce non-positive results in one test system and be positive in another, or may even vary within the same test system, depending for example, on test protocol or whether activation was used. A non-positive result may simply mean that the test selected is not responsive to the particular biologic effect(s) induced by the chemical. It does not preclude that the chemical may be positive in another test with a different endpoint.

In practice, interpretation of non-positive results requires at least as much scrutiny as required for positive results. Thus, an adequate number of tests, properly conducted, using a number of species and measuring all relevant endpoints would be needed to provide convincing evidence that a substance is not likely to cause mutations in humans. A series of non-positive results can weaken the weight-of-evidence and result in a lower score, or may cancel out a single positive when obtained in identical tests. For example, if both a positive and a non-positive are reported for SAL (histidine reversion, Salmonella typhimurium), CHEM may regard this as either a non-positive or equivocal result, to be decided on a case-by-case basis.

In contrast, a non-positive in SAL and a positive in CY5 (in vivo human bone marrow chromosomal aberration) are not comparable, and the non-positive in one test does not affect the significance of the positive in the other (Sobels, 1982). Species and endpoint differences require that we evaluate the results independently, and a non-positive cannot cancel out a positive in this case. In another example, while both the EPA and NRC consider a single positive mouse test (Group I) sufficient evidence of mutagenicity, a non-positive in one of those tests is given little weight, because of the relative insensitivity of the

tests. When interpreting conflicting results therefore, the hierarchical weighting scheme described earlier can be of use. Positive and non-positive results are evaluated with respect to species (mammalian versus submammalian), method (in vivo versus in vitro), and endpoint measured. The pattern that emerges can be translated into a weight-of-evidence classification and, thus, to a relative score. The final judgement, however, requires case-by-case evaluation by the Department. This is illustrated by the following two examples.

Examples of Interpreting Non-positive Results

Epichlorohydrin provides strong evidence of genotoxicity. It is positive in four Group II tests and two Group III tests, representing three endpoints and four species:

+	SRL (Sex-linked recessive lethal, Drosophila)
+	CY7/ + CY8(Chromosomal aberrations, human lymphocyte/leukocyte)
+	RE1(DNA damage, E. coli, without S9)
-	SPH(sperm morphology, human)
+	YEY/ + YEZ(forward/reverse mutations, S. pombe)
+	NEF/ + NER(forward/reverse mutations, N. crassa)
-	SPI(sperm morphology, mouse)

Epichlorohydrin receives a score of `A'. The fact that results in sperm tests have shown consistency from mouse to human provides confidence that epichlorohydrin may not cause abnormal sperm morphology. On the other hand, non-positives in sperm morphology do not cancel out any positives because the endpoints measured are not comparable. The number and diversity of positives result in a score of `A'.

An alternative example is acetone. It produced

non-positive results in all tests reported:

- SAL (histidine reversion, S. typhimurium - Ames Test)

- CY& (chromosomal aberration, in vivo mammalian cells)

- SC2 (sister chromatid exchange, in vitro mammalian cells)

- CTR/ -CTK (cell transformation, rat/mouse embryo)

- CTC(cell transformation, Syrian hamster embryo-clonal assay)

The fact that non-positives are obtained for both mammalian and submammalian organisms, and for all four endpoint categories provides confidence that acetone is not likely to be mutagenic in humans. Thus, acetone receives a score of `E' in CHEM.

6. Threshold and Low-Dose Extrapolation Assumptions

It is generally assumed that there is no threshold for effects like mutations, which may involve one molecule of the chemical and one target molecule. Compared to carcinogenicity, the case for non-threshold is even more straightforward for mutagenicity because once established, DNA damage is heritable and irreversible (NRC, 1983). Linearity in low-dose extrapolations is assumed on the basis of experimental models. This assumption may also provide a greater degree of public health protection since it incorporates a degree of conservatism in estimating low-dose response.

Several groups have advocated this approach, including three NRC committees (NRC, 1975, 1983; NAS, 1977). In addition, the EPA uses this approach in mutagenicity assessment (USEPA, 1980, 1984) and in its water quality criteria (1979). As the NRC states, "The approach taken by this Committee is that, unless there is evidence to the contrary, it will be assumed that there is no threshold. If it is necessary to extrapolate from high-dose data, the best procedure is to interpolate linearly between the effect at zero dose and the lowest reliable data point(s). The lower the doses studied, the more reliable is this interpolation." (NRC, 1983 p. 77).

7. Qualitative and Quantitative Assessment

The mutagenicity score in CHEM pertains only to the weight-of-evidence, representing both the level of confidence and degree of concern generated by the available data. Potency is not a factor in the assessment. While some quantitative measures exist, and are currently being used by some groups (e.g., EPA), the Department does not believe that the science has evolved sufficiently to justify their use in CHEM at this time. Of practical importance as well, the specific data required for assessing potency are not consistently available. Few, if any, of the chemicals evaluated thus far in CHEM have the needed information; and potency data are not yet available from Gene-Tox. The Department acknowledges that quantitative measures are a desirable component in any toxicity assessment, and will, therefore, consider incorporating a potency evaluation into the mutagenicity assessment when the data and the evidence warrant. Currently, when the existence of a dose-response relationship is reported by Gene-Tox, it is noted on the worksheets for CHEM, although it is only of significance in CHEM as a measure of test validity and confidence in the

results. Unlike the other health effects categories then, quantitative assessment is only indirectly used (by Gene-Tox, in their own evaluations of results to be reported) and is not incorporated in CHEM's mutagenicity scoring scheme.

8. Results and Discussion

The results of scoring for 105 chemicals are shown in Table II-19. It can be seen that, although the scoring scheme shown in Table II-18 seems simple, the actual scoring process is considerably more complex and requires a significant amount of objective case-by-case judgement.

Table II-19 shows that no data were reported by the sources used for 63 of the 105 chemicals. For the remaining 42 chemicals, scores were assigned as follows: 8A, 5B, 18C, 9D, and 2E. Thus, the most commonly represented category is `C'. This category includes those chemicals having suggestive evidence of genotoxicity in mammalian and/or non-mammalian short-term assays. The second most represented category is `D' (limited evidence). Altogether, 74 of the 105 chemicals evaluated belong to one of the three lower categories (D, E, ND). This large proportion of "low score" chemicals illustrates the importance of making a distinction between "no data", limited data, equivocal, and non-positive data. In a system which emphasizes classifying only the evidence which is sufficient to meet higher scores of C, B, and A, such as the 'classifiable' evidence in the IARC system, the lower score categories (D, E, ND) would be lumped together into a "nonclassifiable" group. That means that for the 105 chemicals evaluated here, 71% would be eliminated from further consideration without specifying the basis for the exclusion. That basis, however, may be important in assessing the overall hazard of a substance.

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY

Chemical Name	POSITIVE RESULTS[1]	NON-POSITIVE RESULTS[1]	Score[2]
Acetaldehyde	+SCI, +SCL, +SC2, +REI	——	B
Acetone	——	-SAL, -CY&, -SC2, -CTC -CTR, -CTK, -PGM	E
Acrylonitrile	+SAL, +WP2, +WPU, +CTF, +CT7	——	A
Ammonia	——	——	ND
Aniline/Aniline Hydrochloride	+REI, +CTR, +SC2, +CTR	-SAL, -YEH, -RE2, -CTC, -SPI	C
Asbestos	——	-WPU	ND
Benzene	+MNT, +CY8, +CY7, +PGM, +SPI	-SCI, -SCL, -CT7	A
Benzyl Chloride	+SAL, +YEH, +RE2, +REI +REW, +CTC	-HMA	A
Beryllium	——	——	ND
1,3-Butadiene	——	——	ND
n-Butyl Alcohol	——	-SAL, -SC2	ND
Cadmium	——	——	ND
Calcium Chromate	+SAL, +WP2, +CTB, +CTR, +CT7, +CTC	——	A

continued. . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS'	NON-POSITIVE RESULTS'	Score[2]
Carbon Tetrachloride	+YEH, +YEC, +YER	-SAL, -SPI	C
Chlordane	+PGM	——	D
Chlorine	——	——	ND
Chlorobenzene	——	——	ND
Chloroethane	——	——	ND
Chloroform	+YEC, +YEH, +YER	-V79, -CT7	C
Chloroprene	+SRL, +CT7, +SPA	——	C
Chromic Acid	——	——	ND
Chromium (Metal)	——	——	ND
Chromium (VI) Compounds	——	——	ND
p-Cresol	——	——	ND
Cyclohexane	——	-SAL, -CT7	ND
o-Dichlorobenzene	——	——	ND
P-Dichlorobenzene	+PYC	——	D
1,2-Dichloroethane	+SAL, +SRL, +CT7, +DAC, +DAG, +REI	——	A
1,2-Dichloroethylene	——	——	ND

continued . . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS [1]	NON-POSITIVE RESULTS[1]	Score[2]
Dichloromethane	+SAL, +YEH, +YEC, +CTR, YER	-SRL	B
1,2-Dichloropropane	+SAL	—	C
Diethyl amine	—	—	ND
Di-(ethylhexyl)phthalate	+DLT	—	B
Dimethylformamide	—	-CTC, -SPI, -UDP	ND
1,4-Dioxane	—	-CTY	ND
Diphenyl	+SC2	-YEH, -UDH, -UDP	D
Diphenyl amine	+CT7	—	C
Epichlorohydrin	+SAL, +SRL, +CY8, +CY7, +REI,+YEY, +YEZ, +NEF, +NER	-SPH, -SPI	A
Ethanol	+DLT, +PGM, +PYC	-MNT, -SAL, -CYB, -SCI -SCL, -SC2, -CTC, -CTR -ASF, -NEN, -SPI	C
Ethyl Acetate	—	—	ND
Ethyl Acrylate	—	—	ND
Ethyl Benzene	—	-CT7	ND
Ethylene Glycol	—	-SAL, -CT7, -NEN	ND

continued . . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS[1]	NON-POSITIVE RESULTS[1]	Score[2]
Ethyl Ether	+REI	-ASF, -SPI	D
Fluoride	—	-CY%	ND
Formaldehyde	+SRL, +DHT, +YEC, +REI, +YER, +NER	—	B
Heptachlor	+PGM	—	D
Hexachlorocyclopentadiene	—	—	ND
Hexachloroethane	—	—	ND
Hexachlorophene	—	—	ND.
2-Hexanone	—	—	ND
Hydrazine	+SAL	—	C
Hydrogen Chloride	—	-CT7	ND
Hydrogen Fluoride	+SRL	—	C
Hydrogen Sulfide	—	—	ND
Isoamyl Acetate	—	—	ND
Isobutyl Acetate	—	—	ND
Isobutyl Alcohol	—	—	ND

continued . . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS[1]	NON-POSITIVE RESULTS[1]	Score[2]
Isopropyl Acetate	—		ND
Lead	+SPH	=CY#, -CY7	D
Lead Subacetate	—	—	ND
Lindane	+YEC, +PYC		C
Maleic Anhydride	—		ND
Methanol	—	-SC2, -CTC, -CT7	E
2-Methoxy Ethanol	—	—	ND
Methyl Acrylate	—	—	ND
Methyl Bromide	—		ND
Methyl Ethyl Ketone	—	—	ND
Methyl Isobutyl Ketone	—	—	ND
Methyl Methacrylate	—	—	ND
Mirex	—	-DLT	ND
Naphthalene	—	-SAL, -CTR, -CTK	ND
Nickel	—	—	ND
Nickel Oxide	—	—	ND
Nitrobenzene	—	—	ND

continued . . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS[1]	NON-POSITIVE RESULTS[1]	Score[2]
Pentachlorophenol	+YEC, +CT7, +YEF	-MST, -SAL, -HMA, -YEH	D
Phenol	—	-NER	ND
Phosphoric Acid	—	-CT7	ND
Phthalic Anhydride	—	—	ND
PCBs	—	—	ND
Propyl Alcohol	—	-SC2	ND
Propylene Oxide	+SRL, +CT7, +YEZ, +NER	-DLT	C
Resorcinol	+PYC	-SAL, -NEN	D
Selenium	—	—	ND
Selenium Sulfide	—	—	ND
Styrene	+SAL, +SRL, +HMA, +CY8, +MN7, +YEC, +MNP	-V79, -CT7, -UDH	A
Sulfuric Acid	—	—	ND
1, 1,2,2-Tetrachloro-1,2-difluoroethane	—	—	ND
1, 1 , 2 , 2-Tetrachloroethane	+YEH, +YEC, +REI, +YER	-SPI	C
Tetrachloroethylene	+YEH, +YEC, +YER, +CTR	-CT7	C

continued . . .

TABLE II-19. RESULTS OF SCORING FOR MUTAGENICITY, continued

Chemical Name	POSITIVE RESULTS[1]	NON-POSITIVE RESULTS[1]	Score[2]
Tetrahydrofuran	—	—	ND
Toluene	—	-SCI, -CT7, -SPI	E
Toluene Diisocyanate	—	—	ND
o-Toluidine	+REI, + CTR	-YEH, -SPI	C
1,1,1-Trichloroethane	+CTR	-SPI	C
1,1,2-Trichloroethane	—	—	ND
Trichloroethylene	+MST, +HMA, +YEH, +YEC, +CTR, +YER, +PGM, +SPI	-SRL	A
2 , 4 , 6-Trichlorophenol	+YEF	-MST, -SAL, -YEH, -YEC	D
Triethylamine	—		ND
Vanadium	—	—	ND
Vanadium Pentoxide	+REW	—	C
Vinyl Acetate	+CT7	-SAL	C
Vinyl Chloride	+SAL, +SRL, +CY8, +YEC, +RE2, +YEY, +PGM	-MST, -DLT, -DHT, -YEH	B
Vinylidene Chloride	+SAL, +PGM	-DLT	C
Xylenes (m-,o-,p-lsomers)	—	-SCL	ND

1. Test results from EPA Gene-Tox Program 5/87
2. Score based on weight-of -evidence, as presented in Table II-18.

First, one positive result in a group III assay may not be sufficient to classify the potential mutagenicity of a substance for humans, but it may be useful as supporting evidence of carcinogenicity. The same may be true for a set of inconclusive results. This system also makes it possible to identify data gaps and inconsistencies.

Second, the distinction highlights the message to a risk manager that "low score" is not necessarily equivalent to "low risk" and that the specific reasons for assigning a low score to a substance are variable. In general, aside from the high proportion of chemicals for which no data could be found, the methodology produced a relatively even spread of scores from A to E. While lower scores are more numerous, each weight-of-evidence category is well represented. This indicates that the methodology is sensitive to different types of evidence and is able to distinguish between them.

9. Summary

Few effects are as potentially dangerous, yet difficult to measure or prove, as human mutagenicity. Epidemiological data have been of little value thus far, although population monitoring for specific endpoints is currently being advocated (NRC, 1983; Smith, 1982; Brusick, 1982; McLean et al., 1982; Buffler, 1982). It is hoped that more studies of this type can be undertaken in the future. Because of the severe health implications of mutagenicity, and the need for efficient and inexpensive test methods, a large number of bioassays have been developed for identifying potential human mutagens. CHEM uses a battery of long-term and short-term screening assays to assess mutagenicity, each of which has been extensively reviewed by Gene-Tox and other groups. The tests are divided into three groups, reflecting

overall relevance to assessing hazards to humans. A score for each chemical is derived by weighing a number of variables, including the number and type of endpoints measured, the number and type of species represented, the significance of positives and non-positives reported, the relevance of specific tests for predicting effects in humans, the group classification of each test result and overall pattern presented. Non-positive results are always considered, but scoring is more a function of the number and type of positives reported for various endpoints and biological systems.

Unlike other health effects categories, potency and severity of effect are not included. The mutagenicity score is basically descriptive, representing a relative weight-of-evidence classification, since quantitative data are generally not available. Clearly, mutagenicity assessment is in a state of rapid progress, and any assessment method will require periodic review. Nevertheless, the Department believes that the procedures and assumptions outlined represent a valid approach to assessing potential human mutagens, lacking direct human evidence, and in the face of myriad variables which must be individually weighed.

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11. MUTAGENICITY WORKSHEET

The purpose of the mutagenicity worksheet is to record mutagenicity test results, which are used in scoring. All results recorded and used in the future. The tests are divided into three groups, representing the tiering system developed by the Department (see Part II, section E). The three groups are: mammalian, in vito tests; primary short-term tests; and secondary short-term tests. The 73 GENE-TOX tests are listed by three-character code on the worksheet. Two of the codes, "DSM" and "DCA", are listed in quotes because they were assigned by the Department and bring the total number of tests reviewed to 75. All 73 remaining codes are those used by GENE-TOX. Full test names and corresponding codes are those used by GENE-TOX. Full test names and corresponding codes are provided on a separate sheet following this introduction. The scoring methodology, presented in Table II-18, is reproduced here to facilitate the review of the worksheets.

At the top of the worksheet, the following information is included: Chemical name, CAS Registry Number, score received (A-E) and date worksheet was completed. The worksheet contains five columns. The purpose of each is described below.

Codes: Test names are designated by 3-character code, assigned as described above. To avoid doublecounting, tests measuring similar endpoints using similar biological test systems have been grouped together on the same line (e.g., SC1/SCW/SCL).

System: Biological test system (species) used in a given

test is indicated, designated by a letter as follows:

A = human, in vivo
B = other mammal, in vivo
C = human, in vitro
D = other mammal, in vitro
E = bacteria
F = Drosophila
G = fungi
H = plants

Endpoint: Type of mutagenic effect measured by the test.Effects are divided into four broad categories by GENE-TOX, and coded as follows:

G = gene mutation
C = chromosomal effect

Results: Test results reported by GENE-TOX are recorded here. Results are divided into two columns: "Intermediates" and "Final". The purpose of the "intermediates" column is to provide a place to record individual test results when more than one test is listed on the same line, but only one composite designation of positive (+) or non-positive (-) will be made in the "final" column for example, the tests designated as SCI, SCW, and SCL (sister chromatid exchange in various human cells) were grouped together by the Department because they are virtually identical with respect to species used and endpoint measured. For benzene, GENE-TOX reports non-positive results in SC1 and SCL and nothing for SCW because it has not been tested. These results are recorded in the "intermediates column as: "- // -", meaning non-positives in the first

and third tests, no results in the second test. The composite result designation is then a single non-positive (-) recorded under the "final" column. Dividing the results column in this way allows the Department to record all available results, even though only a single composite is used for scoring. Scores are assigned as indicated in Table II-1_8. Equivocal results, designated by `T', are also recorded under the "final" results column.

Comments: Additional information, such as dose-response notations or equivocal results, is listed here. In the future, data from primary sources will also be reported here.

MUTAGENICITY WORKSHEET FOR: DATE:				INITIAL: CAS CODE: SCORE:
CODES	SYSTEM	ENDPOINT	RESULTS	COMMENTS
		INTERMEDIATES	FINAL	
	GROUP I: MAMMALIAN, IN VIVO			
SLT	B	G		
MST	B	M		
'DSM'	B	C		
DCA'	B	C		
DLT	B	G		
HTT	B	G		
MNT	B	G		
	GROUP II: PRIMARY SHORT - TERM TESTS)			
V79		G		
CHO	D	M		
LSI	D	M		
SAL	E	M		
WP2/WPU	E	M		
SRL	F	M		
HMA	B/E	M		
CY5/CY8	A	C		
CY#/CY%	B	C		
CYO/CY9	B	C		
CY7/CYZ	C	C		
CY&	D	C		
MN7	C	C		
MN&	D	C		
DHT	E	C		
SCY	A	C		
SCI/SCW/SCL	C	C		
SC3/SC2	B/D	C		
ASG	G	C		
YEH/YEC	G	C		
RE2/REI	E	N		
REW/REX	E	N		
GROUP III: SECONDARY SHORT TERM TESTS				
YEF/YER/YEY/YEZ	G	M		
ASF/ASR	G	M		
NEF/NER	G	M		
PGM	H	M		
BFU	A	M		
DAC/DAP/DAG	F	C		
YEN/ASN/NEN	G	C		
MNP	H	C		
PYC	H	C		
SPI/SPR/SPA	B	X		
SPF	B	X		
UDH	C	N		
UDT	C	N		
UDP	D	N		

LEGEND

ENDPOINT		SYSTEM	
		A= Human, in vivo	D= Other Mammal, in vitro
N= DNA-related effects	several endpoints	B= other mammal in vivo	E= Bacteria G= Fungi
C= Chromosomal Effects	X= Ancillary Tests	Cs Human, in vitro	F=Drosophila H= Plants

F. Developmental and Reproductive Toxicity

1. Introduction

Conception, survival and healthy adulthood depend on the integrity of the reproductive process. It is well established, particularly in the case of pharmaceutical agents, that chemical exposure can be hazardous to that process, and the high incidence of human reproductive and developmental problems represents a major health concern. For example, it is estimated that as many as 50% of human conceptuses fail to survive to term (Dixon, 1980; Hertig, 1967) and approximately 3% of livebirths are associated with some developmental defect (USEPA, 1982, Mellen and Katzenstein, 1964). Others are born with functional anomalies of the nervous, respiratory, gastrointestinal, or immunologic systems, which may be due to environmental chemical exposures in utero (McKeown and Record, 1963). It is thought that 20% of human congenital malformations are attributable to mutations, 10% to known environmental factors (e.g. drugs, diet, chemical exposures), and the remainder to unknown causes (USEPA, 1984; Wilson, 1977).

Like carcinogenicity and mutagenicity, developmental and reproductive toxicity is not a single entity, but rather a diverse collection of adverse health effects. All living organisms are susceptible to those effects, which may not become apparent until long after birth. Understanding the reproductive process, and identifying specific chemical hazards is therefore a complicated task. Moreover, while the thalidomide disaster of the 1960s, discoveries concerning DES, and exposures to toxic wastes in Love Canal N.Y. State Department of Health, 1981) have served to focus public attention on these matters, the science of developmental and reproductive toxicity is still relatively

new. Very little human data exist, and identifying appropriate animal models has been problematic. For a number of reasons then, the developmental and reproductive toxicity category has been more difficult to establish than any other health effect category in CHEM. The problems encountered include the following:

- Definition - definitions of effects can vary considerably, depending on the perspective of the individual, group, or agency conducting the study. Thus, the same effect may be classified as "teratogenic" by one investigator, and as "fetotoxic" by another. In the literature, terms such as malformations, deformations, anomalies, aberrations, and deviations are commonly used, but are neither universally defined nor applied. In addition, judgments concerning the relevance of a particular effect, and its applicability to humans, often reflect differences of opinion. The lack of standardized definitions makes it difficult to accurately classify effects.

- Choice of animal model - no one animal model is universally appropriate, and selecting a test species for a given chemical exposure involves much uncertainty. Extrapolating from animals to humans involves the same difficulties encountered in other health effects categories, but with an added layer of complexity since placental systems differ among animal species. As a result, responses tend to be species-specific and data from various species are more difficult to evaluate and compare.

- Low-dose extrapolation - there is no widely accepted mathematical model available for extrapolating from

high-dose to low-dose exposures in the evaluation of developmental or reproductive effects. Nevertheless, to compensate for the small number of animals tested, and to increase the likelihood of detecting responses, high doses are generally used in experimental studies. Even in clinical and occupational settings doses are likely to be high, and this limits the understanding and evaluation of potential low-dose effects.

- o Research protocols - the data are difficult to interpret collectively due to the lack of standardized research protocols for developmental and reproductive toxicity studies. Thus, while both the EPA (1984) and FDA (1972) have recommended guidelines for testing, these protocols are not consistently used. When experimental procedures vary, there is no assurance that apparently similar studies are indeed comparable. It then becomes important to evaluate not only the results of testing, but also the adequacy of the experimental design itself.

- o Reporting of effects - without adequate reporting and thorough documentation of all findings, it can be difficult to differentiate true developmental effects from effects which occur secondary to maternal toxicity. Incomplete investigation or reporting can then lead to misclassification of effects.

- o Subjectivity - more than the other health effects categories evaluated in CHEM, the assessment of developmental and reproductive effects involves a great deal of professional judgement. In addition, there is a subjective element in assessing or prioritizing developmental or reproductive effects, which cannot be addressed on a strictly scientific basis. Thus,

opinions regarding which effects are more likely to have a greater impact on those affected and on society as a whole are necessarily individualized, and reflect broad societal and public policy questions - for example, whether infertility is more tragic than miscarriage or stillbirth, or whether congenital malformation is more tragic than neonatal death. Because persuasive arguments are made on both sides of this issue, and because of the broader policy implications, a definitive, universally-accepted conclusion is not likely. Therefore, CHEM evaluates all reproductive and developmental effects and attempts to define and classify each on a consistent basis. Classification is not always easy, however, because study findings are reported within the context of investigator bias. This recalls the problem of definitions, since effects not considered serious are often not reported, or are reported differently than those considered more significant. Thus, fetal wastage is sometimes reported as a teratogenic effect, sometimes as an embryotoxic or fetotoxic effect, and sometimes left out altogether. This creates obvious problems for the evaluation of developmental and reproductive hazards.

Despite these obstacles, scientists in the field are making progress toward identifying developmental and reproductive toxicants. A growing number of chemicals which are encountered primarily in environmental or occupational settings are now being tested by toxicologists. The task facing health planners is how to assess hazards to the human conceptus on the basis of currently available data.

2. Definitions and Application of Terms

a. Reproductive Toxicity

Reproductive toxicity is defined in CHEM as any effect resulting from parental exposure to a substance which interferes with conception, gestation, birth, or development of offspring to healthy adult life. This category is broadly defined in order to include the range of adverse effects of significance to both males and females. Reproductive hazards to the male include decreased ability to perform the sex act, morphologic change in sex organs, and decreased fertility due to reduced gamete production, reduced gamete viability, and/or production of abnormal gametes. Fertility hazards for the female are comparable to those in the male, but susceptibility extends into pregnancy, when the conceptus is also at risk. Thus, the male is at risk before and during mating, the female is at risk during mating and pregnancy, and the fetus is at risk from conception onward (Christian, 1983). As applied in CHEM, however, reproductive toxicity refers only to adverse effects in males and females of reproductive age, and developmental toxicity refers to adverse effects to the conceptus.

b. Developmental Toxicity

As defined in CHEM, developmental toxicity includes teratogenicity, embryotoxicity and fetotoxicity, and postnatal or perinatal developmental toxicity. Due to the wide range of endpoints of significance to the developing conceptus, the Department found it desirable to group similar effects. Use of these three groups makes the review, assessment, and scoring of myriad data a manageable task. Each term is defined and discussed below.

(i) Teratogenicity

A teratogen is defined as any agent that induces structural malformations, metabolic or physiologic dysfunction, or psychological or behavioral alterations in offspring, detected either at birth or in the immediate postnatal period. Effects occurring or detected after that time are classified under postnatal or perinatal developmental toxicity.

Major gross visceral or structural malformations are generally taken as definite indicators of teratogenicity since the incidence of these effects is usually quite low in nature. Thus, normal background rates for various malfunctions are considered in distinguishing between major malformations and more common variations. This is important since most species are prone to high background rates of particular skeletal variations. For example, mice are known to have a high incidence of misshapen sternebrae, rats to have poorly ossified sternebrae, and rabbits to have poorly ossified skullbones. Some variations, such as reduced or unossified sternebrae or vertebral arches may be completely reversible postnatally. Others, such as extra ribs, or vertebrae at the thoracolumbar border, may be normal developmental variations which do not cause dysfunction. A variation is usually defined as a divergence beyond the usual range of structural constitution, but which may not have as severe an effect on survival or health as a malformation. However, as the EPA points out, "distinguishing between variations and malformations is difficult since there exists a continuum of responses from the normal to the extreme variant. There is no generally accepted classification of malformations and variations". (USEPA, 1984, p. 46325).

When minor malformations occur in the presence of a major malformation, or when the minor malformation is rare for the species being tested, and there is a statistically significant increase in the incidence of minor malformations in the exposed versus the control group, the effects are classified as teratogenic in CHEM. However, skeletal and other variations which are common in historical control populations, and which represent the only signs of toxicity in a given study, are not classified as teratogenic. Rather, these effects are classified under embryo/fetal toxicity.

Behavioral and functional abnormalities are usually classified as teratogenic effects. The difficulties that arise in evaluating behavioral effects involve defining and testing for deviations. Although there are no universally accepted testing methods for behavioral teratology, it is generally desirable that data should include several dose levels, and that results should be replicated. The endpoints commonly evaluated include motor ability, sociability, emotionality, and learning ability.

Alterations in physiological function, or in a specific organ, may be early indicators of teratogenicity. In some cases, physiological alterations affecting functional competence may occur at doses lower than those producing major structural malformations or prenatal death, and it is not uncommon to see both types of effects in studies using more than one dose level (Hutchings, 1978). For example, many clinicians believe that prediabetic states, as measured by low serum levels of thyroid hormone, may account for fetal wastage in some women. Furthermore, hormone imbalances associated with toxic chemical exposure can

be teratogenic in themselves (Goldstein et al., 1984). Thus, early detection of abnormal metabolism and/or hormone levels in the maternal organism could provide an indication of potential birth defects.

The evaluation of functional abnormalities involves a range of endpoints and measurement techniques, since a number of organs, systems, and physiological processes may be affected. Test parameters include effects in endocrine systems, immune competence, xenobiotic metabolism, and physiological processes affecting cardiovascular, renal, gastrointestinal, respiratory or liver function. Table II-20 provides examples of various structural, behavioral, and functional abnormalities which are classified as teratogenic effects in CHEM.

(ii) Embryo/fetal Toxicity

Embryo/fetal toxicity includes effects on viability and growth of the developing conceptus. In definition, embryo/fetal toxicity differs from teratogenicity both in type and severity of effects. Whereas teratogenicity covers frank structural malformations and functional or behavioral effects, embryo/fetal toxicity pertains to effects on survival and development of the embryo or fetus, as well as minor malformations and reversible abnormalities.

Toxic effects to the embryo and fetus are more commonly observed than teratogenic effects in experimental studies, because teratogenic effects generally occur only when the embryo is exposed during the relatively brief period of organogenesis and differentiation. It is difficult for the investigator

TABLE II-20. CLASSIFICATION AND EXAMPLES OF TERATOGENIC EFFECTS

General Classifications of Teratogenic Effects*
A. Major Malformations - Gross structural and visceral anomalies B. Minor Malformations - Occuring in conjunction with major malfunction in the species tested (i.e. not a normal variation) C. Behavioral/Functional Abnormalities
Examples of Teratogenic Effects
o Encephaly o Spina bifida o Cleft palate o Acaudia (short tail) o Omphalocele (congenital hernia of the navel) o Missing organ, Malformed organ (e.g. heart with two chambers) o Displaced organ (of a serious nature) o Abnormal organ weight (of a serious nature) o Functional alterations - altered biochemistry, physiology, etc. (of a serious nature) o Aortic arch o Imperforate anus o Micrognathia (abnormal smallness of lower jaw) o Agnathia (lower jaw absent) o Oligodactyly (abnormal number of fingers or toes) o Syndactyly (fusion of two or more toes or fingers) o Hydroencephaly o Anophthalmia (absence of eyes) o Mental retardation o Abnormal motor ability, sociability, emotionality, learning ability

- When found at statistically significant levels and in the absence of maternal toxicity

to identify that precise moment, and provide exposure accordingly. As a result, many experiments will show no true teratogenic effects, but may demonstrate a significant incidence of embryo/fetal effects such as skeletal variations, decreased fetal size, or fetal death. In addition to having the potential to seriously alter normal development, these effects may also represent early indications of overt teratogenicity. As stated earlier, 50% of human fetuses fail to reach term, 3.0% of newborn children are found to have one or more significant malformations at birth, and by the end of the first year, about 3.0% more are found to have serious developmental defects (Dixon, 1980).

Table II-21 provides examples of effects classified under embryo/fetal toxicity in CHEM. The effects are divided into two categories ("Severe" and "Moderate") in order to separate chemicals producing serious, irreversible, or life-threatening defects from those producing effects considered to be reversible and not life-threatening. Several skeletal variations are classified as "severe" embryo/fetal effects rather than teratogenic effects because these defects have been produced in laboratory animals, and the implications for humans are uncertain. "Moderate" embryo/fetal toxicity includes many effects that can have serious consequences, but are distinguished from "severe" effects because they are not life-threatening and are considered reversible.

(iii) Postnatal and Perinatal Developmental Toxicity

While teratogenicity refers to effects manifested immediately after birth, postnatal developmental

TABLE II-21. CLASSIFICATION AND EXAMPLES OF EMBRYO/FETAL EFFECTS

I.	Severe Embrvo/Fetal Effects
o	Lethality
o	Resorptions
o	Individual skeletal variants (missing or poorly ossified sternebrae, vertebral centers, skull)
o	Abnormal umbilical cord length, transumbilical distance
o	Post implantation loss
o	Minor malformations or variations - common in species tested
II.	Moderate Embryo./Fetal Toxic Effects
o	Decreased crown-rump length
o	Reduced birth weight, weight gain
o	Retarded physical development
o	Total skeletal variants increased - but no individually increased incidences that are statistically significant

* When found at statistically significant levels and in the absence of maternal toxicity.

toxicity refers to the effects on embryonic, fetal, or neonatal development which are manifested any time after birth (including adulthood), and which result from exposure prior to, or during, gestation. Perinatal effects result from chemical exposure after the period of major organogenesis, and may be manifested at any time following birth. In studying perinatal effects, only dams are used, and exposure may continue throughout lactation. Effects on labor and delivery, lactation, and nursing are evaluated, as well as numbers of still-born versus live-born, biochemical and behavioral alterations, and gross anomalies. Thus, postnatal developmental toxicity covers a range of effects, including structural, functional, and behavioral abnormalities, any of which may occur as a result of maternal exposure after the period of major embryonic development or during nursing.

c. Other Definitions Used in the Developmental and Reproductive Toxicity Category

In addition, other terms and definitions have been adopted solely for use in the category of developmental and reproductive effects. For example, the term "risk-ratio" (introduced in subsection 4 below), was created by the Department and is used only in the context of evaluating the severity of developmental effects in CHEM. Strictly speaking, it is not a true ratio of "risk", but of toxic doses. Likewise, the term LOEL (subsection 4 below) is used somewhat differently in this chapter than elsewhere, and here refers only to the lowest dose associated with statistically significant developmental or reproductive effects <u>reported in a given study</u>, and not the lowest <u>overall</u> dose associated with those effects. (For purposes of clarity, the lowest observed effect level reported in a

given study is designated as $LOEL_s$, in order to distinguish that value from the overall LOEL selected from among reported values in all the studies evaluated, and then used for scoring in CHEM.) Thus, a low effect level is generated in each study, ($LOEL_s$) and the one which will be used for scoring (LOEL) is selected on a case-by-case basis, after assessing the weight-of-evidence and risk ratio values as well.

In addition, certain phrases are used narrowly throughout this chapter for purposes of clarity when there is some overlap in terminology. For example, when discussing weight-of-evidence, the term "category" is used (i.e., Confirmed, Substantial, Suggestive, Inadequate, No Data), whereas the term "classification" is used when discussing the evaluation of data quality (i.e., Adequate, Supportive, Inadequate). Thus, studies are classified on the basis of their overall adequacy, and the collective evidence is then weighed and categorized for scoring purposes.

3. Toxicity in the Maternal Organism

In some cases, signs of teratogenicity or embryo/fetal toxicity can occur secondary to a toxic effect in the maternal organism. An association between maternal toxicity and fetal malformation suggests that maternal toxicity may be implicated as the cause, rather than the test agent directly. Based on a large survey of the literature, strong associations were also noted between maternal toxicity and embryo/fetal deaths and post developmental effects (Khera 1985). Common indicators of maternal toxicity associated with developmental effects include lethargy, weight loss, decreased food or water consumption, weight-gain abnormalities, or death (Khera, 1984). In order to

distinguish between direct fetal effects and those potentially related to maternal toxicity, it is necessary to evaluate fetal effects in the context of maternal effects. If the pattern of response for maternal toxicity is parallel to embryo or fetal toxicity throughout the same dose range, this is an indication that the embryo- or fetal toxicity stems from the primary effects of exposure to the mother, particularly when both maternal and fetal effects disappear at lower doses (Khera, 1984). For example, if reduced maternal weight gain is observed, and correlates closely with reduced mean pup weight over similar dose ranges, it may be concluded that direct embryo/fetal toxicity has not occurred. Another example of maternal toxicity causing fetal effects is an "all or none" litter response, where some litters are completely destroyed and others are not. In CHEM, teratogenic or embryo/fetal effects observed in the presence of maternal toxicity are given lower "weight" in the final assessment. Evaluation and scoring of various effects are described in sub-section 6 below.

4. Use of Dose-Response Information

Developmental and reproductive toxicity are observed throughout a wide range of doses, depending on the chemical. Because high doses may not be relevant to environmental exposures, it is important to note at which levels adverse effects occur. In CHEM, the lowest observed effect level (LOEL) in a given study is used to evaluate developmental and reproductive effects. The LOEL is the lowest dose at which statistically significant effects are observed, and therefore requires the use of two or more dose levels per treatment group. The LOEL is distinguished potency because it does not reflect the dose-response curve, and is simply an arbitrary, though meaningful, point from which to make comparisons among chemicals. It is arbitrary insofar as it

is frequently the lowest dose selected by the investigator for testing. There may well be effects at levels lower than those selected for the study, and therefore, the LOEL can reflect investigator choice rather than lowest possible effect level or all-inclusive dose-response curve. Thus, the LOEL depends on the dose chosen by the investigator. The investigators' decisions may vary when choosing a dose depending on their specific reason for conducting the study. The choice of LOEL would be less arbitrary if investigators chose doses for the same reason or on the same basis.

An additional component, the "risk ratio", is used in assessing developmental toxicity. The risk ratio compares the relationship between the adult toxic dose (or exposure) to the dose (or exposure) affecting the embryo or fetus. It is derived by dividing a published LD_{50} or LC_{50} value for the chemical by the lowest observed effect level reported for the study. An LD_{50} or LC_{50} is defined as the lethal dose or concentration of a chemical needed to produce death in 50% of the exposed animals. The LD_{50} and LC_{50} value used is selected to correspond exactly to the species and route of exposure used for the LOEL. When more than one LD_{50} or LC_{50} value is available for the same species and route, the Department evaluates the data in order to decide which value to select for use. A variety of factors can affect the value of the LD_{50} and LC_{50} including species and strain, experimental protocol, duration of exposure, gender of test animal, statistical evaluation, and purity of chemical compounds. Evaluation of the data may provide the Department with guidance on the appropriate value to use. If no toxicological basis or reason is found when evaluating the literature, the prudent public health decision is to take the value that provides the highest risk ratio value. This conservative approach is used in CHEM when no other basis exists.

An underlying question when evaluating any developmental effect is whether the chemical agent was directly responsible for producing the effect, or whether the effect observed was secondary (i.e., related to toxicity in the mother). The risk ratio is used to distinguish between doses (exposures) that produce effects in the embryo or fetus, versus doses (exposures) that produce effects in the adult. A large risk ratio indicates greater sensitivity in the fetus as compared to the adult, and helps to identify chemicals of greatest toxicological concern to the embryo/fetus. Smaller risk ratios indicate that embryo/fetal effects occurred only at doses closer to levels producing toxic effects in the adult. In this case, the risks to the embryo/fetus can also be more easily discerned, since the mother may demonstrate signs of toxicity. Thus the risk-ratio represents the magnitude of difference between a substance's developmental effect and its lethal effect, and is designed to identify substances of particular concern due to a wide margin between doses producing maternal and developmental toxicity. It provides an indication of the degree of hazard associated with a given chemical exposure. By definition, the concept of risk-ratio does not apply to reproductive toxicity, but only to effects in the conceptus.

5. Data Sources

The evaluation of developmental and reproductive toxicity makes limited use of secondary sources, relying instead on primary science literature. As discussed earlier, the lack of standardization in terminology, research protocols, and classification systems precludes reliance on secondary sources. Rather, secondary sources such as IARC, NIOSH, CESARS, and EPA are used only as bibliographic references to the original literature. The

list of secondary sources used for this purpose appears in Table II-1.

Developmental and reproductive toxicity is the only health effect category in CHEM which relies solely on primary literature. However, using primary literature necessitates obtaining and evaluating a large amount of data, and has been a time-consuming and complicated process. In order to evaluate and use varying types of data in a rational and consistent manner, a methodology was developed to facilitate that process and includes: description of test protocols, criteria applied to evaluation of data quality, assessment of data quality, and selection of species. Each is discussed below.

a. Description of Test Protocols

A key to evaluating data quality is understanding the research process. Elements of that process are discussed below, in the context of developmental and reproductive studies.

(i) Developmental Studies

One of the most important factors in any research protocol is the proper use of control populations. In animal tests, control animals must be of the same species and strain as test animals, and must be treated identically with respect to feed, housing, and exposure vehicle. For example, if females in the exposed group are administered 1 cc of treated solution by gavage, the control females must receive 1 cc of untreated solution by gavage. This is particularly important in teratology because the vehicle itself (e.g., gavage or injection) or any foreign substance could cause birth

defects. Likewise, the same lot of a chemical should be used throughout the experiment. Since teratogens are highly specific, a slight difference or impurity in the chemical could alter the results. If the chemical is administered by inhalation or in feed, it is important to note how dose was calculated for each animal or group. In addition, for an experiment to represent a true test of teratogenicity, rather than a test of acute maternal toxicity, the chemical should be administered at the appropriate stage of gestation and mothers should be carefully monitored. Table II-22 lists commonly used animal species and critical periods for administration of test substances. Other criteria used in the evaluation of data include statistical significance, number of animals used (statistical power), biological endpoints evaluated, and test methods. Each of these is important in determining how representative the study is, and how likely it is that the findings are valid.

(ii) Reproductive Toxicity Studies

The assessment of fertility and reproductive hazards for males and females involves a range of processes and organ systems. In addition, many effects are not independent, and an increase in one deleterious effect may in turn produce another type of effect. There are two major testing categories for evaluating fertility and reproductive toxicity resulting from chemical exposure: mating and non-mating studies. Typically, non-mating studies in males evaluate effects on testes' weight, morphology, histology, and biochemistry, as well as sperm motility. Non-mating studies in females usually involve studying changes in hormone levels, estrous cycle, and ovarian function

TABLE II-22. COMPARATIVE GESTATIONAL DEVELOPMENT AMONG VARIOUS SPECIES

	Human	Rat	Mouse	Rabbit	Hamster
Implantation period	6-12 days	8 days	5 days	9 days	7 days
13 to 20 somite	27 days	11 days	9 days	10 days	9 days
End of embryonic period	12-14 weeks	14 days	13 days	11 days	10 days
End of metamorphosis	20 weeks	17 days	17 days	15 days	14 days
Fetal development	20-24 weeks	18-20 days	18-20 days	16-32 days	15-16 days
Parturition	20-40 weeks	21 days	19 days	32 days	15 days

SOURCES: Rugh, 1968; Wilson, 1977

following chemical exposure. There are a multitude of other tests that are used to evaluate reproductive hazards in a number of different organs, or for various reproductive processes. Tables II-23 and II-24 describe the reproductive organs and processes which are susceptible to reproductive toxicants in females and males, respectively. The lists are not all-inclusive, but serve to illustrate the range of biological systems and processes at risk.

Mating studies are conducted in a variety of ways. For example, dams may be sacrificed on day 13 of gestation in order to assess effects on the developing embryo, or to evaluate uterine abnormalities. In these studies, males are usually untreated and are mated with treated females. In other studies only males are treated, or both males and females are treated prior to mating. Mating studies also evaluate effects on gestation periods, labor and delivery. When carried further, reproductive function in the offspring can be evaluated. Multigeneration studies are conducted to reveal effects caused by cumulative toxicity, or by agents effective at low concentrations. Effects are typically evaluated over three generations. In many instances, studies on reproductive performance in adults also measure effects in offspring, such as teratogenicity or embryo/fetal toxicity. The overlap among endpoints may or may not result from similar mechanisms of action.

b. Criteria Used to Evaluate Data Quality

In order to provide reliability and consistency to the assessment process, each study is evaluated with respect to its adequacy. The criteria used for evaluating the quality

TABLE II-23. CONSIDERATIONS IN EVALUATING RISK TO FEMALE REPRODUCTION

	NON-PREGNANT	PREGNANT
Vulva/Vagina	Virilization	
Cervix	Structural Abnormalities Mucus production and/or quality	Incompetence
Uterus	Luminal fluid Structural malformations Dysfunctional bleeding Dyssynergia Deficient pseudodecidual response	Untimely parturition Dysfunctional labor Uterine blood flow Gestational trophoblastic disease Deficient decidual response
Fallopian Tube	Gamete transport fluid	Zygote transport
Ovary	Decreased number of oocytes Luteal function Increased rate of follicular atresia Follicular: steroidogenesis maturation rupture fluid quality Oocyte maturation Luteal function Chronic anovulation	Luteal function
Breast	Supernumerary mammary glands Galactorrhea Nongalactorrheic discharge Gynecomastia	Lactation: composition capability Transplacental transport of toxicants Hydatidiform mole Enzymatic activities
Pituitary	Hyperprolactinemia Hypoprolactinemia Altered synthesis and release of trophic hormones	
Hypothalamus	Altered syntheseis and release of neuro-transmitters, neuro-modulators, and neuro-hormones	

continued . . .

TABLE II-23. CONSIDERATIONS IN EVALUATING RISK TO FEMALE REPRODUCTION, continued

Liver	Metabolism Binding protein synthesis	Metabolism Binding protein
Adrenal	Steroidogenesis	Steroidogenesis
Behavior	Sexual Behavior	Maternal Behavior
Reproductive lifespan	Puberty Menopause	

TABLE II-24. CONSIDERATIONS IN EVALUATING RISK TO MALE REPRODUCTION

BODY WEIGHT

TESTIS
- Size in situ
- Weight
- Spermatid reserves
- Gross histology
- Nonfunctional tubules (%)
- Tubules with lumen sperm (%)
- Tubule diameter
- Counts of leptotene spermatocytes

EPIDIDYMIS
- Weight of distal half
- Number of sperm in distal half
- Motility of sperm, distal end (%)
- Gross sperm morphology, distal end (%)
- Detailed sperm morphology, distal end(%) Gross histology

ACCESSORY SEX GLANDS
- Weight of vesicular glands
- Weight of total accessory sex glands

SEMEN
- Total volume
- Gel-free volume
- Sperm concentration
- Total sperm/ejaculate
- Total sperm/day of abstinence
- Sperm motility, visual (%)
- Sperm motility, videotape % and velocity
- Gross sperm morphology
- Detailed sperm morphology
- Concentration of agent in sperm
- Concentration of agent in seminal plasma
- Concentration of agent in blood
- Biochemical analyses of sperm/seminal plasma

ENDOCRINE Luteinizing hormone
- Follicle-stimulating hormone Testosterone
- Gonadotropin-releasing hormone

continued

TABLE II-24. CONSIDERATIONS IN EVALUATING RISK TO MALE REPRODUCTION

BODY WEIGHT

TESTIS
- Size in situ
- Weight
- Spermatid reserves
- Gross histology
- Nonfunctional tubules (%)
- Tubules with lumen sperm (%)
- Tubule diameter •
- Counts of leptotene spermatocytes

EPIDIDYMIS
- Weight of distal half
- Number of sperm in distal half
- Motility of sperm, distal end (%)
- Gross sperm morphology, distal end (%)
- Detailed sperm morphology, distal end(%) Gross histology

ACCESSORY SEX GLANDS
- Weight of vesicular glands
- Weight of total accessory sex glands

SEMEN
- Total volume
- Gel-free volume
- Sperm concentration
- Total sperm/ejaculate
- Total sperm/day of abstinence
- Sperm motility, visual (%)
- Sperm motility, videotape % and velocity
- Gross sperm morphology
- Detailed sperm morphology
- Concentration of agent in sperm
- Concentration of agent in seminal plasma
- Concentration of agent in blood
- Biochemical analyses of sperm/seminal plasma

ENDOCRINE
- Luteinizing hormone
- Follicle-stimulating hormone Testosterone
- Gonadotropin-releasing hormone

continued

TABLE II-24. CONSIDERATIONS IN EVALUATING RISK TO MALE REPRODUCTION, continued

FERTILITY
Ratio exposed: pregnant females
Number of embryos or young per pregnant female
Ratio viable embryos: corpus lutea
Ratio implantation: corpus lutea
Number 2-8 cell eggs
Number unfertilized eggs
Sperm per ovum
Number of corpus lutea
IN VITRO
Incubation of sperm in agent
Hamster egg penetration test

of animal studies are derived from the U.S. Food and Drug Administration (USFDA) Guidelines for Reproductive Studies for Safety Evaluation of Drugs for Human Use (1972) (see Appendix G), and the EPA Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants (1984). The FDA guidelines provide recommended study protocols for testing in the areas of teratogenicity, embryonic and fetal effects, maternal and paternal reproductive toxicity, and postnatal developmental effects. The EPA guidelines provide assistance in evaluating statistical analysis, data quality, and reporting procedures for various types of studies. Worksheets have been designed for the assessment of data quality using FDA and EPA guidelines, and samples are included at the end of this chapter. Studies in humans are evaluated according to IRLG Guidelines for Documentation of Epidemiological Studies (IRLG, 1979). The various guidelines and types of studies are discussed in following sections.

(i) U.S. Food and Drug Administration

The FDA guidelines recommend protocols for experimental studies. Design considerations include use of control groups, number of doses per treatment group, number of animals per dose group, and statistical analysis. Category-specific guidelines are provided for studies of teratogenicity, fertility, reproductive, perinatal, and postnatal toxicity. For teratogenicity studies, the FDA recommends that two or more dose levels be used, only females be treated (so that dose to the target - embryo or fetus - can be calculated), that the treatment period cover the time of organ formation, and that fetuses are delivered by Cesarean section one or two days prior to parturition. According to FDA guidelines, the experimental

parameters which should be evaluated include the following:

- Number of fetuses (total)
- Number of live versus dead fetuses
- Number of resorptions (early and late)
- Placement in uterine horn
- Correlation of fetuses with corpus lutea
- Fetal weight
- External anomalies
- Internal anomalies (one-third for dissection or Wilson slicing for visceral anomalies; two-thirds for cleaning and bone staining with alizarin).

Likewise, specific parameters are also recommended for evaluating reproductive toxicity, and perinatal and postnatal developmental toxicity.

(ii) U.S. Environmental Protection Agency

The EPA guidelines are also used to judge data quality and reliability. They assist by further defining the validity and significance of findings, based on statistical methods recommended by FDA. For example, in teratogenicity studies, malformations may be reported as the number of affected fetuses per litter, or the percent of affected litters per treatment group. As EPA points out, reporting the number of affected fetuses per litter is more informative, since in any given litter the percent of malformed fetuses could range from 0-100%. Simply knowing that some percentage of litters was affected, without knowing the precise number of individuals per group, is not very useful. Thus, while the FDA recommends statistical

evaluation of experimental results, EPA goes further in specifying analytical and reporting procedures. In the worksheets developed for CHEM, the preferred methods of data analysis are listed in order of descending value to assist in the evaluation of data quality.

The EPA-proposed guidelines are also used to broaden the range of endpoints which may be considered. The guidelines incorporate additional parameters, such as biochemical studies in the fetus and evaluations of maternal toxicity, which were not specifically discussed by FDA.

EPA's guidelines for studying teratogenic hazards differ from FDA recommendations with respect to the selection of species as well. While both FDA and EPA recommend that two species be used, FDA recommends that one should be a rodent and one a non-rodent, whereas EPA does not make such a stipulation. CHEM follows the EPA criterion in this regard because ideal animal models have not been agreed upon, and because most of the available data pertain to rodents only. Worksheets listing FDA and EPA parameters used in the assessment of developmental and reproductive toxicity studies are presented at the end of this chapter. FDA Guidelines for Reproductive Studies are given in Appendix G.

c. Assessment of Data Quality

The assessment of developmental and reproductive effects is based entirely on data obtained from primary literature, rather than the peer-reviewed, committee-based secondary sources used in other health effects categories of CHEM. Given the variable design, documentation, and quality of experimental studies, it is necessary to evaluate the quality of each study before incorporating the data reported, or relying on the results. Consistency is obviously of paramount importance when evaluating and

comparing a large number of studies. At the same time, the decision as to whether a given study should be included in the database and used for scoring necessarily involves a case-by-case analysis of the particular strengths and weaknesses of that study. As described in the preceding section, the Department has relied upon criteria recommended by IRLG, FDA, and EPA, in making this judgement, and the adequacy of each study is judged by the extent to which the study design and documentation conform to recommended protocols. Since the approach and methods applied to epidemiological studies differ from those used in laboratory studies with animals, the criteria used to evaluate the quality of each are discussed separately below.

(i) Epidemiological Studies

Epidemiological studies can provide strong evidence from which public health decisions can be made. Epidemiology provides a direct measure of risk to humans, and avoids many of the difficulties inherent in interspecies extrapolations.

Epidemiological studies used for scoring in CHEM must be well-conducted and adequately documented. The Guidelines for Documentation of Epidemiological Studies prepared by the Epidemiology Work Group of the Interagency Regulatory Liaison Group (IRLG, 1979) provide the framework for evaluation in CHEM. The types of epidemiological studies addressed by the IRLG, each of which contributes a different level of insight concerning the etiology of environmentally-related diseases, are shown in Table II-25. For each kind of study, the IRLG guidelines outline the type and extent of information considered important for the objective evaluation and interpretation of epidemiological

TABLE II-25. TYPES OF EPIDEMIOLOGICAL STUDIES

Ecological	An evaluation is made of the spatial and/or temporal patterns of morbidity or mortality in human populations where classification is made on the basis of aggregates of individuals as distinct from single individuals. In this type of study all individuals, both in the numerator and the denominator, are not classifiable according to the study of association. An example is the comparison of cancer mortality in counties classified according to parameter(s) such as the density of selected industries, the average hardness of water, background radiation, or the proportion of population of specified ethnicity.
Demographic	An evaluation is made of the risk of morbidity or mortality in human populations composed of individuals classifiable by limited demographic characteristics such as geographic area of residence, age, sex, ethnicity, or calendar time. In this type of study all individuals, both in the numerator and the denominator are classifiable according to the study parameters, and, thus, this type of study does permit a direct measure of association.
Cross-section	An evaluation is made of the differential prevalence of disease at a specified time among two or more groups, the individuals of which are classified by level of exposure at that specified time.
Case-control	An evaluation is made of the past differential exposure to an agent between two groups, the individuals of which are defined according to the presence or absence of a specific disease or injury and are representative of the population from which the cases arose.
Cohort	An evaluation is made of the differential incidence of disease among two or more groups, the individuals of which are classified by level of exposure to a specific agent, with each group's being followed over some period of time.

SOURCE: IRLG, 1979

studies. The major elements for evaluating epidemiological studies include:

- Background and objectives of the study
- Study design
- Study subjects
- Comparison subjects
- Data collection procedures
- Analytical methods and statistical procedures
- Data interpretation
- Limitations and inferences
- Supportive documentation

In CHEM, the reliability of any epidemiological study is judged on the basis of the IRLG guidelines, and classified as providing "adequate," "supportive," or "inadequate" evidence of developmental or reproductive toxicity.

In order to be classified as "adequate", the study must have been conducted in accordance with IRLG guidelines. Studies which do not conform to those guidelines in some important respect, or fail to establish a conclusive link between exposure and response, are classified as "supportive" or "inadequate", depending on the nature and magnitude of the limitations involved. For example, confounding variables are often difficult to account for in epidemiological studies, especially when important factors are not considered in the study design. Precise measurements of dose are difficult to obtain in epidemiological studies, especially when the study involves workers exposed to varying levels over time,

or to mixtures of chemicals. Many well-conducted studies may therefore provide evidence suggestive of a cause and effect relationship but because of limitations in the study they are considered less than "adequate" and are classified as "supportive".

Studies which have been poorly conducted, and/or poorly documented are classified as "inadequate". For example, when no justification is provided for combining subgroups of study subjects, or confounding variables such as age, sex, ethnic group or lifestyle have not been evaluated, the study is judged to be too limited for scoring and is not used in CHEM. For assigning weight-of-evidence and selecting the LOEL, only studies classified as "adequate" are used.

(ii) Experimental Studies

The quality of experimental studies is evaluated on the basis of the FDA and EPA criteria described above and outlined in the worksheets.
Studies are classified as "adequate", "supportive", or "inadequate", as described below.

- Adequate Quality: a study classified as adequate is conducted according to FDA and EPA guidelines, and all endpoints of interest are evaluated using FDA and EPA criteria. In some cases a study may be judged to be "adequate" despite some deviations from the established protocol, so long as those deviations are not expected to alter the conclusions.

  Some deviations from a referenced protocol are appropriate. As stated in a report by the

National Academy of Sciences, "since reference protocols are developed for general application before it is known what results are important or what effects are to be screened, some deviations from the guidelines are needed." (NAS, 1984, p. 9) Behavioral studies provide an obvious example. The FDA teratology guidelines recommend that the investigator stain the fetal skeleton with alizarin and dissect the fetus. Clearly it is impossible to do this and subsequently gather behavioral data.

In another example, FDA guidelines recommend the use of two doses in teratology studies. However, some studies utilize one dose, and test on several individual days of gestation. This method is also useful, since the data collected are relevant to the assessment of teratogenicity, and provide information on critical periods of embryo or fetal sensitivity, dose, and severity of effects. A third example concerns numbers of animals used. The guidelines recommend 20 or more rodents per group. However, when fewer animals are used and the study demonstrates statistically significant major malformations in a dose-response pattern, the evidence is not discarded. This assures that data on severe chemical hazards to the developmental and reproductive process are not overlooked.

- Supportive quality: studies classified as supportive are limited in some respects, but are not flawed to the point of being termed "inadequate". Examples of limitations which disqualify a study from the "adequate" category

include flaws in data presentation or tabulation of effects, lack of information on maternal toxicity or specific test methods, insufficient number of animals, or other deviations from EPA and FDA protocols. These studies are not directly used in scoring because of their limitations. Nevertheless, the information provided can corroborate findings from "adequate" studies and add significance to those results.

Such studies also provide information on potential effects, as well as on pharmacokinetics, species sensitivity, and placental transport, and contribute to the overall evaluation of developmental and reproductive toxicity for those chemicals. Thus, "supportive" studies are used to supplement weight-of-evidence categories but are not used for quantitative assessment.

- Inadequate quality: studies classified as inadequate include test results which are reported in abstract form only, studies conducted in non-mammalian or in vitro systems (e.g., chick embryo), and studies with a number of serious departures from the FDA and EPA proposed guidelines.

The Department's review of 188 studies showed that 45% did not meet the minimum criteria for "adequate" quality. As a result, these studies were eliminated from consideration for scoring. One alternative the Department is considering is contacting the investigators and requesting further information on how these studies were

conducted. It is hoped that the availability of the proposed FDA and EPA guidelines for the evaluation of developmental toxicity will improve the uneven quality of published literature.

Example of Assessment of Experimental Studies

The evaluation of benzene provides examples of studies classified as adequate, supportive, and inadequate. There are a total of nine studies gathered from the literature. Of these, five were classified as adequate, one as supportive, and three as inadequate for scoring.

Adequate: Of the five "adequate" studies, one showed severe embryo/fetal toxicity in the mouse; two studies demonstrated minor embryo/fetal toxicity in rabbits and rats, each in the presence of maternal toxicity; and two studies demonstrated minor embryo/fetal toxicity in rats in the presence of maternal toxicity.

In the mouse study (Murray et al., 1979), concordance with the adopted criteria for "adequate" quality in CHEM included: use of concurrent controls, more than 20 animals, statistical analysis (on number of affected fetuses per litter), untreated males, treatment covering period of organ formation, and Cesarean delivery one day prior to parturition. The parameters evaluated included numbers of fetuses, placement in uterine horn, number of live and dead fetuses, numbers of resorptions, fetal weight, external and internal anomalies, biochemical and hematological analyses. Maternal toxicity was evaluated on the basis of body weight, food and water consumption, and percent of successful conceptions. The study was, therefore,

classified as adequate, based on experimental design, methodology, parameters investigated, and appropriate data analysis.

The study had two limitations, however. First, the investigators did not correlate fetuses with corpus lutea. Since this deviation does not detract from the findings, however, the study can be used for scoring in CHEM. The second limitation is the use of only one dose. Because embryo/fetal toxicity was clearly demonstrated at that dose, the use of a single dose does not disqualify the study from being used to evaluate the weight-of-evidence, and it is classified as "adequate". It cannot provide dose-response information, however, and therefore limits scoring to qualitative considerations, since LOEL and RR cannot be calculated on the basis of a single dose.

Supportive: A study of perinatal and postnatal developmental toxicity (Gofmekler, 1968) provides an example of a "supportive" study. The experimental design included concurrent controls, and seven different doses, but only 10-12 rats were used in each dose group, and statistical analysis was somewhat limited (i.e., average values per pup). Females were exposed prior to mating and during gestation; males were exposed for 6-8 days during mating. Toxicity was evaluated on the basis of gross anomalies, pup weight, and organ weight. Statistically significant changes in organ weights were seen in the lungs, spleen, kidneys, adrenals, and livers of pups. The study was not considered adequate because, with both males and females being exposed, dose to the fetus could not be quantified. Other limitations include the use of fewer than 20 animals per group and imprecise estimations of

gestation periods (calculated from beginning of mating periods). All other methods used were suitable.

Although there are limitations in this study, it does suggest that exposure to benzene during the reproductive process can affect development of various organs, particularly the fetal lung, where a dose-response relationship was observed. However, since no perinatal or postnatal developmental studies to support these findings are available, and since the study quality is less than adequate, the information is recorded on the worksheets but not used in scoring.

Inadequate: three studies on benzene were classified as inadequate. One study (Gofmekler and Pushkina, 1968) was quite limited in terms of endpoints evaluated (effects on concentrations of ascorbic acid, DNA, and total nucleic acids in cells of various organs). This study also did not report the number of animals per treatment group, nor did it describe test methods. Another study of teratogenicity by the same researchers (Pushkina and Gofmekler, 1968), was severely limited in that males and females were both exposed, only 5-10 animals per treatment group were used, and no details were provided as to methods of sacrifice. The third study classified as inadequate (Nawrot and Staples, 1979), was only available as an abstract, and numerous details about experimental design and methods were not included.

d. Selection of Species

Researchers have found that almost all human teratogens are also teratogenic in test animals, but not necessarily in all species. Among known or suspect human teratogens, 85%

are teratogenic in mice, 80% in rabbits, 45% in hamsters, and 30% in monkeys (USFDA, 1980). This does not imply that the mouse is the most suitable animal model, or that a given chemical is more likely to cause teratogenic effects in mice than in monkeys. Rather, the implication of these findings is that positive results in animals should be considered indicative of potential teratogenicity in humans, and that negative results in animals do not rule out teratogenicity in humans (e.g., thalidomide). Furthermore, the above findings underscore the difficulties encountered in teratology testing, such that teratogenic effects are not always readily detectable.

The best or most relevant species for testing developmental toxicants has yet to be agreed upon (NAS, 1977). Each species seems to have some unique disadvantage, and no species has been uniformly predictive for humans. The mouse has been considered useful because of its general suitability for laboratory research - including size, ease of handling, high fertility, and sensitivity to teratogens. However, the mouse exhibits high background rates of spontaneous malformations and resorptions, particularly in some strains, and this can make test results ambiguous. The rat has all the positive characteristics of a small laboratory animal, has a low rate of spontaneous malformation (less than 1%), and is genetically stable. The rat has a very low sensitivity to teratogens, however, and may produce false negatives in testing.

Rabbits have sometimes been preferred on the basis of ease of insemination and optimal fetal size, but there are no pure strains. Dogs have a low spontaneous malformation rate and a placenta more similar to humans, but are disadvantageous in terms of cost, availability, and breeding habits. Primates share many anatomical and phylogenetic

similarities with humans. They have a chlorioallantoic placenta similar to humans, rather than the inverted yolk sac placenta of rabbits and rodents. They have been shown to have some metabolic pathways similar to humans, are susceptible to comparable doses of some agents, and have low spontaneous malformation rates. However, teratogenicity is not readily observed in primates due to difficulties identifying optimum exposure times in relation to gestational stage, and embryo/fetal toxicity is more readily detected. In addition, there are major logistical problems with using primates, including size, cost, difficulty in handling, and low fecundity. For these reasons, primates are not generally used in experimental studies, and few data exist for primates. Therefore, CHEM relies on the best available evidence from a variety of species.

The chick embryo is generally not recommended for teratogenicity testing because the species is non-placentary and may therefore be particularly susceptible to teratogenic agents. Chick embryo data are not considered in CHEM. Nevertheless, the chick embryo has been shown to be responsive to a broad range of agents known to affect mammalian embryos, and can be useful as a screening system in experimental settings.

6. Evaluation and Scoring of Developmental and Reproductive Toxicity

In CHEM, the evaluation of developmental and reproductive toxicity involves three separate elements: the weight-of-evidence, the lowest-observed-effect-level (LOEL), and, for developmental toxicity, the risk-ratio (RR). Based on the results of these qualitative and quantitative assessments, each chemical is assigned a letter score (A-E)

reflecting relative overall hazard. Each of the three elements is discussed in detail below.

a. Weight-of-Evidence Evaluation

As with carcinogenicity and mutagenicity, there is no attempt to classify chemicals into categories of teratogens or non-teratogens, embryo/fetal toxicants or non-toxicants, etc. Rather, CHEM focuses on sorting out the qualitative data and evaluating the likelihood that a chemical may produce developmental and/or reproductive toxicity in humans. All studies are evaluated with respect to their relevance to humans and, based on the quality and amount of available data, assigned into weight-of-evidence categories.

Since a chemical may produce more than one developmental or reproductive effect, the weight-of-evidence is generally categorized for each endpoint independently of the others. Teratogenic and severe embryo/fetal effects are an exception to the rule, however. Due to the uncertainties involved in defining and distinguishing teratogenicity and severe embryo/fetal toxicity, results in each are sometimes grouped together. For example, two positive animal tests showing teratogenicity are assigned to the same weight-of-evidence category as one positive teratogenicity study plus one showing severe embryo/fetal toxicity (see Table II-26, "Substantial Evidence - Group I). It should be noted that the broad weight-of-evidence categories (e.g., Confirmed, Substantial, Suggestive, etc.) have been further divided (e.g., Substantial Evidence - Group I). Evidence categories and subcategories for developmental and reproductive toxicity are presented and defined in Tables II-26 and II-27, respectively.

TABLE II-26. WEIGHT OF EVIDENCE CLASSIFICATION FOR DEVELOPMENTAL TOXICITY

CATEGORY	DESCRIPTION OF EVIDENCE
CONFIRMED EVIDENCE	Human evidence showing causal association between exposure to the chemical and adverse effects of development.
SUBSTANTIAL EVIDENCE	
Group I	Evidence from two or more positive animal tests showing teratogenicity [or more severe embryo/fetal effects, perinatal, or postnatal developmental effects]. ---Or, Evidence from one positive animal test for teratogenicity and some evidence of teratogenicity in humans, although data are not sufficient: to conclusively demonstrate a causal association [same evidence for severe embryo/fetal toxicity, perinatal, or postnatal developmental effects]. ---Or, Evidence from one positive animal test demonstrating teratogenicity in animals and one positive test indicating severe embryo/fetal toxicity in animals.
Group II	Evidence from two or more positive animal tests showing minor embryo/fetal effects. ---Or, Evidence from one positive teratogenicity study in animals and one positive test in animals showing minor embryo/fetal toxicity. ---Or, Evidence from one positive animal study showing minor embryo/fetal toxicity and some evidence of embryo/fetal toxicity in humans (of a mild nature), although data are not sufficient to conclusively demonstrate a causal association.

continued

TABLE II-26. WEIGHT-OF EVIDENCE CLASSIFICATION FOR DEVELOPMENTAL TOXICITY, continued

SUGGESTIVE EVIDENCE	
Group I	Evidence from one positive animal test showing teratogenicity or severe embryo/fetal toxicity, perinatal, or postnatal developmental effects.
Group II	Evidence from one positive animal test showing minor embryo/fetal toxicity.
Group III	Evidence of teratogenicity, embryo/fetal toxicity, perinatal, or postnatal developmental toxicity in animals occurring in conjunction with maternal toxicity.
INSUFFICIENT EVIDENCE	Chemical cannot be classified as teratogenic, embryo/fetal toxicity or producing perinatal or postnatal developmental effects, because tests did not yield statistically significant results, or studies too limited for classification, or test results non-positive.
NO DATA	Chemical has not been tested.

TABLE II-27. WEIGHT-OF-EVIDENCE CLASSIFICATION FOR REPRODUCTIVE TOXICITY

CATEGORY	DESCRIPTION OF EVIDENCE
CONFIRMED EVIDENCE	Human evidence showing causal association between exposure to the chemical and adverse reproductive effects.
SUBSTANTIAL EVIDENCE	Evidence from two or more positive animal tests showing reproductive effects. ---Or, Evidence from one positive animal test of reproductive effects and some evidence of reproductive effects in humans, although data are not sufficient to conclusively demonstrate a causal association.
SUGGESTIVE EVIDENCE	Evidence from one positive animal test showing reproductive toxicity
INADEQUATE EVIDENCE	Chemical cannot be classified as a reproductive toxicant because tests did not yield statistically statistically significant results, or studies too limited to provide reliable data, or effects found only at very high levels or test results non-positive.
NO DATA	Chemical has not been tested.

b. Determination of Lowest Observed Effect Level (LOEL)

(i) Definition

Chemical toxicity varies over a wide range of doses. The $LOEL_s$ is the lowest level or dose at which statistically significant effects are observed in a given study, and is therefore a measure of toxicity. It is expressed as the daily dose per unit of body weight.

Inherent in the use of LOEL is the assumption that developmental and reproductive toxicity are dose-related, and that a threshold exists below which no adverse effects are observed. Although the existence of a threshold cannot be proven, it is believed that the embryo has some capacity for repair of damage (USEPA, 1984d). LOEL is used in CHEM rather the NOEL (no-observed-effect-level) because the former is more often reported. The LOEL is not synonymous with potency, since potency is determined by the dose-response curve, and characterizes the degree of toxicity associated with a given exposure level. Because of the uncertainties involved (e.g., shape of dose-response curves for low-level exposures to various chemicals), accepted methods for calculating developmental and reproductive potency have not been developed. Lacking potency values for most chemicals then, the LOEL represents a key quantitative measure of relative toxicity. It should be noted that the LOEL is used in CHEM only for animal data, and does not apply to evidence derived from studies in humans.

A major variable among developmental and reproductive studies is dosing regimen. For

teratogenicity studies, exposure usually takes place throughout the gestation period, which varies for different species. Other types of studies vary dosing regimen and may include premating exposures or exposures during specific stages of gestation. Unless exposure takes place on one day only, it is unknown whether the daily dose or the cumulative dose during all or part of the gestation period is principally responsible for the observed effects. In most cases the data are insufficient to make the distinction. For lack of a better measure therefore, the daily dose per unit of body weight is used in CHEM to determine LOEL, without considering cumulative dose. This approach offers a standardized method for comparing a large number of chemicals. The daily dose can be directly obtained from experiments where gavage, intravenous, intraperitoneal, and dermal routes are used. For oral or inhalation data, it is usually necessary to convert the exposure units (e.g., concentration in air or feed) into daily dose units. Standard parameters used for conversion are presented in Table II-28.

(ii) Application

Since $LOEL_s$ is an arbitrary dosing level selected by the study investigator (and may not reflect the lowest effect level), and in view of the uncertainties in defining and estimating LOEL, it should not be over-interpreted. Its contribution to the system lies not in being a measure of absolute potency, but as a quantitative basis for distinguishing between substances which cause comparable effects at different exposure levels. Only data from studies classified as "adequate" are used to calculate $LOEL_s$. The doses considered relevant in CHEM range from zero to 500

TABLE II-28. STANDARD PARAMETERS USED TO CALCULATE LOEL

Inhalation[1,2]

Animal Species	Body Weight (kg)	Inhalation Volume (m^3/day)
Rat	0.35	0.105
Mouse	0.03	0.034
Hamster	0.092	0.086
Rabbit	2.40	1.54
Guinea Pig	--	0.20

[1]When exposure is by inhalation:

$$\text{mg/kg/d} = \frac{(\text{mg/m}^3 \text{ in air})(\text{m}^3\text{/day})}{\text{kg body wt.}}$$

[2]When exposure in the inhalation study is only a fraction of a day, the fraction of the daily inhalation rate in the animal species is used.

Ingestion (Feed)[3]

Animal Species	Body Weight (kg)	Daily Food Consumption (kg)
Rat	0.35	0.020
Mouse	0.03	0.004
Dog	10.0	0.400
Pig	60.0	2.400
Rhesus Monkey	6.0	0.250

[3]When exposure is by diet:

$$\text{mg/kg/d} == \frac{(\text{mg in food})\ (\text{daily food consumption (kg)})}{\text{kg body wt}}$$

SOURCES: Barsotti et al. (1975); Hoar (1976); Hoffman et al. (1968); James et al. (1980); Kozma et al. (1974); USEPA (1980).

mg/(kg-day). Adverse effects which occur at doses higher than 500 mg/(kg-day) are considered irrelevant to environmental exposures, and are automatically scored `E', (See "Derivation of Final Score", section d. below.) The choice of 500 mg/(kg-day) as an upper limit for relevant quantitative data has some scientific basis. In a recent study, where a number of chemicals were tested for teratogenic potential, the dose which produced 50% malformations ranged from 4.6-750 mg/(kg-day). In most cases, the effective dose was below 500 mg/(kg-day).

It is noteworthy that the daily dose of 500 mg/(kg-day) to a worker corresponds to a workroom air concentration of 200 ppm for a chemical with a molecular weight of 100. The cut-off point above which acute/chronic toxicity is scored E is 250 ppm, except in cases of severe effects (see Table II-3). Thus, there is consistency between the upper limit of relevant doses in both health effects categories.

Within each weight-of-evidence category, the range of possible LOEL values is divided into groups for scoring purposes. The cut-off points are different for each weight-of- evidence category. Table II-29 illustrates how LOEL values are subdivided in each weight-of-evidence category. The rationale and some examples are provided in the section titled "Derivation of Final Score" below.

c. Calculation of Risk Ratio

Among chemicals that produce developmental effects, of greatest concern are the ones which are toxic to the developing embryo or fetus without harming the mother. The

TABLE II-29. RANGE OF LOEL VALUES USED IN CHEM BY WEIGHT-OF-EVIDENCE CATEGORY*

	LOEL Values (mg/kg/day)
Substantial Evidence	
Group 1	0 < LOEL ≤ 50 50 < " ≤ 200 200 < " ≤ 400 400 < " ≤ 500 500 < "
Group 2	0 < LOEL < 25 25 < " ≤ 150 150 < " ≤ 350 350 < " ≤ 500 500 < "
Suggestive Evidence	
Group 1	0 < LOEL ≤ 5 5 < " ≤ 100 100 < " ≤ 325 325 < " ≤ 500 500 < "
Group 2	0 < LOEL ≤ 2 2 < " ≤ 75 75 < " ≤ 300 300 < " ≤ 500 500 < "
Group 3	0 < LOEL ≤ 2 25 < " ≤ 500 500 < "

* From Tables II-31 and II-32.

risk-ratio addresses this concern. It is not a true ratio of risk, but rather the ratio of an adult toxic dose (expressed as LD_{50} or LC_{50}) to the fetal toxic dose (expressed as LOEL). The risk-ratio provides a quantitative estimate of the degree to which a chemical can exert toxicity to the fetus (or embryo) without producing maternal toxicity. It also provides a measure by which chemicals can be compared on a relative basis. A large risk ratio means that developmental toxicity occurs at doses far lower than those producing toxicity to the mother. A small risk-ratio implies that the dose exerting toxicity in the fetus may be close to the dose producing adult toxicity, and observed effects may be a result of maternal toxicity.

The concept of risk-ratio is analogous to the "therapeutic index" used for clinical data, or the "potency ratio" used for pharmacological effects (Fabro et al., 1982; Goldstein et al., 1974). A similar quantitative estimate, the Relative Teratogenic Index, has been tested with several chemicals using lethal and teratogenic doses to animals (Fabro et al., 1982). The latter study indicated that the index was a useful indicator of developmental toxicity occurring well below adult toxicity. In CHEM, the risk-ratio is a useful index for comparing chemicals within the framework of a relative hazard assessment.

The LD_{50} or LC_{50} is defined as the lethal dose or concentration of a chemical needed to produce death in 50% of the dosed animals. Lethality is selected as the measure of adult toxicity since it is applicable to the majority of test chemicals, unlike pharmacological activity or body weight changes, and is more generally available. The Department recognizes that a dose causing maternal toxicity would be more appropriate to use than LD_{50} or LC_{50} values. However, since these values are rarely reported, use of that

parameter on a consistent basis is not presently possible.

The principal criterion used in the selection of LD_{50} or LC_{50} values is consistency of species and route of exposure with those from which the matching LOEL has been derived. For example, if the LOEL pertains to inhalation in the guinea pig, then the LC_{50} must have been derived on the basis of inhalation studies in the guinea pig. This consistency is rigorously maintained. When species and route-specific LD_{50} and LC_{50} values cannot be obtained, a risk-ratio cannot be calculated. This is signified by an asterisk (*) following the score for that chemical. Similarly, when effects have been observed only at one dose, or only one dose has been tested, an asterisk follows the score, indicating that the score is based on weight-of-evidence, and the quantitative dose-response data are lacking.

As stated before, the concept of risk-ratio does not apply to reproductive toxicity. In addition, risk ratio and LOEL are not used in CHEM where human evidence of developmental toxicity exists (Confirmed Evidence) or where the quality of a given study is less than Adequate (i.e., Supportive or Inadequate), and the study will therefore not be used for scoring.

Risk-ratio values which have been calculated in CHEM range from less than one (overt maternal toxicity) to greater than 250. Based on this information risk-ratio values under each weight-of-evidence category are divided into their respective subcategories (see Table II-30). Table II-31 illustrates how LOEL and risk-ratio are used in scoring developmental hazards. Table II-32 presents the scoring scheme for reproductive toxicity.

TABLE II-30. RANGE OF RISK RATIO VALUES USED IN CHEM BY WEIGHT-OF-EVIDENCE CATEGORY*

Substantial Evidence	
Group 1	100 ≤ RR 20 ≤ " < 100 2 ≤ ″ < 20 1 ≤ " < 2 " < 1
Group 2	150 ≤ RR 30 ≤ " < 150 3 ≤ " < 30 1 ≤ " < 3 " < 1
Suggestive Evidence	
Group 1	200 ≤ RR 40 ≤ " < 200 4 ≤ " < 40 1 ≤ " < 4 " < 1
Group 2	250 ≤ RR 50 ≤ " < 250 5 ≤ " < 50 1 ≤ " < 5 " < 1
Group 3	Not Applicable

* From Table II-31

TABLE II-31 SCORING MATRIX FOR DEVELOPMENTAL TOXICITY

WEIGHT-OF-EVIDENCE SCORE	LOEL (mg/kg/day)		RISK RATIO	SCORE
Confirmed Evidence	NA		NA	A
Substantial Evidence				
Group I	0 < LOEL < 50	or	100 < RR	
Group II	0 < LOEL < 25	or	150 < RR	A
Suggestive Evidence				
Group I	0 < LOEL < 5	and	200 < RR	
Group II	0 < LOEL < 2	and	250 < RR	A
Substantial Evidence				
Group I	50 < LOEL < 200	or	20 < RR < 100	
Group II	25 < LOEL < 150	or	30 < RR < 150	B
Suggestive Evidence				
Group I	5 < LOEL < 100	and	40 < RR < 200	
Group II	2 < LOEL < 75	and	50 < RR < 250	B
Substantial Evidence				
Group I	200 < LOEL < 400	or	2 < RR < 20	
Group II	150 < LOEL < 350		3 < RR < 30	C
Suggestive Evidence				
Group I	100 < LOEL < 325	or	4 < RR < 40	
Group II	75 < LOEL < 300		5 < RR < 50	
	LOEL < 25		NA	C
Substantial Evidence				
Group I	400 < LOEL < 500	or	1 < RR < 2	
Group II	350 < LOEL < 500		1 < RR < 3	D
Suggestive Evidence				
Group I	325 < LOEL < 500	or	1 < RR < 4	
Group II	300 < LOEL < 500		1 < RR < 5	
	25 < LOEL < 500		NA	D

continued . . .

TABLE II-31. SCORING MATRIX FOR DEVELOPMENTAL TOXICITY, continued

WEIGHT OF EVIDENCE SCORE	LOEL (mg/kg/day)		RISK RATIO	SCORE
Substantial or Suggestive Evidence (Groups I, II or III)	500 < LOEL	or	RR < 1	E
Insufficient Evidence	NA		NA	E
No Data				ND

TABLE II-32. SCORING FOR REPRODUCTIVE TOXICITY

WEIGHT-OF-EVIDENCE	LOEL	SCORE
Confirmed Evidence	NA	A
Substantial Evidence	0 < LOEL ≤ 50	A
Suggestive Evidence	0 < LOEL ≤ 5	A
Substantial Evidence	50 < LOEL ≤ 200	B
Suggestive Evidence	5 < LOEL ≤ 100	B
Substantial Evidence	200 < LOEL ≤ 400	C
Suggestive Evidence	100 < LOEL ≤ 325	C
Substantial Evidence	400 < LOEL ≤ 500	D
Suggestive Evidence	325 < LOEL ≤ 500	D
Substantial or Suggestive Evidence	500 < LOEL	E
Inadequate Evidence or No Data		ND

d. Derivation of Final Score

As indicated above, developmental effects are scored on the basis of weight-of-evidence, LOEL, and risk-ratio; reproductive effects are scored using weight-of-evidence and LOEL. Since more than one element is involved, scoring necessarily requires weighing the significance of each component individually, and then combining the results to produce a composite score using a matrix approach. Thus, the final score reflects a qualitative and quantitative assessment of relative overall hazard in a given effect category (e.g., teratogenicity or embryo/fetal toxicity). Tables II-31 and II-32 present the scoring schemes used. Weight-of-evidence categories and subgroups were described in Tables II-26 and II-27.

Scoring actually involves a series of steps. First, weight-of-evidence categories are assigned for all developmental and/or reproductive effects, based on the total amount of evidence available for each. Next, where applicable, risk-ratio and/or LOEL values are calculated for each study considered "adequate". When there are several adequate studies demonstrating a particular type of effect, and more than one LOEL or risk-ratio can be calculated, the study producing the highest risk ratio or lowest LOEL is used for scoring. When more than one weight-of-evidence category is involved, or a chemical causes more than one type of effect, scoring is generally based on the effect and associated quantitative values which produce the highest score. Thus, the scoring matrix shows that, with the exception of "Confirmed" evidence, chemicals with the same weight-of-evidence for developmental or reproductive toxicity may receive widely different scores depending on their LOEL and risk ratio values. For example, in the case of a chemical having "Suggestive" evidence of both

teratogenicity and reproductive toxicity (based on separate studies), but having differing LOELs, scoring is based on the effect associated with the lowest LOEL.

All "Confirmed" human evidence receives a score of `A', regardless of the quantitative data. Score `A' is also assigned in two other cases: chemicals having "Substantial" evidence of toxicity and either a low LOEL or high risk ratio; or those chemicals with "Suggestive" evidence and both a low LOEL and a high risk ratio (see tables II-31 and II-32). Thus, in order to qualify for a given hazard score, weaker qualitative evidence of potential hazard must be compensated for by stronger quantitative evidence. The approach is conceptually analogous to that taken in the assessment of carcinogenicity. It reflects the Department's belief that chemical-specific assessments of potential toxicity for humans should be based on both qualitative and quantitative evidence. While lack of data is not equivalent to lack of hazard, a distinction should be made between substances with a clearly demonstrated ability to produce adverse health effects and those where the evidence of that potential is scant or inconclusive. Likewise, a distinction must be made between substances causing developmental effects at very low doses, and those which require massive doses or cause maternal toxicity first.

Since three elements are involved in scoring, and choices must frequently be made about the relative significance of any one variable, scoring is somewhat more complex than the matrices presented in Tables II-31 and II-32 suggest, and requires case-by-case assessment by the Department. For example, for some chemicals the particular combination of weight-of-evidence, LOEL, and risk ratio values does not correspond to any of the permutations listed in Table II-31. In such cases, the score is assigned in two

steps. First, the weight-of-evidence is combined with the LOEL value, and a score derived; next, the weight-of-evidence is combined with the risk-ratio value, and a second, alternative score is derived, thereby identifying two potential scores. Then, a score one grade lower than the higher of these two is assigned. Acetaldehyde is a case in point. There is "Suggestive - Group I" evidence that acetaldehyde can cause severe embryo/fetal toxicity. On the basis of that evidence, a LOEL of 50 mg/(kg-day) and a risk ratio of 10 were calculated. There is no such combination of qualitative and quantitative values listed in Table II-31. In looking at the scoring matrix, a chemical having "Suggestive - Group I" evidence associated with a LOEL of 50 mg/(kg-day) would receive a score of `B'. On the other hand, "Suggestive - Group I" evidence associated with a risk-ratio of 10 would normally score a `C'. In this case, a score of `C' is assigned.

As stated before, risk-ratio does not apply to reproductive toxicity. For chemicals showing only these effects, the score is determined by the weight-of-evidence and LOEL, according to the matrix in Table II-32.

7. Results and Discussion

Table II-33 presents the results of relative scoring for the 118 chemicals and mixtures evaluated. Some data were found for 47 of those chemicals and the remaining 71 automatically received a score of `ND' (No Data). For the 47 with data, a total of 188 studies were evaluated, and 85 (45%) were disqualified from consideration because they were not adequate. Because LD_{50} or LC_{50} values for the same species and route as the LOEL are not available for all chemicals, a risk ratio cannot always be calculated.

Likewise, when only one dose is used in a study, or effects are found only at the highest dose level, the LOEL is not reflective of a dose-response curve, and is therefore of less value. In these cases the score is followed by an asterisk(*) to indicate some uncertainty in the quantitative data.

Table II-33 shows that the methodology produced a wide stratification of scores. Of the 118 substances that were evaluated, the scoring breakdown was as follows: 14 A, 17 B, 3 C, 9 D, 4 E, and 71 No Data (ND). Thus, among chemicals having at least some positive evidence of developmental and/or reproductive toxicity, those of moderately high hazard (`B') are most commonly represented, followed by the highest toxicity category `A'. This disproportionate representation of high and moderately high hazard chemicals probably reflects the selection process for experimental testing which favors substances which are more likely to cause adverse effects.

Table II-33 also shows that substances are classified into hazard categories on the basis of all three scoring components (as applicable). For example, among "B" scores, one or more of those components contribute to the score: low LOEL (e.g. nickel), high risk ratio (e.g. DEHP, pentachlorophenol), or substantial weight-of-evidence (e.g. toluene). The effects represented are also wide-ranging: teratogenicity (acetaldehyde), embryo/fetal toxicity (chloroprene), postnatal or perinatal developmental toxicity (1,2-dichloroethane), maternal reproductive toxicity (epichlorohydrin), or paternal reproductive toxicity (2-methoxy ethanol).

The system described here represents a mixture of two possible approaches to assessing the hazard of developmental

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
ACETALDEHYDE	Teratogenicity Severe Embryo/fetal Toxicity	Suggestive	50	10	B
ACETONE		No Data			ND
ACRYLONITRILE	Teratogenicity	Substantial	13*		A*
AMMONIA		No Data			ND
ANILINE	Post Developmental Maternal Reproductive Toxicity	Suggestive	560		E
ANILINE HYDROCHLORIDE		No Data			ND
ASBESTOS		No Data			ND
BENZENE	Mild Embryo/fetal Toxicity	Suggestive	14.0		C
BENZYL CHLORIDE		No Data			ND

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
BERYLLIUM		No Data			ND
1,3-BUTADIENE	Maternal Reproductive Paternal Reproductive	Suggestive	387		D
n-BUTYL ALCOHOL		No Data			ND
CADMIUM	Teratogenicity	Substantial	1.25		A
CALCIUM CHROMATE		No Data			ND
CARBON TETRACHLORIDE	Moderate Embryo/fetal	Suggestive	164		D
CHLORDANE	Teratogenicity	Suggestive	0.16*		B*
CHLORINE		No Data			ND
CHLOROBENZENE		No Data			ND
CHLOROETHANE		No Data			ND
CHLOROFORM	Moderate Embryo/fetal	Suggestive	20.0		B

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
CHLOROPRENE	Moderate Embryo/fetal	Suggestive	1.8		B
CHROMIC ACID		No Data			ND
CHROMIUM (metal)		No Data			ND
CHROMIUM (VI) COMPOUNDS		No Data			ND
p-CRESOL		No Data			ND
CYCLOHEXANE		No Data			ND
o-Dichlorobenzene		No Data			ND
p-DICHLOROBENZENE		No Data			ND
1,2-DICHLOROETHANE	Post/perinatal	Suggestive	8.6		B
1,2-DICHLOROETHYLENE		No Data			ND
DICHLOROMETHANE	Severe Embryo/fetal	Suggestive	381*		D*

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued . . .

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
1,2-DICHLOROPROPANE		No Data			ND
DIETHYLAMINE		No Data			ND
Dl (2-ETHYLHEXYL) PHTHALATE	Teratogenicity	Suggestive	70	376	B
DIMETHYLFORMAMIDE	Severe Embryo/fetal	Inadequate Data			ND
1,4-DIOXANE		No Data			ND
DIPHENYL		No Data			ND
DIPHENYLAMINE		No Data			ND
EPICHLOROHYDRIN	Maternal Reproductive	Suggestive	80		B
ETHANOL	Teratogenicity	Substantial	316	56	B
ETHYL ACETATE		No Data			ND
ETHYL ACRYLATE	Moderate Embryo/fetal	Suggestive	15.35		B

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
ETHYL BENZENE		No Data			ND
ETHYLENE GLYCOL		No Data			ND
ETHYL ETHER		No Data			ND
FLUORIDE		No Data			ND
FORMALDEHYDE	Paternal Reproductive	Substantial	0.023*		A
HEPTACHLOR		Inadequate Data			ND
HEXACHLOROCYCLOPENTADIENE	Moderate Embryo/fetal	Suggestive	75*		D*
HEXACHLOROETHANE	Severe Embryo/fetal	Suggestive	39		D
HEXACHLOROPHENE	Peri/Postnatal	Substantial	5	12	A
2-HEXANONE		No Data			ND
HYDRAZINE	Post Developmental Toxicity	Suggestive	8*		C*

continued .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
HYDROGEN CHLORIDE		No Data			ND
HYDROGEN FLUORIDE		No Data			ND
HYDROGEN SULFIDE		No Data			ND
ISOAMYL ACETATE		No Data			ND
ISOBUTYL ACETATE		No Data			ND
ISOBUTYL ALCOHOL		No Data			ND
ISOPROPYL ALCOHOL		No Data			ND
LEAD (metal)	Severe Embryo/fetal	Substantial	0.113*		A*
LEAD ACETATE		No Data			E
LEAD CHLORIDE		No Data			ND
LEAD NITRATE	Teratogenicity	Substantial	25		E

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
LEAD SUBACETATE	Paternal Reproductive	Suggestive	1952		E
LINDANE		No Data			ND
MALEIC ANHYDRIDE		No Data			ND
METHANOL	Teratogenicity	Substantial	NA	NA	B
2-METHOXY ETHANOL	Paternal Reproductive Toxicity	Substantial	100*		B*
METHYL ACRYLATE		No Data			ND
METHYL BROMIDE		No Data			ND
METHYL ETHYL KETONE	Teratogenicity	Suggestive	407		D
METHYL ISOBUTYL KETONE		No Data			ND
METHYL METHACRYLATE	Severe Embryo/fetal Toxicity	Suggestive	435*		D*
MIREX		No Data			ND

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
NAPTHTHALENE		No Data			ND
NICKEL	Peri/postnatal Toxicity	Suggestive		0.5	B
NICKEL CARBONYL	Teratogenicity Embryo/fetal Toxicity	Suggestive	0.25	437	A
NICKEL OXIDE		No Data			ND
NITROBENZENE		No Data			ND
PENTACHLOROPHENOL	Severe Embryo/fetal Toxicity	Suggestive	5	27	B
PHENOL		No Data			ND
PHOSPHORIC ACID		No Data			ND
PHTHALIC ANHYDRIDE		No Data			ND
PCB AROCHLOR 1242	Maternal Reproductive Toxicity	Substantial	0.94		A

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
PCB AROCHLOR 1248	Maternal Reproductive Toxicity Embryo/fetal Toxicity Postdevelopmental Toxicity	Suggestive	0.08		A
PCB AROCHLOR 1254	Postnatal Developmental Toxicity	Substantial	0.06*	21,583	A*
PCB KANACHLOR 300		No Data			ND
PCB KANACHLOR 400		Insufficient Data	Epidemiology		E
PCB KANACHLOR 500	Teratogenicity Postdevelopmental Toxicity	Substantial	20		A
PROPYL ALCOHOL		No Data			ND
PROPYLENE OXIDE		No Data			ND
RESORCINOL		No Data			
SELENIUM	Teratogenicity Reproductive Toxicity	Inadequate Data			ND

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
1, 1, 1-TRICHLOROETHANE	Moderate Embryo/fetal Toxicity; Maternal Reproductive Toxicity	Suggestive	415		D*
1, 1 , 2-TRICHLOROETHANE		No Data			ND
TRICHLOROETHYLENE	Severe Embryo/fetal Toxicity	Substantial	27.3*		A
2 , 4 , 6-TRICHLOROPHENOL					
TRIETHYLAMINE	Maternal Reproductive Toxicity	Suggestive	2.5		A
VANADIUM		No Data			ND
VANADIUM PENTOXIDE		No Data			ND
VINYL ACETATE		No Data			ND
VINYL CHLORIDE	Moderate Embryo/fetal Toxicity	Suggestive	42.6*		B*

continued . . .

TABLE II-33. SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS continued

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL (mg/kg/day)	RISK RATIO	SCORE
VINYLIDENE CHLORIDE	Moderate Embryo/fetal Toxicity	Suggestive	28		D
m-XYLENE	Severe Embryo/fetal Toxicity	Insufficient	900*		E
O-XYLENE	Maternal Reproductive	Suggestive	45		B
p-XYLENE	Moderate Embryo/fetal Toxicity	Suggestive	45		B
MIXED XYLENES	Teratogenicity Embryo/fetal toxicity	Suggestive	2.06		C

1. Lowest Observable Effect Level, when accompanied by an asterisk (*) then value was not taken from a dose-response curve, because only one dose used in study.
2. Risk Ratio is equal to LOEL - LD using same species and route of exposure.
3. + = only one dose used in study; score is aligned with effect(s) to which it corresponds.

and reproductive toxicants: one which gives the highest rank to those which are most likely to produce adverse effects in humans; the other which ranks highest those which may produce adverse effects at lower exposure levels. Neither approach alone would make full use of all available data and therefore chemicals which appear hazardous on either count could be missed. In addition, by relying on some but not all data, either approach alone overinterprets two highly uncertain procedures: extrapolation of animal data to humans and quantitative estimation of "safe" exposure. Finally, neither approach alone allows for a relative ranking of hazard among chemicals.

The system described here addresses each of these points. It offers a methodology for evaluating the quality of the data, and for stratifying it into types of effects, weight-of-evidence categories, and ranges of potency. Finally, the system offers a methodology for combining these elements in a two- or three-dimensional matrix in order to assign agents into broad hazard categories. Thus, all available valid data are utilized, and the uncertainties are addressed by not over-emphasizing any one component. The methodology provides a useful risk assessment tool. It can be used to rank substances according to hazards, to identify a range of adverse developmental/reproductive effects, and to highlight areas needing further investigation.

8. Summary

Developmental and reproductive toxicity covers all male and female reproductive effects, as well as effects in the developing embryo or fetus, resulting from chemical exposure. It includes teratogenicity (structural, functional, and behavioral abnormality), embryo or fetal

toxicity, postnatal and perinatal developmental toxicity, and reproductive toxicity.

Three parameters are used in scoring for developmental and reproductive toxicity: weight-of-evidence, low observed effect level (LOEL), and/or risk ratio. Weight-of-evidence categories are assigned on the basis of "adequate" data from epidemiological and experimental studies. Each endpoint studied is evaluated independently, then assigned to a weight-of-evidence category. The LOEL corresponds to the lowest dose at which statistically significant adverse effects were observed. The risk-ratio is the published LD_{50} or LC_{50} for a given species and route of exposure divided by the LOEL for the same species and route. Risk-ratio is designed to eliminate maternal toxicity as a factor in observed effects and therefore applies only to developmental effects. Both LOEL and risk-ratio provide a quantitative basis for comparing and distinguishing chemicals in regard to degree of hazard. Only studies classified as providing "adequate" data are used to calculate LOEL or risk-ratio values.

All information, including data quality analyses, study findings and relevant calculations, is listed on worksheets. Based on all the available data, a score from A-E or ND is assigned. Scoring reflects a balance between the qualitative and quantitative evidence, such that weight-of-evidence, LOEL, and risk-ratio are factored together and assessed on the basis of a scoring matrix designed for this purpose. The system combines the flexibility of case-by-case analysis and the consistency of a standardized approach.

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10. Developmental and Reproductive Toxicity Worksheets

The evaluation of developmental/reproductive toxicity involves the use of up to six separate worksheets for studies obtained for a given chemical. Four are used to assess data quality since CHEM relies on primary literature, one is used to describe the effects and response levels observed, and one is used to summarize all the above data for scoring purposes. To aid in the organization of a large number of studies, each study is assigned an identification number for easy reference. For example, if ten studies were evaluated for a given chemical, each is assigned a number in the order it was obtained, and subsequently identified as study #1 of 10, #2 of 10, etc. The worksheets for one sample chemical are ordered as follows:

- "Assessment of Studies for Scoring" - one page per chemical, summarizing effects, dose levels, data quality assessments, and other information for each study judged to be of "adequate" quality, and used for scoring.
- "Description of Effects" - one page for each study, used to record information about species tested, exposure conditions, and effects observed.
- "General Information" - one page for each study, used as a checklist to record information pertaining to the data quality assessment.
- "Teratogenic Study" - if the study described above is a study of teratogenicity, this worksheet is filled out, to assess data quality.
- Perinatal and Postnatal Study" - if the study pertains to perinatal or postnatal developmental toxicity, this worksheet is filled out.
- "Fertility and Reproductive Study" - if the study pertains to effects on fertility or reproduction, in males or females, this worksheet is filled out.

Thus, for each study, the "Description of Effects" and

"General Information" worksheets are filled out, as well as one of the effect category worksheets above as appropriate. For reference purposes, each worksheet page pertaining to a particular study is numbered, e.g., page 1 of 3, page 2 of 3 etc. Since more than one study, or type of study, may be available, each chemical may have a number of worksheets and pages. Worksheets are described below, in the order in which they appear.

ASSESSMENT OF STUDIES FOR SCORING

This worksheet is used to summarize the data contained in all the other worksheets, for scoring purposes. At the top of the worksheet, the following information is given: type and title of worksheet, chemical name, CAS code, date worksheet was completed, Final Score, and Final Weight-of-Evidence. Worksheet columns are described in detail below.

Study #: identification number assigned to each study. Numbers are assigned in the order studies are obtained, begining with #1. Once assigned, numbers do not change, so that a study has the same numbers throughout all the worksheets. A file of studies for each chemical has been established, and the same identification number is written on the first page of the study as well. However, since this worksheet is used for scoring, studies judged by the Department to be "inadequate" are not included here. Therefore, missing sequential numbers result because some studies were excluded.

Author: last name of first author and date of publication appear here.

Animal/Route: animal species used in experiment, and route of administration of test chemical.

Dose-Response: when a study provides evidence of a dose-response relationship, a `yes' is entered, otherwise a `no' appears. This column is useful in determining the LOEL. For example, when a study is conducted using one dose, no dose-response relationship can be determined and the LOEL is marked with an asterisk.

Effect and Lowest Dose: type of developmental or reproductive effect and lowest dose at which the effect was observed. Definitions of each type of effect appear in Part II, section F. Tables II-20 and II-21 list examples of each.

Maternal Toxicity: a `yes' or `no' appears in this column, indicating whether maternal toxicity was observed in conjunction with embryo or fetal effects at the lowest dose recorded in the previous column. This information is used in assigning the weight-of-evidence for scoring each study. For example, when there is evidence of teratogenicity in a single study, and no maternal toxicity is observed, the evidence is classified as "Suggestive- Group A". If maternal toxicity did occur in conjunction with teratogenicity, the weight-of-evidence would be "Suggestive- Group C", and would score lower.

NOTE: Due to the extensive amount of data included in this worksheet, the information presented for each study continues in the next block of columns on the lower half of the worksheet. The additional columns are described below.

Study #: this column is used to identify the continuing information on each study from the above block of information, so that study #1 in the first block of columns is the same as study #1 in the lower block. Thus, in the lower block, more information on the same study is presented.

LOEL (Lowest Observed Effect Level): the lowest dose at which effects occurred, as recorded previously, expressed as mg/kg/day. The LOEL is calculated only for studies judged to be "adequate". `Not Applicable' appears in this column when the study is judged to be "supportive" due to limitations in the study. "Supportive" studies are used for informational purposes only, and do not contribute to the Final Weight-of-Evidence or Final Score for each chemical. An asterisk appears next to the LOEL value when a dose-response relationship is not reported. LOEL is defined in Part II, section F.

Risk Ratio: the risk ratio is calculated when a study shows developmental toxicity, unless maternal toxicity also occurred at the LOEL. Risk ratio is not calculated for reproductive effects. In either of these cases, `not applicable' appears in this column.

Quality of Study: only those studies judged to be of "adequate" or "supportive" quality appear on this worksheet. Data quality is identified in this column.

Weight-of-Evidence: a preliminary weight-of-evidence classification is recorded in this column for each "adequate" study, based on the evidence supplied by that study. (Each single study generally provides "Suggestive" evidence.) This information is used to

assign the Final Weight-of-Evidence, which represents the total amount of evidence obtained from all studies combined. For example, if study #1 provides evidence of teratogenicity, the evidence for study #1 is classified as "Suggestive." If study #5 also provides evidence of teratogenicity, study #5 is also "Suggestive." When these two studies are considered together for the Final Weight-of-Evidence evaluation, there is "Substantial" evidence of teratogenicity. Weight-of-evidence categories are defined in Tables II-26 and II-27.

Score: preliminary scores assigned to each study individually are recorded here, based on the weight-of-evidence, LOEL, and risk ratio values according to the scoring matrix provided in Table II-31. Unless studies have been combined for the weight-of-evidence determination, the Final Score will be the same as the highest individual score received. When two or more individual studies (each providing "Suggestive" evidence) showing same effects are combined, together they provide "Substantial" evidence for the effects. The Final Score is then determined using "Substantial" evidence and the lowest LOEL and/or highest risk ratio of the two (or more) studies.

DESCRIPTION OF EFFECTS WORKSHEET

This worksheet is filled out for each study obtained for a chemical. For easy reference, the identification number of each study is given, as well as the worksheet page number (e.g., 1 of 3). Other information provided at the top of the worksheet includes: worksheet title, chemical name, CAS code, date worksheet was completed, reference, classification of study quality, study dose (lowest dose

producing statistically significant effects), effect (measured at lowest dose), LOEL, and risk ratio. Risk ratio is `Not Applicable' for reproductive or fertility studies, or when maternal toxicity occurs in conjunction with embryo or fetal effects. Worksheet Columns are described below.

Animal/Route: animal species and route of administration used in experiment.

Exposure Conditions: specific days (d) during which exposure took place (generally gestational days in developmental studies).

Dose: level(s) of chemical to which animal is exposed, expressed as mg/kg/day.

Teratogenicity: any teratogenic effects observed in the study. This column is also used to list perinatal and postnatal developmental effects.

NOTE: Columns in the lower half of the worksheet are continuations of those in the upper half, but could not be fit together in a continuous line. It should be noted therefore that "Embryo/fetal Toxicity" and "Maternal/Paternal Toxicity" contain reports of effects occurring at the same dose levels already recorded under "Dose" on the top half of the page, just as for "Teratogenicity."

Embryofetal Toxicity: embryo/fetal effects observed in the study at the dose levels indicated above ("Dose"), which are statistically significant ($p < .05$).

Maternal/Paternal Toxicity: reproductive effects in males and females are recorded here. In addition, toxicity

in the maternal organism which occurs in conjunction with developmental effects in the embryo or fetus, is recorded here as well.

Other: any other pertinent information about the study is recorded in this column.

Comments: additional information used to evaluate the study, such as comments by the researcher or information supplied through CHEM, is recorded here. This column is also used to describe the reasons why a study has been judged to be of "supportive" or "inadequate" quality.

GENERAL INFORMATION WORKSHEET AND FOLLOWING WORKSHEETS

The last four worksheets serve as a series of checklists for assessing the quality of each study obtained from the primary literature. The first worksheet, titled `General Information', is filled out for each study. Then, depending on which type of study it is (teratogenic, perinatal or postnatal, fertility or reproductive), the specific worksheet for that type of study is also filled out. The worksheets basically outline FDA and EPA proposed guidelines for evaluating each of those effects. A brief description of the worksheets is provided below:

GENERAL INFORMATION

At the top of the page, worksheet title, study and page number, chemical name, CAS code, and reference are provided. The worksheet then describes features of experimental design, how the data are reported, whether statistical analysis was carried out, and type of study. A checkmark (X) is used to note which features were included in the

study. Depending on which type of study is checked at the bottom, one of the three following worksheets is filled out as well:

TERATOGENIC STUDY

This worksheet represents a checklist of U.S. FDA guidelines for carrying out a teratogenicity study (see Appendix G). On this worksheet are specific experimental procedures in the areas of Study Design and Parameters Evaluated. A checkmark next to these parameters indicates that the procedure was followed.

"Other Parameters Evaluated" includes a list of toxicity endpoints often studied in teratogenicity studies. A checkmark next to the parameter indicates that it was studied.

Conclusions on Quality of Study: "Adequate", "Supportive" or "Inadequate" are the terms used for describing the quality of the study.

FERTILITY AND REPRODUCTIVE STUDY

At the top of this worksheet information such as chemical name, CAS Code, reference page and study identification number is indicated. The rest of the worksheet outlines the U.S. FDA recommended guidelines including information on Study Design (Number of Animals and Dosing Schedule), Parameters Evaluated (Non-mating studies and mating studies), and continues onto an additional page due to the length and detail of the specific protocol requirements. These specific parameters basically outline the minimum recommended experimental requirements developed by the U.S. FDA (see Appendix G). In all cases, a

checkmark indicates that the procedure was used in the study. Occasionally, on a space following the specific parameter more information is specified; for example, for a study on the reproductive performance of offspring, the number of generations (typically 2 or 3) may be indicated.

Conclusions on Quality of Study: "Adequate", "Supportive" or "Inadequate" are the terms used to describe the quality of a study.

PERINATAL AND POSTNATAL STUDY

This worksheet is used for studies testing perinatal and/or postnatal developmental toxicity of chemicals. At the top of the worksheet, the title, chemical name, CAS Code, and reference are located. In the upper right hand corner of the worksheet the study identification number and page number are listed.

This worksheet outlines information on the Study Design (dosing schedule) and Parameters Evaluated. These specific experimental procedures are those recommended by the U.S. FDA (see Appendix G). As in all previous cases, a checkmark indicates that the FDA procedure was used.

Conclusions on Quality of Study: "Adequate", "Supportive" or "Inadequate" are the terms used to describe the quality of a study.

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

Assessment of Studies for Scoring

For:
CAS Code:
Final Score:
Final Weight of Evidence:
Date:

STUDY #	AUTHOR	ANIMAL ROUTE	DOSE RESPONSE	EFFECT AND LOWEST DOSE	MATERNAL TOXICITY	LOEL	RISK RATIO	QUALITY OF STUDY	WEIGHT OF EVIDENCE	SCORE

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

study #_____

DESCRIPTION OF EFFECTS

page # _____

FOR:

CAS CODE: REFERENCE: EFFECT:

DATE: QUALITY: LOEL:

STUDY DOSE: RISK RATIO:

ANIMAL/ ROUTE	EXPOSURE CONDITIONS	DOSE	TERATOGENICITY	EMBRYO/ FETAL TOXICITY	MATERNAL/ PATERNAL REPROD. TOXICITY	PERI/POST -NATAL TOXICITY	COMMENTS

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

Study # _____of_____
page _____ of _____

GENERAL INFORMATION
FOR:
CAS CODE:
REFERENCE:

EXPERIMENTAL DESIGN

- Controls

_____concurrent
_____historical

- Dosing Regimen

_____two or more doses. Number of doses = _____
_____high dose non-toxic to dams
_____low dose (= a No Observed Effect Level)

- Number Animals Treated (does not pertain to fertility And reproductive study protocol)

_____at least 20 rodents
_____less than 20 rodents (Number = _____)
_____at least 10 rodents
_____less than 10 rabbits (Number = _____)
_____primates (Number = _____)

DATA REPORTED AS:

_____number of affected fetuses
_____per litter
_____per treatment group
_____per total exposed
_____percent of affected fetuses
_____per litter
_____per treatment group
_____per total exposed
_____number of affected litters
_____per treatment group
_____per total exposed
_____percent of affected litters
_____per treatment group
_____per total exposed
_____average value per pup

STATISTIC

_____yes
_____no

TYPE OF STUDY

_____teratogenic study
_____fertility and reproductive study
_____perinatal and postnatal study

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

Study #_____of_____
page _____of_____

TERATOGENIC STUDY

FOR: CAS CODE: REFERENCE:

STUDY DESIGN

_____control group
_____untreated males
_____treatment period covers time of organ formation
_____fetus delivered by Cesarean section one or two days prior to parturition.

PARAMETERS EVALUATED

- FDA recommended
  _____number of fetuses
  _____placement in uterine horn
  _____correlation of fetuses with corpus lutea
  _____number of live and dead fetuses
  _____number of resorptions
    _____early
    _____late
  _____fetal weight
  _____external anomalies
  _____internal anomalies
    _____one third for dissection or Wilson slicing method for visceral anomalies; if not one third, then _____
    _____two thirds for clearing and bone staining with alizarin: if not two thirds, then _____

- Other parameters evaluated
  _____biochemistry
  _____fetal histology
  _____cellular morphology
  _____maternal toxicity
    _____body weight
    _____organ weight
    _____death
    _____percent pregnant
    _____food consumption
    _____clinical signs of toxicity
    _____other_____
    _____crown-rump length
    _____hematology
    _____organ weight
    _____placenta weight
    _____other_____

CONCLUSION ON QUALITY OF STUDY:

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

FERTILITY AND REPRODUCTIVE STUDY
FOR:
CAS CODE:
REFERENCE:

STUDY DESIGN

- Number of Animals (minimum)

___ 10 males (rodents)
___ 20 females (rodents)
___ 10 females (rabbits)
___ number of primates = ___
___ 10 males/20 females (mating studies)
___ other _____

- Dosing Schedule

___ minimum age of 40 days for males for premating exposure
___ female premating exposure following establishment of estrous cycle by daily vaginal smears
___ mating study
  ___ premating exposure
  ___ organogenesis exposure
  ___ gestation exposure
  ___ lactation exposure
___ other _____
  _____

- Mating studies

___ preimplantation studies
___ sacrifice on day 13 of gestation
  ___ number and distribution of embryos
  ___ presence of empty implantation sites
  ___ number of embryos undergoing resorption
  ___ uterine abnormalities
  ___ other _____
___ sacrifice on day 20 of gestation
  ___ number of fetuses
  ___ placement in uterine horn
___ correlation of fetuses w/ corpora lutea
___ number of live and dead fetuses
___ number of resorptions
  ___ early
  ___ late
___ fetal weight
___ external anomalies
___ internal anomalies
  ___ one third for dissection or Wilson method for visceral anomalies
  ___ two thirds for clearing and bone staining with alizarin

PARAMETERS EVALUATED

- Non-mating Studies

___ studies using males
  ___ testes
    ___ weight
    ___ morphology
    ___ histology
    ___ biochemistry
    ___ other _____
___ sperm
  ___ motility
  ___ morphology
___ studies using females
  ___ hormonal changes
  ___ estrous changes
  ___ other
  ___ biochemistry
  ___ fetal histology
  ___ cellular morphology
  ___ maternal toxicity
  ___ body weight
  ___ organ weight
  ___ death
  ___ percent pregnant
  ___ food consumption
  ___ water consumption
  ___ clinical signs of toxicity
  ___ other _____
___ crown-rump length
___ hematology
___ placenta weight

FERTILITY AND REPRODUCTIVE STUDY (continued)
FOR:
CAS CODE:
REFERENCE:

_____dams delivering
- _____ observe labor and delivery
- _____ calculate duration of gestation
- _____ observations
  - _____litter size
  - _____ratio male to female pups
  - _____number of stillborn
  - _____number of live born
  - _____gross anomalies
  - _____skeletal observations
  - _____pup weight
    - _____day 1
    - _____day 4
    - _____day 21
    - _____other day _____
    - _____behavior
    - _____ biochemistry
  - _____reproductive performance of offspring
    - _____ number of generations = _____
    - _____age at production of first litter
    - _____ ratio of males to females
    - _____ runts
    - _____deaths
    - _____stillborn offspring
    - _____failure to breed
    - _____congenital abnormalities

CONCLUSIONS ON QUALITY OF STUDY:

DEVELOPMENTAL/REPRODUCTIVE TOXICITY WORKSHEET

Study #_____of_____
page _____of _____

PERINATAL AND POSTNATAL STUDY
FOR:
CAS CODE:
REFERENCE:

STUDY DESIGN

! Dosing Schedule
_____premating
_____organogenesis
_____gestation
_____perinatal
_____dams treated pups exposed through lactation
_____pups treated
_____other _____

PARAMETERS EVALUATED

_____observe labor and delivery
_____calculate duration of gestation
_____observations
_____litter size
_____ratio of males to females
_____number of stillborn
_____number of liveborn
_____gross anomalies
_____skeletal observations
_____biochemistry
_____ continued dosing through lactation observe effects on
_____lactation
_____nursing
_____instinct
_____ toxic effects
_____ other _____

CONCLUSION ON QUALITY OF STUDY:

G. Summary of Health Effects Score Codes

As described throughout Part II, CHEM produces a score code for each chemical in each health effect category. Scores range from A to E or F, representing the relative hazard associated with each chemical. Table II-34 illustrates the scoring procedure for ten sample chemicals, evaluated for acute/chronic toxicity (A/C), carcinogenicity (C), mutagenicity (M), and developmental/reproductive toxicity (D/R). See Tables II-2, II-3, II-9, II-18, II-31 and II-32 for the scoring schemes for each of the health effects categories. When toxicity data pertaining to a particular effect are not available, this is indicated by 'ND' (no data) in the appropriate column. In the column for carcinogenicity, an asterisk (*) following the letter score indicates that potency data were not available to the Department and the score is based on weight-of-evidence alone. Likewise, an asterisk following developmental/reproductive toxicity scores indicates that adequate quantitative data for calculating LOEL or risk ratio were not available, and qualitative data have been used for scoring. The final scores for all chemicals evaluated are presented in Table II-35. Missing acute/chronic toxicity scores indicate the lack of an occupational limit from NIOSH, ACGIH, or OSHA for those chemicals (e.g., mirex).

TABLE II-34. SCORING BASES FOR TEN SAMPLE CHEMICALS

Chemical	Selection of MAOL	Scoring for Acute/Chronic Toxicity	Scoring for Carcinogenicity	Scoring for Mutagenicity	Scoring for Reproductive Toxicity
Ammonia	25 ppm (ACGIH) selected rather than 50 ppm (NIOSH) because: o irritant effects below 50 and 25 ppm	MAOL is 25 ppm; severity factor assigned is 2, based on: o severe and chronic irritant effects Score is 'C'	No data available Score is 'ND'	No data available Score is 'ND'	No data available Score is 'ND'
Benzene	1 ppm (NIOSH) selected rather than 10 ppm (ACGIH) because o systemic effects below 10 ppm (chromosomal damage)	MAOL is l ppm; severity factor assigned is 3, based on: o severe or irreversible systemic effects (nervous system, bone marrow, blood) Score is 'A'	Human Carcinogen unit risk is 8.1×10^{-6} (CAG, human study) Score is 'A'	"Sufficient" evidence of mutagenicity; positive results: o one Group I o two Group II o two Group III biossays Score is 'A'	"Suggestive" evidence Group 3 (minor embryo/ fetal toxicity and maternal toxicity study 5) LOEL: 14mg/kg/d Risk Ratio: not applicable Score is 'C'

continued . . .

TABLE II-34. SCORING BASES FOR TEN SAMPLE CHEMICALS, continued

Chemical	Selection of MAOL	Scoring for Acute/Chronic Toxicity	Scoring for Carcinogenicity	Scoring for Mutagenicity	Scoring for Reproductive Toxicity
1,3-Buta-diene	10 ppm (ACGIH) selected because: o ACGIH review of toxicity data more recent, more related to known effects	MAOL is 10 ppm; severity factor assigned is 1, based on: o mild irritant effects (only acute or chronic effects documented) Score is 'C'	Probable Human Carcinogen (evidence in mice and rats) Unit risk is 2.9×10^{-6} (CAG) Score is 'A'	No data available Score is 'ND'	"Suggestive" evidence of Maternal and Paternal Repro-ductive toxicity LOEL: 397 mg/kg/d Risk Ratio: not applicable Score is 'D'
Dichloro-methane	50ppm (ACGIH) selected rather than 75ppm (NIOSH) because: o Systemic effects below 75ppm (carboxyhemo-globin formation)	MAOL is 50ppm; severity factor assigned is 3, based on: o severe or irreversible systemic effects (liver, heart, kidney, nervous system; anoxia) Score is 'B'	Probable Human Carcinogen - evidence of carcinogenicity in mice and rats Unit risk is 4.1×10^{-6} CAG, animal study Score is 'B'	"Substantial" evidence of mutagenicity-positive results in: o 3 Group II one Group III bioassays Score is 'B'	"Suggestive Evidence Group 3" (severe embryo/ fetal toxicity study 4) LOAEL: 381 mg/kg/d Risk Ratio: N/A Score is 'D*'

continued . . .

TABLE II-34. SCORING BASES FOR TEN SAMPLE CHEMICALS, continued

Chemical	Selection of MAOL	Scoring for Acute/Chronic Toxicity	Scoring for Carcinogenicity	Scoring for Mutagenicity	Scoring for Reproductive Toxicity
Epi-chloro-hydrin	0.5 ppm (NIOSH) selected rather than 2 ppm (ACGIH) because: o Systemic effects below 2 ppm (liver kidney, nervous system)	MAOL is 0.5 ppm; severity factor assigned is 3, based on: o severe or irreversible irritant effect (lung) Score is 'A'	Probable Human Carcinogen - evidence of carcinogenicity in mice and rats Unit risk is 1.2×10^{-6} (CAG, inhalation study in rats) Score is 'B'	"Sufficient" evidence of mutagenicity-positive results in: o five Group II two Group III bioassays Score is 'A'	"Suggestive" evidence of Maternal Reproductive Toxicity LOAEL: 8O mg/kg/d Score is 'B'
Formalde-hyde	1 ppm (ACGIH) selected rather than l ppm (NIOSH) because: o ACGIH review more recent	MAOL is 1 ppm; severity factor assigned is 2, based on: o moderate to severe or chronic irritant effects o Sensitization Score is 'B'	Probable Human Carcinogen Unit risk is 1.3×10^{-5} (CIIT, inhala-tion study in mice and rats) Score is 'B'	"Substantial" evidence of mutagenicity-positive results in: o four Group II o two Group III bioassays No mammalian systems used so evidence not sufficient Score is 'B'	"Suggestive evidence Paternal Repro-ductive Toxicity" LOEL: 6 mg/kg/d Risk Ratio; N/A Score is 'B*'

continued . . .

TABLE II-34. SCORING BASES FOR TEN SAMPLE CHEMICALS, continued

Chemical	Selection of MAOL	Scoring for Acute/Chronic Toxicity	Scoring for Carcinogenicity	Scoring for Mutagenicity	Scoring for Reproductive Toxicity
Hydrogen Sulfide	1O ppm (ACGIH) selected rather than 1O ppm (NIOSH) because: o ACGIH review more recent	MAOL is 1O ppm; severity factor assigned is 2, based on: o Severe irritant Effects Score is ‘B’	No available data Score is 'ND'	No available data Score is 'ND'	No available data Score is 'ND'
Methyl Meth-acrylat	1OO ppm (ACGIH) selected rather than 1O0 ppm (NIOSH) because: o ACGIH review more recent	MAOL is 1OO ppm; severity factor assigned is 1, based on: o mild or transient irritant effects (nose, throat only) Score is 'D'	Non-positive evidence. No cancer in rats and mice. Score is ‘F’	No available data Score is ‘ND’	"Suggestive evidence Group 3" (severe embryo/fetal toxicity) LOEL: 435 mg/kg/d Risk Ratio: N/A Score is ‘D*’

continued . . .

TABLE II-34. SCORING BASES FOR TEN SAMPLE CHEMICALS, continued

Chemical	Selection of MAOL	Scoring for Acute/Chronic Toxicity	Scoring for Carcinogenicity	Scoring for Mutagenicity	Scoring for Reproductive Toxicity
Styrene	50 ppm (NIOSH) selected rather than 50 ppm (ACGIH) because: o NIOSH review more recent	MAOL is 50 ppm; severity factor assigned is 3, based on: o severe or irreversible systemic effects (liver, nervous system) Score is 'B'	Possible Human Carcinogen. Evidence of Carcinogenicity in rats and male mice Unit risk is 5.7×10^{-7} (EPA, inhalation study in rats) Score is 'C'	"Sufficient" evidence of mutagenicity-positive results in: o six Group 11 o one Group III bioassays Score is 'A'	"Suggestive evidence of severe embryo/ fetal toxicity: LOEL: 237.8 mg/kg/d Risk Ratio: Pending (species/ route-specific LD50 not available) Score is 'C*'
Tetra-chloro-ethylene	50 ppm (ACGIH) selected rather than 50 ppm (NIOSH) because: o ACGIH review more recent	MAOL is 50 ppm; severity factor assigned is 3, based on: o severe or irreversible systemic effects (liver, nervous system, heart) Score is 'B'	Probable Human Carcinogen. Evidence of carcinogenicity in mice and rats Unit risk is 5.52×10^{-5} (NCI, gavage study in mice) Score is 'B'	"Substantial" evidence of mutagenicity-positive results in: o one Group 11 o one Group III bioassays Score is 'C'	No data available Score is 'ND'

TABLE II-35. SUMMARY OF HEALTH EFFECTS SCORES

Chemical Name	LETTER CODE SCORES A/C	C	M	D/R
Acetaldehyde	D	B	B	B
Acetone	E	ND	E	ND
Acrylonitrile	A	A	A	A*
Ammonia	C	ND	ND	ND
Aniline	A	C	C	E
Asbestos	A	A	ND	ND
Benzene	A	A	A	C
Benzyl Chloride	B	C*	A	ND
Beryllium	A	A	ND	ND
1,3-Butadiene	C	A	ND	D
n-Butyl Alcohol	C	ND	ND	ND
Cadmium	A	A	ND	A
Calcium Chromate	A	A	A	ND
Carbon Tetrachloride	B	B	C	D
Chlordane	A	A	D	B*
Chlorine	B	ND	ND	ND
Chlorobenzene	C	C	ND	ND
Chloroethane	E	ND	ND	ND
Chloroform	B	B	C	B
Chloroprene	A	ND	C	B
Chromic Acid	A	A	ND	ND
Chromium (Metal)	B	ND	ND	ND

continued . . .

TABLE II-35. SUMMARY OF HEALTH EFFECTS SCORES, continued

Chemical Name	LETTER CODE SCORES A/C	C	M	D/R
Chromium (VI) Compounds	A	A	ND	ND
p-Cresol	B	ND	ND	ND
Cyclohexane	E	ND	ND	ND
o-Dichlorobenzene	C	F	ND	ND
p-Dichlorobenzene	C	B	D	ND
1,2-Dichloroethane	B	B	A	B
1,2-Dichloroethylene	E	ND	ND	ND
Dichloromethane	B	B	B	D*
1,2-Dichloropropane	B	C	C	ND
Diethylamine	B	ND	ND	ND
Di-(ethyl)hexylphthalate	A	B	B	B
Dimethylformamide	B	ND	ND	ND
1,4-Dioxane	B	B	ND	ND
Diphenyl	A	ND	D	ND
Diphenylamine	A	ND	C	ND
Epichlorohydrin	A	B	A	B
Ethanol	C	ND	C	B
Ethyl Acetate	E	ND	ND	ND
Ethyl Acrylate	B	B*	ND	B
Ethyl Benzene	D	ND	ND	ND
Ethylene Glycol	D	ND	ND	ND
Ethyl Ether	D	ND	D	ND

continued . . .

TABLE II-35. SUMMARY OF HEALTH EFFECTS SCORES, continued

Chemical Name	LETTER CODE SCORES A/C	C	M	D/R
Fluoride	B	ND	ND	ND
Formaldehyde	B	B	B	B*
Heptachlor	B	A	D	ND
Hexachlorocyclopentadiene	A	ND	ND	D*
Hexachloroethane	B	C	ND	D
Hexachlorophene	-	ND	ND	A
2-Hexanone	B	ND	ND	ND
Hydrazine	A	B*	C	C*
Hydrogen Chloride	B	ND	ND	ND
Hydrogen Fluoride	B	ND	C	ND
Hydrogen Sulfide	B	ND	ND	ND
Isoamyl Acetate	D	ND	ND	ND
Isobutyl Acetate	E	ND	ND	ND
Isobutyl Alcohol	D	ND	ND	ND
Isopropyl Acetate	E	ND	ND	ND
Lead	A	ND	D	A*
Lead subacetate	A	B*	ND	E
Lindane	A	B*	C	ND
Maleic Anhydride	B	ND	ND	ND
Methanoi	C	ND	E	B
2-Methoxy Ethanol	B	ND	ND	B*
Methyl Acrylate	C	ND	ND	ND

continued

TABLE II-35. SUMMARY OF HEALTH EFFECTS SCORES, continued

Chemical Name	LETTER CODE SCORES A/C	C	M	D/R
Methyl Bromide	B	ND	ND	ND
Methyl Ethyl Ketone	C	ND	ND	D
Methyl Isobutyl Ketone	B	ND	ND	ND
Methyl Methacrylate	D	F	ND	D*
Mirex	-	B*	ND	ND
Naphthalene	B	ND	ND	ND
Nickel	B	C*	ND	B
Nickel Oxide	B	B*	ND	ND
Nitrobenzene	B	ND	ND	ND
Pentachlorophenol	A	ND	D	B
Phenol	B	E •	ND	ND
Phosphoric Acid	B	ND	ND	ND
Phthalic Anhydride	B	E	ND	ND
PCBs	A	A	ND	A
Propyl Alcohol	E	ND	ND	ND
Propylene Oxide	B	C	C	ND
Resorcinol	C	ND	D	ND
Selenium	A	ND	ND	ND
Selenium Sulfide	A	B	ND	ND
Styrene	B	C	A	C*
Sulfuric Acid	B	ND	ND	ND
1,1,2,2-Tetrachloro-l, 2-di-fluoroethane	D	ND	ND	ND

continued

TABLE II-35. SUMMARY OF HEALTH EFFECTS SCORES, continued

Chemical Name	LETTER CODE SCORES A/C	C	M	D/R
1,1,2,2-Tetrachloroethane	A	C	C	ND
Tetrachloroethylene	B	B	C	ND
Tetrahydrofuran	D	ND	ND	ND
Toluene	C	ND	E	B
Toluene Diisocyanate	A	B	ND	ND
o-Toluidine	B	B	C	ND
1 , 1 , 1-Trichlo roe thane	D	E	C	D*
1 , 1 , 2-Trichloroethane	B	C	ND	ND
Trichloroethylene	B	B	A	A
2,4,6-Trichlorophenol	-	B	D	ND
Triethylamine	B	ND	ND	A
Vanadium	B	ND	ND	ND
Vanadium Pentoxide	B	ND	C	ND
Vinyl Acetate	B	ND	C	ND
Vinyl Chloride	B	A	B	B*
Vinylidene Chloride	B	C	C	D
Xylenes (m-,o-,p- isomers)	C	F	ND	B

* - Score based on on qualitative data only

A/C - Acute/Chronic Toxicity

C - Carcinogenicity

M - Mutagenicity

D/R - Developmental/Reproductive Toxicity

COMMONWEALTH OF MASSACHUSETTS
DEPARTMENT OF ENVIRONMENTAL PROTECTION

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

VOLUME II

1 Winter Street
Boston, Massachusetts 02108

February 1990

Table of Contents

VOLUME I

LIST OF TABLES

List of Tables, continued

List of Tables, continued

VOLUME I (cont.)

VOLUME II

List of Figures

VOLUME II

LIST OF APPENDICES

VOLUME II

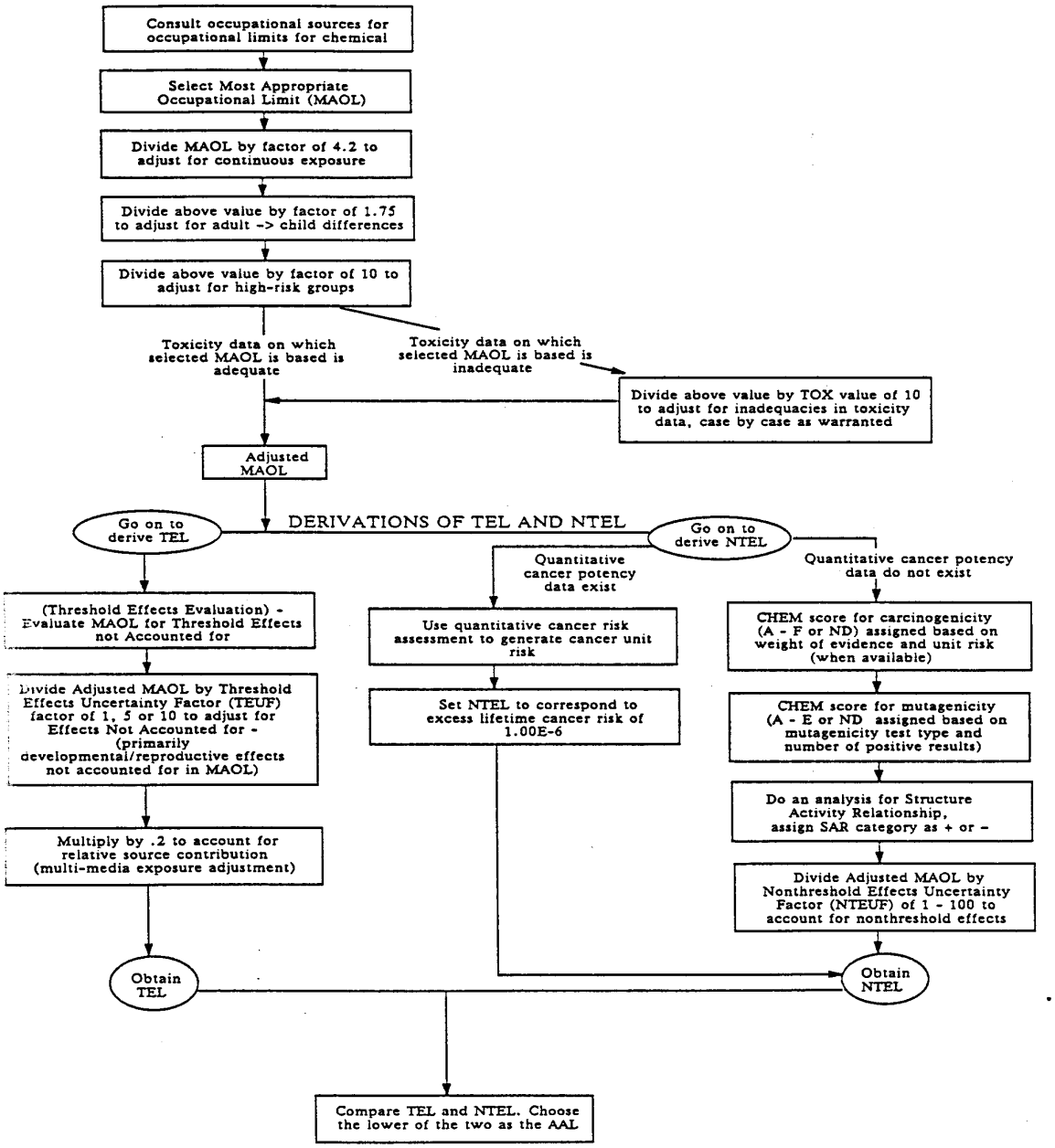
Preface to Part III

The Method to Derive Allowable Ambient Limits has changed considerably since the draft version published in the Peer Review Document of June, 1985. The purpose of this preface is to describe the changes made, and the reasons for making those changes, for the benefit of past reviewers and those having in their possession the 1985 draft document.

As described in Part I, the changes resulted from Department consideration of comments received on the draft, and an extensive in-house review of the proposed methodology. This effort involved updating the toxicological data on the 100 chemicals evaluated, assessing the adequacy of the draft AALs using currently accepted methods of risk assessment, and reexamining the scientific concepts embodied in the draft methodology. As a result of this review the Department determined that the previous proposal did not make full use of the available toxicological data, and did not fully address the Department's goal of protecting public health. The changes incorporated in the present methodology provide for greater flexibility in selecting and using the best scientific data in deriving AALs, and more precisely addressing differing types of effects and differing types of data. Some of the changes and additions include assessment of available pharmacokinetic data, consideration of non-positive data, separate assessment of threshold and nonthreshold effects, and use of quantitative cancer risk assessment in the derivation of AALs for those chemicals meeting strict criteria. These changes reflect the Department's commitment to utilizing the best available scientific approach to protecting public health.

In the past, the Department proposed to derive allowable ambient limits by applying a series of adjustment and uncertainty factors to selected occupational limits. Thus, while specific

FIGURE III – 1. Derivation of AAL



factors were applied on a case-by-case basis, the procedure itself was standardized and applied to all chemicals, including those associated with nonthreshold effects (i.e., carcinogenicity, mutagenicity). However, because of the variability in occupational limits, individual potencies, and types of effects among the 100 chemicals, the uncertainty factor approach was found to be inadequate to compensate for that variability in the case of nonthreshold effects for some chemicals. Based on current calculations of potency and unit risk, the proposed AALs for carcinogens were shown to be associated with variable levels of excess cancer risk, most of which were considered unacceptably high (greater than 1×10^{-5}). Since the same uncertainty factors were used for both threshold and nonthreshold effects, and since carcinogenic potency was not directly factored into the AAL derivation procedure, AALs were not derived on the basis of cancer risk, and were not as uniformly protective against threshold and nonthreshold effects as those now proposed.

The methodology now proposed addresses those limitations by distinguishing threshold from nonthreshold effects, using cancer potency data directly in the determination of acceptable exposure limits, establishing an upper limit of allowable risk for all carcinogens (1×10^{-6}), and selecting the final AAL on the basis of the most sensitive effect. The effect of these changes is to produce AALs which are consistently and uniformly protective for all chemicals. A brief overview of the methodology is presented below, followed by a detailed description of each step.

A. Introduction

The Method to Derive Allowable Ambient Limits can be divided into three distinct phases, each with its own concepts and assumptions. The process is illustrated schematically in Figure III-1. A central concept throughout is that threshold effects

should be distinguished from nonthreshold effects, and each evaluated separately. In this context, a threshold effect is one for which a threshold, or dose below which the adverse effect has not been observed, is currently assumed. As described in CHEM, threshold effects may include acute and chronic effects such as eye irritation, nervous system effects, allergic reactions, and liver or kidney damage, as well as developmental and reproductive effects. In contrast, nonthreshold effects are defined as effects for which there is no conclusive or compelling evidence of a threshold, and therefore, no "safe" level of exposure since even the smallest dose can exert some incremental effect or risk. Carcinogenicity and mutagenicity are considered to be nonthreshold effects, and are generally assumed to present some degree of risk at any level of exposure. For this reason, the Department believes it is important to distinguish threshold from nonthreshold effects, and has developed methodologies to address each.

The first phase of the AAL derivation procedure is the threshold effects evaluation. In this phase the occupational limit selected as the MAOL (see Part II, section B "Most Appropriate Occupational Limit") is adjusted to account for (1) differences between workplace and environmental exposures, (2) physiological differences between healthy adult workers and healthy children, (3) differences in sensitivity between healthy workers and high risk groups within the general population, and (4) any limitations or inadequacies in the toxicological database used by the occupational agency to set the MAOL. Each of these factors is described in detail in section B(2) below. In addition, an uncertainity factor for documented threshold effects not accounted for in the MAOL is applied on a case-by-case basis as warranted. This value is then divided by a factor of five (20% of the derived exposure limit, as discussed in Part II, section A-2) to account for other routes of exposure to the chemical, such as food or drinking water. This factor will be

applied in all cases unless permitting or other relevant evaluations show that exposure from pathways other than air will not occur. The product of this procedure is the Threshold Effects Exposure Limit or TEL, which is designed to account for all documented or potential threshold effects (i.e., acute and chronic toxicity, developmental and reproductive toxicity). Thus, the TEL represents an acceptable exposure limit for threshold effects developed using the CHEM database, to provide protection to the general public against the effects covered. Later in the process this value will be compared to the Nonthreshold Effects Exposure Limit (NTEL), and the lower of the two is then selected as the Allowable Ambient Limit(AAL). This assures that the AAL covers all types of effects, including the most sensitive effect.

The second phase of the Method to Derive Allowable Ambient Limits consists of the nonthreshold effects evaluation. Here, chemicals having adequate quantitative evidence of carcinogenicity are distinguished from those that do not, based on the carcinogenicity assessment performed through CHEM (see Part II, section D). The validity and relevance of carcinogenicity bioassays is determined on the basis of the amount, type, and quality of the data available. The criteria and procedures for identifying and using valid cancer potency data are detailed in Appendix D. In addition, positive and non-positive qualitative mutagenicity data are considered in the evaluation of nonthreshold effects, especially when a chemical has not been tested for carcinogenicity, but quantitative data on mutagenic potency are not factored into the AAL derivation procedure. Thus, mutagenicity data carry somewhat less weight in the Department's AAL methodology at this time because there is no reliable procedure available as yet for quantifying mutagenic effects on a consistent basis.

This second phase of the Department's methodology

incorporates two separate processes for developing the Nonthreshold Effects Exposure Limit (NTEL). As noted above, the basis for the distinction between these two processes lies in whether or not there are adequate cancer potency data. The Department believes that when valid cancer potency data exist this information should be used to calculate a unit risk for humans, which can then be used to generate allowable exposure levels for nonthreshold effects. However, rather than assuming that all chemicals not meeting these criteria are in fact noncarcinogens, the Department has developed an alternate methodology for assessing nonthreshold effects when quantitative data are lacking, so that potentially significant effects are not overlooked. Included in the latter group are chemicals having good qualitative evidence of carcinogenicity or mutagenicity but lacking quantitative data on carcinogenic potency, chemicals producing only non-positive or inconclusive evidence of carcinogenicity or mutagenicity, chemicals tested only in flawed bioassays or producing results of questionable significance to humans, and chemicals which have not been tested. Both positive and non-positive evidence are considered, and structure-activity relationship (SAR) analysis is carried out to supplement the weight-of-evidence evaluation. Based on the amount, type, and quality of the data available (and SAR analysis), uncertainty factors called Nonthreshold Effects Uncertainty Factors (NTEUF) are applied to the adjusted MAOL to arrive at an acceptable nonthreshold effects exposure limit (NTEL). The procedure is similar to that used in Phase One to derive the threshold effects exposure limit, or TEL.

In summary, the NTEL is derived either on the basis of quantitative cancer risk assessment, set at a level representing a one in one million excess lifetime cancer risk, or on the basis of an uncertainty factor approach, where the adjusted MAOL (most appropriate occupational limit) is divided by a selected uncertainty factor as warranted. Each of these steps is

described in detail in following sections. The purpose of the methodology is to derive an Allowable Ambient Limit based on the available data, and an evaluation of all potential risks.

In phase three of the methodology the final AAL is determined by selecting the lower of the two values obtained (TEL or NTEL), so that both threshold and nonthreshold effects are addressed. Thus, the Method to Derive Allowable Ambient Limits is designed to achieve the Department's goals of minimizing risk and protecting public health.

B. Threshold Effects Evaluation

1. Introduction

The first phase of the Method to Derive Allowable Ambient Limits begins with the "most appropriate occupational limit" (MAOL) selected as outlined in Part II. The MAOL is then adjusted to provide protection for the general public against acute and chronic effects. Since occupational limits have been designed for specified occupational conditions, and not for environmental/ambient air settings, it is important to account for these differences and to carefully define the context in which occupational limits are used.

Next, a threshold effects uncertainty factor (TEUF) for effects not accounted for in the MAOL is applied to the adjusted MAOL on a case-by-case basis. The operant concept is that occupational data provide a reasonable starting point for deriving allowable ambient limits for humans, and that the health data developed through CHEM can be used to account for chemical-specific toxicity. The Department recognizes the limitations in using occupationally-derived exposure concentrations to develop ambient air guidelines for the general population, and therefore proposes a methodology to address

those limitations by adjusting MAOLs to account for a range of effects and conditions. Adjustment and uncertainty factors are described in detail below.

2. Adjustment Factors

Occupational limits are designed to be protective of healthy adult workers exposed during a 40-hour work week. In contrast, the general population is more heterogeneous, less healthy, and includes children and high risk groups who may be exposed continuously. Thus, the Department has developed a five-step procedure to adjust the MAOL to reflect environmental exposure conditions and provide protection to the general population against acute and chronic health effects. The adjustment and uncertainty factors are described in Figure III-2 and discussed in detail below.

First, the Department extrapolates the MAOL, based on a 40-hour per week exposure, to a value based on continuous exposure (168 hours per week), in order to account for exposure differences between occupational and environmental settings. The next step involves extrapolating from an adult (worker) to a child, in order to account for ventilation rate and body weight differences between adults and children. In the third step, the two adjustment factors are combined, producing a factor of 7.35. Dividing the MAOL by 7.35 provides that the dose per kilogram of body weight per day is normalized from the healthy adult (worker) exposed for eight hours per day, five days per week, to a healthy child exposed for 24 hours a day, seven days per week. In step four the adjusted MAOL is divided by an uncertainty factor to account for high risk groups within the population. Finally, an uncertainty factor (Tox) for inadequacies in the toxicological database used to set the MAOL is applied on a case-by-case basis. The resulting value is known as the "Adjusted MAOL". The adjusted MAOL will then be used to calculate

FIGURE III-2. ADJUSTMENT AND UNCERTAINTY FACTORS USED IN THE DERIVATION OF TEL AND NTEL*

Adjustment Factors

Occupational Exposure > Environmental Exposure	4.2	Derived by converting a 40-hr. workweek occupational exposure to a 168-hr. week continuous environmental exposure (168 hr./40 hr. = 4.2)
Adult > Child	1.75	Derived by converting an exposure based on the adult average body weight (70 kg.) and ventilation volume (20 m^3/24 hrs.) to an exposure based on the child average body weight (20 kg.) and ventilation volume (10 m^3/24 hrs.) $\frac{(10\ m^3/24\ hrs.)\ (70\ kg.)}{(20\ m^3/24\ hrs.)\ (20\ kg.)} = 1.75$
Occupational Population > High Risk Group (intraspecies variability)	10	Uncertainty factor to extrapolate from an occupational population to high risk groups in the general population.
Tox factor	1-10	Uncertainty factor to compensate for inadequacies or limitations in the toxicity data used to set MAOL.

(MAOL divided by above factors = ADJUSTED MAOL)

Threshold Effects Uncertainty Factor (TEUF) for Effects Not Accounted for) – Uncertainty factor of 1, 5 or 10 which accounts primarily for documented developmental/ reproductive effects not accounted for in the MAOL. Dividing the ADJUSTED MAOL by the TEUF and multiplying by a factor of 0.2 produces the TEL (Threshold Effects Exposure Limit.)

Nonthreshold Effects Uncertainty Factor (NTEUF) – Uncertainty factor of 1-100 (based on carcinogenicity weight of evidence, mutagenicity weight of evidence and structure-activity relationship analysis.) Dividing the ADJUSTED MAOL by the NTEUF produces the NTEL (Nonthreshold Effects Exposure Limit).*

*when adequate quantitative carcinogenicity data are not available

the TEL, and also the NTEL when quantitative data are not available. Table III-1 shows how the Adjusted MAOL is derived for ten sample chemicals. Details of each step are provided below.

Step 1: Extrapolate from Occupational Exposure to Environmental Exposure

While occupational limits are designed to account for a normal work week of 40 hours, with rest (i.e., non-exposure) periods of 14-16 hours per day, and two days per week, ambient exposure to contaminants may be continuous. In order to account for these differences, the MAOL is extrapolated to represent a 7-day continuous exposure:

$$\frac{\text{168-hour week}}{\text{40-hour workweek}} = 4.2$$

This is an exposure adjustment, not a "safety factor", since an individual being exposed to the lower concentration continuously will receive the same dose per unit of body weight as the worker who is exposed at proportionately higher levels over a shorter period of time (Hickey and Reist, 1978). In applying a factor of 4.2 to the MAOL for all chemicals, the Department is ensuring that the total dose to the public within given time frames will never exceed that allowed for workers in a shorter period of time.

Regardless of the type of effect associated with a given chemical, the Department believes that exposures to a more diverse and sensitive public should be well under levels considered acceptable for the worker who is assumed to have daily rest or non-exposure periods. The 4.2 factor applied is the only available method for addressing the issues of total dose and possible continuous exposure to the

TABLE III-1. ADJUSTMENT FACTORS APPLIED TO MAOL FOR 10 SAMPLE CHEMICALS

CHEMICAL	MAOL (ppm)	(A) ÷ 4.2	(B) ÷ 1.75	(C) ÷ 10	(D) ÷ 1 or 10	ADJUSTED MAOL ppb)
Ammonia	25.0	5.95	3.4	0.34	10	34.01
Benzene	1.0	0.23	1.36	0.014	1	13.61
1,3-Butadiene	10.0	2.38	1.36	0.14	10	13.61
Dichloromethane	50.0	11.90	6.80	0.68	10	68.03
Epichlorohydrin	0.5	0.119	0.068	0.007	1	6.80
Formaldehyde	1.0	0.238	0.136	0.014	1	13.61
Hydrogen Sulfide	10.0	2.38	1.36	0.14	10	13.61
Methyl Methacrylate	100.0	23.8	13.61	1.3	10	136.05
Styrene	50.0	11.9	6.8	0.68	1	680.27
Tetrachloroethylene	50.0	11.9	6.8	0.68	1	680.27

where:

(A) = Adjustment factor for eextrapolation of a 40-hour work week Exposure to a continuous weekly exposure (168 hours)

(B) = Adjustment factor for extrapolating the dose from exposure in (A) above for an adult (assuming 20 m3/day for a 70 kg man) to a child (assuming 10 m3/day for a 20 kg child).

(C) = Uncertainty factor for high risk groups

(D) = Uncertainty factor applied on a case-by-case basis, for inadequate toxicity data. See part III, Section B for a complete description.

public. Moreover, it can rarely be said with certainty that a given chemical will cause only acute threshold effects. The concept assumes equivalent daily dose on the basis of equivalent total dose. In fact, it is likely that total dose and daily dose will not always be equivalent toxicologically, since continuous exposures may often present a greater risk than intermittent exposures at the same level, due to the lack of a recovery period. Nevertheless, since neither chemical-specific nor exposure-specific information are generally available, and the Department must make practical assumptions on a consistent basis, the only method available in this context is to assume the toxicological equivalence of total doses, and to account for differences in exposure duration only.

Step 2: Extrapolate from Adult to Child:

$$\frac{(10m^3/24 \text{ hours}) \times (70kg)}{(20m^3/24 \text{ hours}) \times (20kg)} = 1.75$$

where: $20m^3/24$ hours = average adult ventilation volume per 24 hours

70kg = average body weight of adult (male)

$10m^3/24$ hours = average child's ventilation volume per 24 hours

20kg = average body weight of (6 year old) child

It is crucial to account for exposure to children because children are particularly susceptible to the effects of air pollution on the basis of:

- Increased ventilation rates per unit of body weight.
- Immature enzyme detoxification systems.
- Immature immune systems.

o Higher absorption rates, lowered excretion rates. (Calabrese, 1978)

Thus, the extrapolation only assures that per unit of body weight, the dose to a child exposed continuously to a given chemical will not exceed the dose allowed for an adult worker, and is therefore distinguished from a safety or uncertainty factor. In fact, Phalen et al. (1985) have demonstrated greater deposition rates in children:

> "The computed particle deposition efficiencies indicate that under most circumstances smaller (younger) people will have greater trachoebronchial deposition efficiencies than larger (older) people. For example, tracheobronchial dose on a per kilogram body mass basis for 5-um diameter particles may be more than 6 times higher in the resting newborn than in the resting adult assuming equivalent deposition efficiencies above the larynx."

Also, in addition to the differences between adults and children described above, increased cellular proliferation in children may serve to increase the effectiveness of co-carcinogens. While these differences cannot be accounted for quantitatively in the above equation, such findings underscore the need for considering the greater susceptibility of children when deriving acceptable exposure levels for the public.

Step 3: Divide MAOL by Both Adjustment Factors:

Since the method begins with the "most appropriate occupational limit" (MAOL) for each chemical, and each MAOL represents acceptable workplace exposures for healthy adult workers, the adjustment factors are applied to all chemicals. The following formula illustrates the method

using steps 1,2, and 3.

$$\frac{\text{MAOL}}{(4.2) \times (1.75)} = \frac{\text{MAOL}}{7.35}$$

Thus, the MAOL is divided by 7.35 in order to account for a healthy child who may be continuously exposed to a given chemical. The assumption is that since children are more susceptible to the effects of air pollution, protecting the healthy child will afford protection to the healthy adult as well. A second assumption is that given the variable operating schedules of industrial emission sources, the only way to provide adequate protection to residents throughout the state is to make the conservative assumption, i.e., continuous exposure. Since continuous exposure cannot be ruled out, and is in fact likely in some areas, this approach seems to be a reasonable one if a mobile and variously exposed diverse population is to be protected (IARC, 1982). It should be emphasized that the adjustment factors do not actually reduce the MAOL, but only normalize the dose over a 168-hour, seven-day period for a 20kg child breathing $10m^3$ of air per day, and thus assuring a total dose no greater (per kg of body weight) than the 70kg worker breathing $20m^3$ of air per day will receive over a 40-hour period.

Step 4: Account for High Risk Groups (Sensitive Populations)

The adjustment factors described above account for healthy populations by making a time adjustment, and by considering certain physiological differences between healthy adults and children.

However, it is equally important to provide protection for high risk groups, including the elderly, the chronically ill, and the hypersensitive. As defined in CHEM, a high risk group includes those individuals who would experience

the adverse health effects of the pollutant significantly before or to a much greater degree than the general population because of factors such as the following:

- o Genetic or developmental disorders
- o Serum disorders
- o Homeostatic regulatory disorders
- o Immunological disorders
- o Malabsorptive or metabolic disorders
- o Dietary deficiencies
- o Chronic illness
- o Disease states
- o Behavioral factors
- o pregnancy
- o deficiencies in DNA repair systems
- o excessive cellular proliferation in suspected target tissues

High risk groups are therefore distinguished from healthy children and adults, for whom the adjusted MAOL is assumed to provide protection against the acute and chronic effects of chemical exposure. In order to provide protection for high risk groups, an uncertainty factor of 10 is applied to the figure derived in step 3 as follows:

$$\frac{\text{MAOL}}{7.35 \times 10} = \frac{\text{MAOL}}{73.5}$$

The derivation of the factor of 10 is described in section E(2) below.

Step 5: Uncertainty Factor For Inadequate Toxicity Data (TOX)

The TOX factor described below is designed to account for unknown effects, due to gaps or inadequacies in the toxicological database used to set the occupational limit. Since the MAOL is used to derive allowable ambient limits for most chemicals, its adequacy directly affects the adequacy of the derived AAL. A crucial consideration then is the type and amount of data used to set the original occupational number. Whenever possible, NIOSH, ACGIH, and OSHA use long-term human evidence to establish occupational

limits. However, toxicological data are scarce for many of the chemicals currently in commercial use, and this fact is reflected in the variable quality of the data available to the three occupational agencies. The Department considers the following types of data inadequate for determining long-term exposure levels for the general population:

- Exposure - when the data used to derive the MAOL are limited to acute or high-level exposures (e.g., industrial accidents or fatalities), and no low-level or chronic exposure data exist.

- Data - when no human toxicity data exist, and the MAOL is based on extrapolations from animal data only.

- Effects - when the MAOL is set on the basis of acute or subacute effects only (e.g., irritant properties), and no data exist as to chronic effects for humans or animals.

The Department uses an uncertainty factor of 10 to account for the inadequacies or limitations in the toxicity data used by NIOSH, ACGIH, or OSHA to set their occupational limits. Such factors have commonly been recommended by regulators and scientists when human data are unavailable, or when chemicals have not been tested at low levels or in chronic exposures. The typical approach (e.g., NAS, EPA) involves applying an uncertainty factor of 10 for each type of limitation in the data, as follows:

- 10 for interspecies variability (when animal data must be used)

- 10 for subchronic to chronic extrapolation (when long-term exposure data are not available)

- 10 for intraspecies variability (to protect high risk groups within the population at large)

- 1-10 for LOAEL to NOAEL extrapolation (when a no-observed-adverse-effect level cannot be identified from the available data)

Each of these factors is described in detail in subsection E(2) below.

Thus, in approaches such as that used by EPA, uncertainty factors of up to 10,000 can be applied to experimental data when there is a lack of both human data and low-level or chronic exposure data, and "no effect" levels are unidentified (NAS, 1977; USEPA, 1980). However, occupational data differ from experimental data in that occupational limits generally rely on both human and animal data where available, and are derived specifically for repeated human exposures. Therefore, where the EPA would apply a factor of 100, 1000, or more, to account for specific deficiencies in the experimental data, the Department uses a single factor of 10 to account for uncertainties caused by limitations in the toxicological database, since the AAL derivation procedure begins with an occupational limit rather than experimental data.

Table III-2 provides examples of chemicals given an uncertainty factor of 10 for various inadequacies in the occupational data. Toxicity information is referenced in each case. The origin, rationale behind, and use of safety or uncertainty factors are discussed in Section E(2) below.

3. Application to MAOL

It is acknowledged that some occupational levels incorporate a "margin of safety" for particular effects, although most do not. Nevertheless, margins of safety should not be confused with safety or uncertainty factors, since each is defined and used quite differently, with different results. A margin of safety, as employed by NIOSH, ACGIH, and OSHA, is meant to provide some degree of protection against specified effects for a specified

TABLE III-2. UNCERTAINTY FACTOR FOR INADEQUATE TOXICITY DATAFOR FOUR SAMPLE CHEMICALS, continued

CHEMICAL	SOURCE	TOXICITY DATA PROVIDED	BASIS FOR APPLICATION OF SAFETY FACTOR	APPLIED SAFETY FACTOR
Ethyl Acrylate	ACGIH 1980	Rats and Rabbits (1949): 300 ppm, 7/hour/day for 30 days lethal Rabbits and Guinea Pigs (1949): 257 ppm, 10-30 7-hour periods-lethal 75'75 ppm, 7-hour periods x 50 - "no visible toxicity" Rabbits, Guinea Pigs, Rats, 1 Monkey (1949): 25 ppm, 30 days (over period of 199 days) - "no overt signs of intoxication" Rats and Mice (unpublished data, 1978 communication): 25 ppm, 6-hr/day, 5 days/week, 90 days-irritation, inflammation 75 ppm - effects more pronounced Rats (1949): 275 ppm, 10-30 7-hour periods - irritation; lethargy; dyspnea; convulsive movements; pulmonary edema; liver, kidney, cardiac effects 500 ppm – lethal Humans (1949): Sensitization in workers (no dose noted)	Lack of chronic toxicity data in humans Lack of low-level exposures (lowest level tested: 25 ppm - animal) Lack of long-term exposures (longest experimental period: 90 days - animal)	10

continued . . .

TABLE III-2. UNCERTAINTY FACTOR FOR INADEQUATE TOXICITY DATA FOR FOUR SAMPLE CHEMICALS, continued

CHEMICAL	SOURCE	TOXICITY DATA PROVIDED	BASIS FOR APPLICATION OF SAFETY FACTOR	APPLIED SAFETY FACTOR
Ethylene Glycol	ACGIH 1980	Rats, Rabbits (1970): 12 mg/m^3, 24-hr/day, 90 days irritation Human, 1974: 30 mg/m, four weeks – irritation, headache, backache	Lack of long-term exposure data or chronic effects data for humans (lowest level tested: 30 mg/m^3; longest duration: 4 weeks-human; 12 mg/m^3, 90 days-animal	10
Methyl Meth-acrylate	NIOSH 1981 ACGIH 1983	Rabbits 13,500 ppm, 3 hours – lethal Human Dental technician molding polymer by hand developed dermatitis "The TLV...considered to be sufficiently low to protect. against discomfort from irritation and against acute systematic effects based upon current available data. However, ... information is not available to determine whether this level will be protective under conditions of chronic longterm exposure." (p. 285. 1)	Lack of low-level, long-term exposure data for humans	10

continued . . .

TABLE III-2. UNCERTAINTY FACTORS FOR INADEQUATE TOXICITY DATA FOR FOUR SAMPLE CHEMICALS, continued

CHEMICAL	SOURCE	TOXICITY DATA PROVIDED	BASIS FOR APPLICATION OF SAFETY FACTOR	APPLIED SAFETY FACTOR
Hydrogen Sulfide	NIOSH 1981	Human (1952): 400-760 mg/m^3 - unconsciousness (no duration specified) Human (1951): 350 mg/m, 20 minutes – cramps low blood pressure, unconsciousness Human (1934): 20-35 mg/m, eye irritation, headache loss of appetite, weight loss, dizziness, (no duration specified) Human (1969): 15-20 mg/m^3, 4-7 hours – con-junctivitis Human (1964): 0.003-11 mg/m^3, intermittent episodes over 2 mos. nausea, headache, shortness of breath,	Lack of long-term low level exposure date	10
	ACGIH 1980	sleep disturbance, throat and eye irritation Human (Various, 1937-1966) 4-30 ppm - eye irritation, nervousness, cough, nausea, headache, insomnia		

working population. It is usually represented as some number which is below the lowest observed adverse effect level (LOAEL) for humans or animals, often by a factor of two or less. Thus, the resulting number may be regarded as a no-effect level for the population and effects specified. In contrast, an uncertainty factor normally involves reducing documented effect levels by one to three orders of magnitude (10,100,1000), and is designed to account for uncertainties in the qualitative and quantitative data (including calculations of LOAEL and "margins of safety"), as well as intra- or inter-species variations. Thus, a margin of safety should not be construed as a safety or uncertainty factor, particularly when using an occupational limit to derive allowable ambient limits for the general population. The application of adjustment and uncertainty factors to the MAOL, even when the MAOL may include some "margin of safety", does not represent an overlap of factors, or an overly conservative approach, since one is designed to protect against a specific effect, while the other is designed to account for uncertainties or gaps in the data (i.e., when specific effects or dose levels cannot be quantified or are unknown).

By applying a total adjustment factor of 73.5 or 735 to the MAOL, the Department assumes that adequate protection will thus be afforded against those threshold effects accounted for by the occupational limit selected as the MAOL. In other words, whatever degree of protection was afforded to workers by the occupational limit, is now extended to the general public, including those more susceptible to adverse health effects. In addition, other potentially adverse chronic effects are also addressed. In this context, the MAOL could be regarded as a "no observed adverse effect level" (NOAEL) for healthy adult workers which is then extrapolated to a NOAEL for the general population. However, occupational limits vary considerably in the degree of protection afforded against specific effects, and often leave out other health effects entirely (e.g., chronic toxicity,

carcinogenicity, mutagenicity, developmental/reproductive toxicity). In fact, fewer than 50% of the occupational limits reviewed thus far provide protection against the acute and/or chronic effects documented, even for healthy workers. In many cases then, it is more accurate to say that occupational limits, as a group, represent low-observed-adverse-effect levels (LOAELs) for the populations specified and for certain effects. Certainly they should not be considered LOAELs for the general public, and not NOAELs.

Clearly, some occupational limits do attempt to incorporate a margin of safety against certain effects, and some are clearly more adequate than others. However, since the "safety" provided is limited, and quite variable with respect to specific effects and specific individuals, it would not be helpful to attempt to make arbitrary distinctions among MAOLs based on subjective judgments of "adequacy". Rather, the Department applies adjustment and High Risk Group factors to the MAOL on a consistent basis, characterizing the MAOL as a low-observed-adverse-effect level for humans derived from long-term experience with human populations in controlled occupational settings. In this context, the application of adjustment and uncertainty factors to the MAOL can be seen as a reasonable approach to deriving allowable ambient limits for a large number of chemicals, to protect a diverse population against a range of effects, in a consistent manner.

As indicated, both the adjustment factors and uncertainty factor for high risk groups are applied to all chemicals, resulting in an adjustment factor of 73.5. When all the known threshold effects associated with a chemical have been accounted for in the MAOL, and the chemical has been sufficiently studied to warrant confidence in that limit, further reduction factors are considered unnecessary and MAOL/73.5 is assumed to be adequate to protect public health against those threshold

effects. However, as described above, when adequate long-term human toxicity data are not available, an uncertainity factor (TOX) is applied. The resulting total adjustment factor applied to the MAOL may then be 735. In addition, when known threshold effects (identified in CHEM) have not been accounted for in the MAOL (e.g., teratogenicity), the adjusted MAOL may still be inadequate. Therefore, an additional factor, called a threshold effects uncertainty factor (TEUF), may be applied to further reduce the adjusted MAOL. The TEUF is discussed in detail below. Nonthreshold effects are addressed separately. The procedure for evaluating non-threshold effects is described in section C.

4. Threshold Effects Uncertainty Factor (TEUF)

The Department uses the health effects data developed through CHEM to assign chemical-specific "threshold effects uncertainty factors" to account for known threshold effects, since the adjustment factors described in section B(2) above pertain only to exposure conditions and inter- or intraspecies variability, and do not account for specific toxic effects.

As described in Part II, occupational limits are developed by NIOSH, ACGIH, and OSHA, who provide documentation as to the health effects and prevention objectives considered in setting their respective occupational limits. In CHEM, this documentation is used to select the MAOL and to provide health data for scoring acute/chronic toxicity. All the health effects data obtained from NIOSH, ACGIH, and OSHA are recorded on worksheets for acute/chronic toxicity, and summarized again on the worksheets used in the selection of the MAOL. Since each occupational agency clearly identifies the health effects accounted for in the occupational limit, as well as the extent of protection intended, identifying those effects not accounted for in the MAOL is generally a straightforward exercise. Information about effects not accounted for can come either from the

occupational sources themselves or from the comprehensive health effects data developed through CHEM.

For example, because many occupational limits were developed prior to the availability of current experimental results, developmental toxicity is often not considered by NIOSH, ACGIH, and OSHA in setting their occupational limits. When the health effects assessment indicates that a chemical is associated with developmental or reproductive toxicity, and this evidence was not considered by NIOSH, ACGIH, or OSHA in setting an occupational limit, the methodology to derive AALs incorporates a threshold effects uncertainty factor to account for this effect. The size of the factor is determined by the score for that health effect category. Since health effects scores are basically descriptive, and represent a relative ranking with respect to degree of hazard, selection of the threshold effects uncertainty factor bears a direct relationship to estimated hazard. Thus, high scores (`A' or `B') receive a factor of 10, while lower scores (`C' or `D') receive a factor of 5. In the case of acute and chronic toxicity, an uncertainty factor will be applied only if effects have been documented at levels below the adjusted MAOL, since the MAOL is intended to cover most threshold effects other than developmental and reproductive toxicity. Therefore, the TEUF factor pertains primarily to documented developmental and reproductive effects not accounted for in the MAOL. However, exceptions may at times be warranted. One example might be immune competence. If immune system effects were detected in humans or animals at a level below the adjusted MAOL, an ENA factor could be applied for acute and chronic toxicity. In any case, the ENA factor can be applied only once, either for acute and chronic toxicity, or for developmental and reproductive toxicity, unless the demonstrated effect level is so low that even a factor of 10 is inadequate. The Department is not aware of any examples of such a case, however. Of the more than 100 chemicals evaluated to date, 26 received a Threshold Effects

Uncertainty Factor (TEUF) of 5 or 10 for developmental or reproductive effects not accounted for, and none received a factor based on acute or chronic effects unaccounted for (see Table III-5).

5. Threshold Effects Exposure Limit (TEL)

The Threshold Effects Exposure Limit (TEL) is derived by dividing the adjusted MAOL by the appropriate TEUF and applying the relative source contribution factor of 20% (Ambient air is assumed to represent 20% of the total exposure to any given compound). The TEL is derived based on information developed through the CHEM assessment of threshold effects and is the result of the threshold effects evaluation. The TEL is the concentration that is allowable based on protection against threshold health effects. Thus,

$$\text{TEL} = \frac{\text{Adjusted MAOL}}{(\text{TEUF})(5)} = \frac{(\text{MAOL}) \text{ 73.5 or 735)}}{(1 \text{ or } 5 \text{ or } 10)(20\% \text{ factor})}$$

C. Nonthreshold Effects Evaluation

1. Introduction

As described in the introductory overview, the nonthreshold effects evaluation is the second phase in the AAL derivation methodology, and comprises two separate procedures. The product of the evaluation is the Nonthreshold Effects Exposure Limit (NTEL), which is designed to provide protection against nonthreshold effects based on estimates of potential risks to humans from carcinogenicity and mutagenicity. Which procedure is used depends upon the availability of quantitative data on cancer potency. When there are sufficient valid data on cancer potency to calculate a unit risk, the derived NTEL is based on quantitative cancer risk estimates. In this case the

NTEL is set at a concentration corresponding to an excess lifetime risk of one in one million (1×10^{-6}). How this number will be used is described in Part I, section C-4, and Part III, section E. Mutagenic potency is not factored in because there is no reliable method for interpreting these data as yet.

When quantitative cancer potency data are either not available or not toxicologically adequate, an alternate methodology is used to derive the NTEL. This alternative approach is based on the use of uncertainty factors to estimate potential risks from nonthreshold effects. The procedure involves evaluating the weight-of-evidence for carcinogenicity and mutagenicity, and applying nonthreshold effects uncertainty factors (NTEUF) ranging from 1 - 100 on a case-by-case basis depending on the amount and type of evidence available. Both positive and non-positive evidence are considered (see Part II, sections D and E, weight-of-evidence Tables II-7 and II-18). At least two adequate animal bioassays producing non-positive results are required for a designation of non-positive evidence. In assigning uncertainty factors to a given chemical, one with substantial positive evidence of carcinogenicity would receive a larger factor than a chemical having only equivocal evidence. Mutagenicity evidence is considered in the same way. When a chemical has not been tested for carcinogenicity and/or mutagenicity, Structure-Activity Relationship (SAR) analysis is carried out according to FDA procedures for classifying direct food additives (see Appendix H), and this information is also considered in assigning uncertainty factors. The procedures used are described in detail below (Section 3). The specific uncertainty factors and criteria for their selection are provided in Table III-3.

2. Procedure One - Use of Quantitative Cancer Risk Assessment to Determine the Nonthreshold Effects Exposure Limit (NTEL)

This procedure is used to determine the NTEL when adequate quantitative data on carcinogenicity exist. The data sources for quantitative carcinogenicity data were discussed in Part II Section D(2). Procedure One is used when there is a unit risk value developed by the Department, the EPA, or some other qualified party, and adopted by the Department. Appendix D describes the criteria used to determine whether a particular study is adequate for quantitative risk assessment, and the procedures used to calculate unit risk, when the data are adequate. Appendix E presents detailed summaries of the cancer unit risk calculations for the chemicals evaluated thus far. A list of the chemicals for which the unit risk is used to determine the NTEL, and the unit risk value, are listed in Table D-2 in Appendix D.

The unit risk is an estimate of the excess lifetime carcinogenic risk for lifetime exposure to 1 ug/m^3 of the chemical in air. This value is used to calculate the concentration which corresponds to a cancer risk of one in one million (10^{-6}). This risk level has been adopted by the Department as the maximum allowable risk for a single pollutant. For chemicals meeting the criteria outlined in Appendix D the NTEL will be the concentration calculated to correspond to that level.

3. Procedure Two - Use of Nonthreshold Effects Uncertainty Factors (NTEUF) to Determine the Nonthreshold Effects Exposure Limit (NTEL)

The purpose of the second procedure for evaluating

TABLE III-3. DERIVATION OF NONTHRESHOLD EFFECTS UNCERTAINTY FACTORS

Carcinogenicity Score[1]	Mutagenicity Score	SAR Analysis	Nonthreshold Effects Uncertainty Factor
A or B	Any (A,B,C,D,E,orND)	Any (+ or -)	100
C or D	Any (A,B,C,D,E,orND)	Any (+ or -)	75
E, F, or ND	A or B	Any (+ or -)	50
E F, or ND	C or D	+	20
E or ND	ND	+	10
E or ND	E	+	5
F	ND	+	5
F	E	+	1
E, F, or ND	C or D	-	10
E, F, or ND	E or ND	-	1
E or ND	E or ND	-	1
F	E or ND	-	1

1. As assigned in CHEM (see Table II-8. And II-17.)

2. Structure Activity Relationship Analysis, performed according to FDA procedures for classifying direct food additives (1982). See discussion in text. Section D.3., and Appendix G.

nonthreshold effects is to determine the NTEL when adequate quantitative data on carcinogenicity are unavailable. This situation arises when a chemical has not been tested for those effects, or when existing quantitative data are either unavailable to the Department (e.g., hydrazine) or inadequate toxicologically for calculating unit risk for humans. One example of the latter case is ethyl acrylate. Gavage studies in rodents produced only localized tumors of the forestomach, an effect apparently linked to the high local concentration caused by gavage exposure. Since the route of exposure and tumor type produced are of questionable relevance to humans, a unit risk was not calculated for this chemical (detailed discussions of this and other evaluations are provided in Appendix E). Nevertheless, positive evidence of carcinogencicity in adequately conducted studies cannot be dismissed, even though the data may not meet the Department's criteria for conducting quantitative dose-response assessment. In these cases, the weight-of-evidence for carcinogenicity and mutagenicity are considered in assigning uncertainty factors for nonthreshold effects, as described below.

Since lack of data is not equivalent to lack of hazard or risk, the Department has the responsibility to evaluate potential risks to humans, even in the absence of quantitative data, and to protect the public against those risks to the extent possible. Accordingly, the Department has developed a methodology to evaluate the potential for nonthreshold effects which may be associated with a given chemical, and uses that information to derive an NTEL by applying an uncertainty factor to the adjusted MAOL (adjusted MAOL divided by specified uncertainty factor). The numerical value of the factor assigned in each case depends upon the amount, quality, and type of data available on carcinogenicity and mutagenicity, as well as an

evaluation of structure-activity relationships. Thus, assignment of the Nonthreshold Effects Uncertainty Factor (NTEUF) is based on an evaluation of three factors: weight-of-evidence for both carcinogenicity and mutagenicity, and structure-activity relationship (SAR) analysis. Table III-3 shows the matrix approach used for weighting the three factors. As the table shows, both positive and non-positive (null) data are reviewed and evaluated, using the scores and assessment methods developed through CHEM (see Part II, sections A, D, and E). Chemical structure is also evaluated in order to account for serious, unknown toxic effects. The Department currently relies upon established Food and Drug Administration (FDA) procedures for classifying direct food additives (1982) to identify substances with a high risk chemical structure (those belonging to FDA's highest toxicity classification). However, the Department plans to adopt the guidelines and information developed by EPA's Office of Toxic Substances when these become available.

In the FDA procedure, chemicals are assigned to one of three structural classes (A, B, or C) on the basis of their structural similarity to known toxicants. Category A represents structures or chemicals of least concern; Category B, moderate concern; and Category C, a high level of concern. Each of these sub-structure tables is reproduced in Appendix H of this document. Nonthreshold effects uncertainty factors are assigned on the basis of Sub-structure Category C (most toxic) only. Thus, in Tables III-3 and III-6, a positive or negative sign in the SAR column means that the chemical is (+) or is not (-) associated with the highest toxicity category (Category/Table C).

As shown in Table III-3, nonthreshold effects

uncertainty factors ranging from 1 - 100 are applied to the adjusted MAOL, depending on the amount of positive or non-positive evidence of carcinogenicity and/or mutagenicity, and the presence or absence of high toxicity chemical structure. If no data exist for a given chemical, and SAR analysis does not indicate high toxicity, a factor of 1 is applied.

Likewise, when a chemical has been adequately tested and is shown to be non-positive with respect to nonthreshold effects, an uncertainty factor of 1 is applied in this case as well. On the other hand, an uncertainty factor of 100 is applied when there is substantial evidence of carcinogenicity, a factor of 50 for sufficient or substantial evidence of mutagenicity, a factor of ten when the chemical has not been studied but SAR analysis indicates high toxicity, and so on. The SAR analysis is supplementary to the weight-of-evidence evaluation, so that lack of data is not translated into lack of risk, and potential effects are not overlooked simply because a chemical has not yet been tested. The advantages of the method described are that lack of usable data is distinguished from non-positive data, and the nonthreshold effects exposure limit (NTEL) accounts for all potential nonthreshold effects. Criteria published by EPA (1984b, 1984c, 1984d), IARC (1980, 1982), and NAS (1977, 1983) are used to judge the reliability of tests producing non-positive results, as described in CHEM, Part II of this document.

D. Selection of the AAL

The final step in the derivation of the AAL is a comparison of the TEL and the NTEL. The lower of these two values is selected as the AAL. This procedure insures that

the AAL set by the Department provides protection for the most sensitive health endpoint. The AAL in all cases corresponds to a maximum allowable excess lifetime cancer risk of one in one million (10^{-6}) or less.

E. Regulatory Context for the Use of Uncertainty Factors

1. Risk Assessment and Risk Management

Risk assessment is the component of a regulatory process which defines the magnitude of adverse health consequences associated with exposure to toxic chemicals. The other component, risk management, combines the products of risk assessment with socioeconomic, technical, political, and other considerations to reach a decision as to whether and how much to control exposure to the toxic chemical.

The National Research Council (NRC) has defined risk assessment as being comprised of some or all of the following components: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC, 1983). The Massachusetts Chemical Health Effects Assessment Methodology (CHEM) represents a tool for performing two of the risk assessment steps for substances which may cause adverse health effects in humans. CHEM focuses on hazard identification and dose-response assessment. It does not address exposure assessment or risk characterization. Hazard identification involves evaluation of qualitative data for purposes of assessing the likelihood that an agent may present a hazard to humans. In CHEM, hazard identification is done through the "weight-of-evidence" classification. Dose-response assessment involves estimating the magnitude of an effect at a given dose. It is performed in CHEM for all health effects categories except mutagenicity. Each health effect

category requires unique considerations regarding definition and interpretation of biological endpoints. As a result, a different approach for assessing dose-response is used in each category. Thus, the carcinogenicity category uses a unit risk value, acute/chronic toxicity relies on the numerical value of the occupational exposure limit, and the developmental/reproductive toxicity category uses low-adverse-effect level and risk ratio concepts.

As described in the foregoing sections, the method to derive Allowable Ambient Limits is one of the tools used by the Department to conduct risk management. This tool is a complex design consisting of several components: most appropriate occupational limit as one measure of potential hazards to humans, hazard assessment in four health effects categories codified through CHEM, application of uncertainty factors in extrapolation of toxicological data, policy decisions regarding uncertainty and lack of toxicity data, and quantitative cancer risk assessment for carcinogens. Allowable Ambient Limits (AALs) are an essential bridge between scientific documentation of a substance's ability to produce adverse health effects, and regulatory policy aimed at protection of the general population from these effects. In the case of carcinogens for example, the Department has designated one chance in one million as the maximum allowable excess lifetime cancer risk for individual chemicals, and has set AALs for carcinogens at or below that level. The AALs, in combination with an air toxics implementation plan, constitute the risk management component of the Department's Air Toxics Program. The present document does not include a discussion of the implementation plan.

2. History and Rationale Behind the Use of Uncertainty Factors in Regulation of Toxic Substances

Uncertainty factors reflect the degree of uncertainty that must be considered when quantitative predictions are made about the consequences of human exposure to toxic substances. They are used extensively by regulatory agencies in extrapolating animal data to humans and to account for gaps in the data. In that context, they are usually applied to a no-observed-adverse-effect level (NOAEL) or lowest observed-adverse-effect level (LOAEL), and thus are used for effects currently assumed to have a threshold. Uncertainty factors provide a useful mechanism for dealing with an inadequate database and the uncertainty inherent in extrapolation of animal data to humans. If it were not for the uncertainties about extrapolation processes, there would be little need for such factors (Calabrese, 1978).

The National Academy of Science has developed guidelines for using uncertainty factors in conjunction with the methodology to determine "acceptable daily intake" (ADI) of toxic substances through ingestion (NAS, 1977). As used by EPA, FDA, NAS and others, uncertainty factors are designed to account for:

- Intraspecies variability.
- Interspecies variability.
- Extrapolation from subchronic exposure to chronic exposure.
- Extrapolation from lowest observed-adverse-effect level (LOAEL) to no-observed-adverse effect level (NOAEL).

The history and scientific bases of uncertainty factors in regulation of toxic substances have been reviewed by Dourson and Stara (1983) and are discussed in detail below.

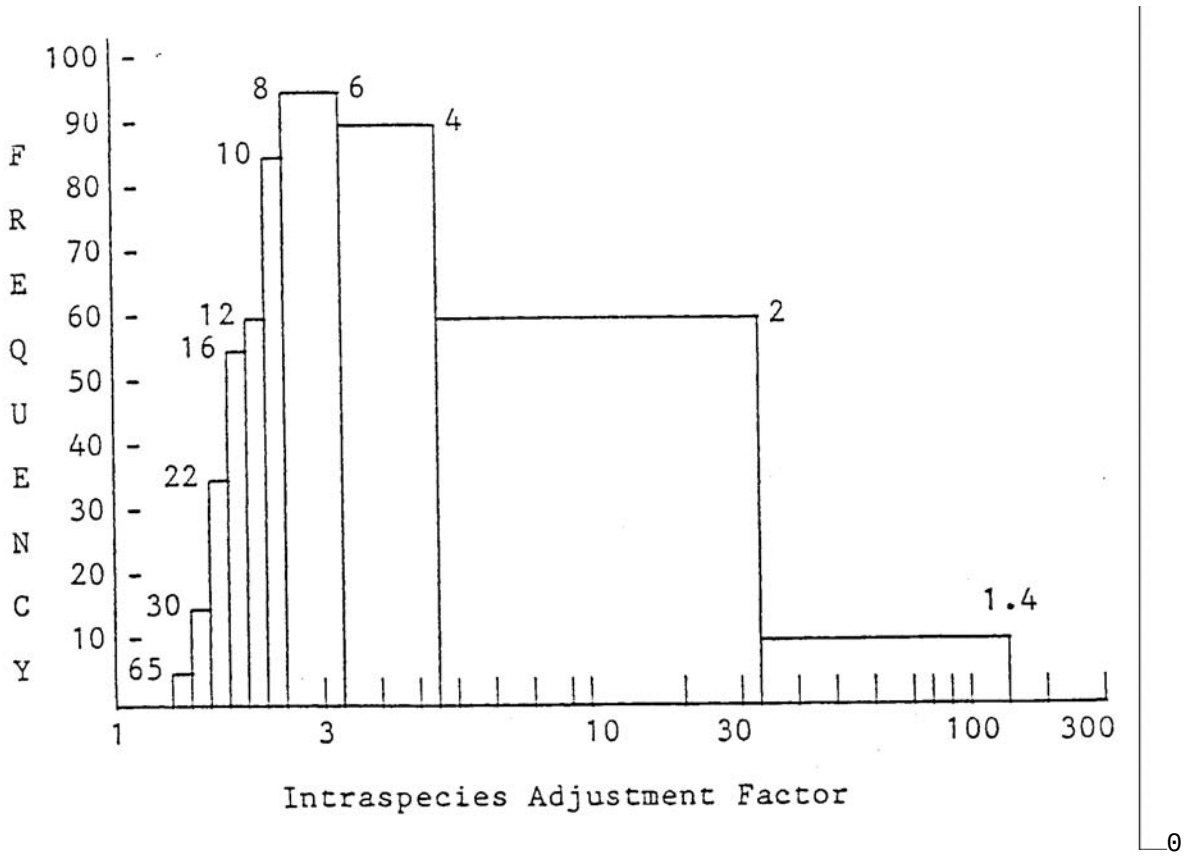
The discussion pertains not to the CHEM and AAL methodology, but to the use of uncertainty factors by other agencies or groups in various regulatory contexts, in order to provide background information about the origin of such factors.

a. Intraspecies Variability

The uncertainty factor of 10 for intraspecies variability is to protect high risk groups, or those individuals who will experience an adverse health effect to one or more pollutants to a greater degree or significantly before the general population, because of one or more factors which predispose the individual to those effects. In an attempt to ascertain the extent to which a 10-fold dose reduction protects sensitive members of the animal population, Dourson and Stara (1983) examined the range of probit, log-dose slopes from 490 animal studies of acute lethality compiled by Weil (1972). As shown in Figure III-3, the slopes varied from approximately 1.4 to 65. The adjustment factors in Figure III-3 represent reductions in the milligrams per kilogram (mg/kg) body weight dose needed to scale down a median response by three probits. Approximately 92% of the probit, log-dose slopes had values greater than three. This would require a dose reduction of ten to drop the median response at least three standard deviations, to a level protective of the sensitive laboratory animal. However, for those chemicals in the sample having a probit, log-dose slope of less than three, a 10-fold reduction in dose could not achieve a similar reduction in response.

While a 10-fold reduction may appear conservative, the calculated slopes were derived on the basis of laboratory rats which are less heterogeneous in response to toxicity than human populations. Thus, the 10-fold factor may be

FIGURE III-3 Intraspecies Adjustment Factor



Frequency v-s an intraspecies adjustment factor obtained by raising 10 to the power (3 standard deviations - the probit, log-dose slope). Probit, log-dose slopes are shown within the figure.

SOURCE: Dourson and Stara, 19.83 (from Weil, 1972)

protective of the sensitive laboratory animal, but may not be adequate to protect humans, because the human population is more heterogeneous than the animal population. Laboratory animals are usually inbred and genetically homogeneous, are tested under highly standardized conditions, with controlled environments (e.g. diet, temperature, humidity, light-dark cycles), and subject to limited, controlled exposures. In contrast, humans are heterogeneous with respect to genetic make-up, lifestyle, medical history, exposure history, age, sex, immunological status, and sensitivity to the adverse effects of chemical exposures. They live under a variety of environmental conditions, are subject to a variety of chemical exposures, and are likely to include subgroups of unusual sensitivity to toxic substances. Greater heterogeneity is associated with lower slopes and requires correspondingly greater dose reductions. Experimental work by Krasovskii (1976) supports the use of an intraspecies variability factor between 18-30. Other writers discuss the use of even higher factors (Mantel and Bryan, 1961; Munro and Krewski, 1981; Oser, 1969).

Contributing to the problem of defining risk is the fact that all members of the population are exposed to environmental pollutants regardless of the differences described above. The range of individual variability in terms of physiological measures is ill-defined and is often not "normally distributed" in the healthy population. Moreover, the variability for those who are diseased is generally much larger than that of the healthy population. Recent work on human populations by Vessell et al. (1984) at Pennsylvania State University has clearly demonstrated that individual variability in response to therapeutic drugs varies from 3 to 40-fold. It is expected that future work in this area will permit statistical derivation of a human intraspecies variability factor which will protect most

members of the population. On the basis of the available data then, an uncertainty factor of at least 10 is supported by most investigators (Calabrese, 1985), and is used in the Massachusetts system to account for high risk groups within the general population. (see section B, step 4).

b. Interspecies Variability

An uncertainty factor of 10 is often used to account for interspecies variability. In order to use experimental data, and to extrapolate results from animals to humans, it is necessary to account for differences in size among various species. Thus, comparison among species and interpretation of experimental data depends upon accurate calculations of equivalent doses. Species with greater body weight (e.g., humans) can be more sensitive to the toxicity of contaminants than species of lower body weight (e.g., rodents) (Evans et al., 1944; Hayes, 1967; Lehman and Fitzhugh, 1954). As the NAS states,

> "On a body-weight basis, man is generally more vulnerable than the experimental animal, probably by a factor of 6-12. Comparative studies have shown generally that absorption, metabolism, and excretion of various drugs are slower, dose-for-dose, in man; that there is a greater retention of such drugs; and that higher concentrations occur in body fluids and tissues in man than in small mammals. With an awareness of these quantitative differences, appropriate safety factors can be applied to calculate relatively safe therapeutic dosages for man." (NAS, 1977, p.52)

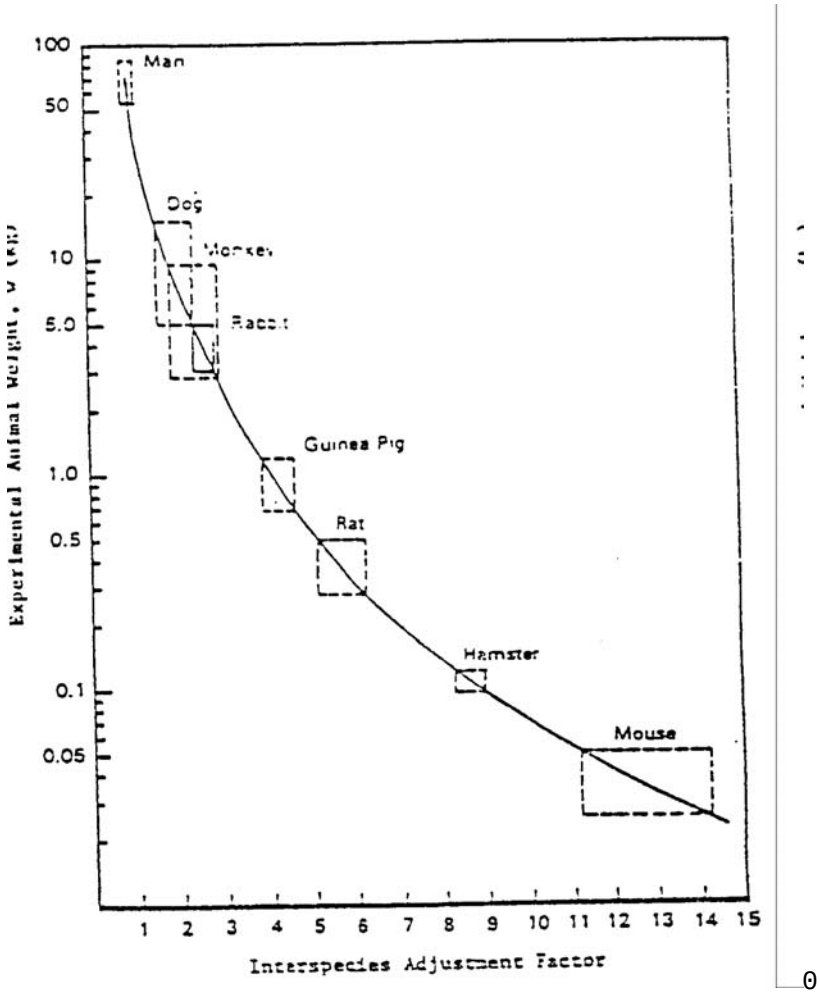
Dose conversions based on body surface area are considered to more accurately reflect differences among species when compared to conversions based on mg/kg of body weight (Mantel and Schneiderman, 1975). Figure III-4 is a plot of experimental animal weight versus an interspecies adjustment factor. These factors account for differences in

milligrams per kilogram body weight dose due to differences in body surface area between experimental animals and humans, based on the assumption that different species are equally sensitive to the effects of a toxicant on a dose per unit of surface area basis. They represent the reductions in experimental animal dose (mg/kg of body weight) needed to estimate a comparable human dose in mg/kg body weight.

The differential in sensitivity between humans and animals to equivalent dose in mg/kg body weight increases as the body weight of the experimental animal decreases (NAS,1977). Figure III-4 provides support for the 10-fold uncertainty factor to account for interspecies variability. This is an adjustment factor, which may vary up to a factor of 10 or more in a consistent way based on body weight. The adjustment factors range from about 2 for a dog, to about 6 for a rat, to about 12.5 for a mouse. Thus, in most cases, a 10-fold reduction in mg/kg body weight animal dose is considered adequate to protect humans. From these data it seems reasonable to use an uncertainty factor of 10 to account for interspecies variability in response to doses equivalent on the basis of body weight, and the Massachusetts system therefore uses this factor to account for uncertainties in the data when only animal evidence is available (see section B, step 5). This factor of 10 has to cover both the mean size of the adjustment factor, and its variability, so is not overly conservative.

There is considerable support for the use of such factors, based on experimental results (Hayes, 1967; Lehman and Fitzhugh, 1954; NAS, 1977). In fact, some investigators have advocated the use of an interspecies adjustment factor of 100, based on other differences between humans and animals (Hoel et al., 1975; Bigwood, 1973; Vettorazzi, 1976, 1980). Nevertheless, as noted above, Massachusetts applies

FIGURE III - 4 Interspecies Adjustment Factors



Experimental animal weight *(w)* vs an interspecies adjusment factor calculated as the cubed root of the ratio between the assumed average human body weight (70 kg) and *w*. Enclosed areas along the function represent general ranges of average body weights of experimental adult animals. Rabbit values are represented by the box with solid lines. Values are from Altman and Dittmer (1962).

Source: Dourson and Stara, 1983

a factor of 10 to account for interspecies variability.

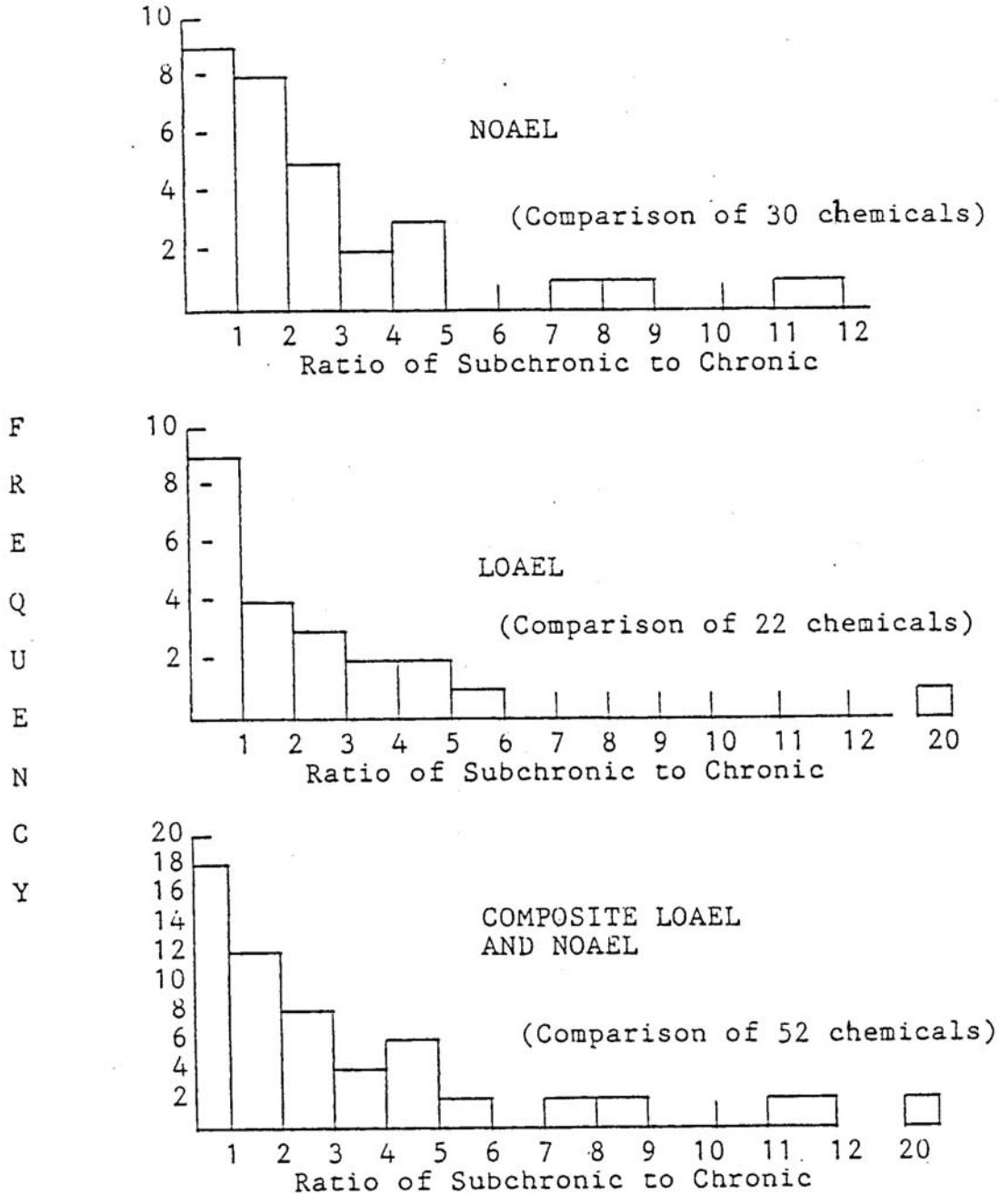
c. Extrapolations from Subchronic to Chronic Exposures

The third commonly applied uncertainty factor is one used when chronic exposure studies are not available, and a subchronic study is used in deriving an acceptable exposure level. This factor of 10 receives scientific support from the study of Weil and McCollister (1963). In this study the no-observed-adverse-effect levels for a group of chemicals were experimentally determined for both chronic exposures (i.e., 2 years) and subchronic exposures (between 30 and 210 days) for rats and dogs. From these data, a frequency plot of the ratio of subchronic NOAELs and LOAELs to the corresponding chronic NOAELs and LOAELs was obtained (Weil and McCollister, 1963).

Figure III-5 is a plot of frequency versus ratios of subchronic to chronic exposure for either NOAELs, LOAELs, or both. The ratios represent reductions in subchronic NOELs, NOAELs, or LOAELs, in order to yield the corresponding chronic effect level. These data show that approximately 96% of the ratios are below a value of 10, which reasonably supports a 10-fold safety factor. A factor of 10 is supported by other experimental work as well (Dourson and Stara, 1983).

In the Massachusetts system uncertainty factors are applied to occupational data rather than experimental data, and therefore, this factor is not used by the Department in setting AALs. Occupational limits are designed for long-term exposure, and the system therefore relies on the assumption that the uncertainty factor for extrapolating from subchronic to chronic exposures is not necessary when using occupational rather than experimental data, provided

FIGURE III-5 A Plot of Frequency vs the Ratio of Subchronic to Chronic Exposures for Either NOAELs, LOAELs, or Composite NOAEL-LOAEL Values



SOURCE: Dourson and Stara, 1983 (from Weil and McCollister, 1963)

that the chronic exposure data have been derived on the basis of human studies rather than in animals.

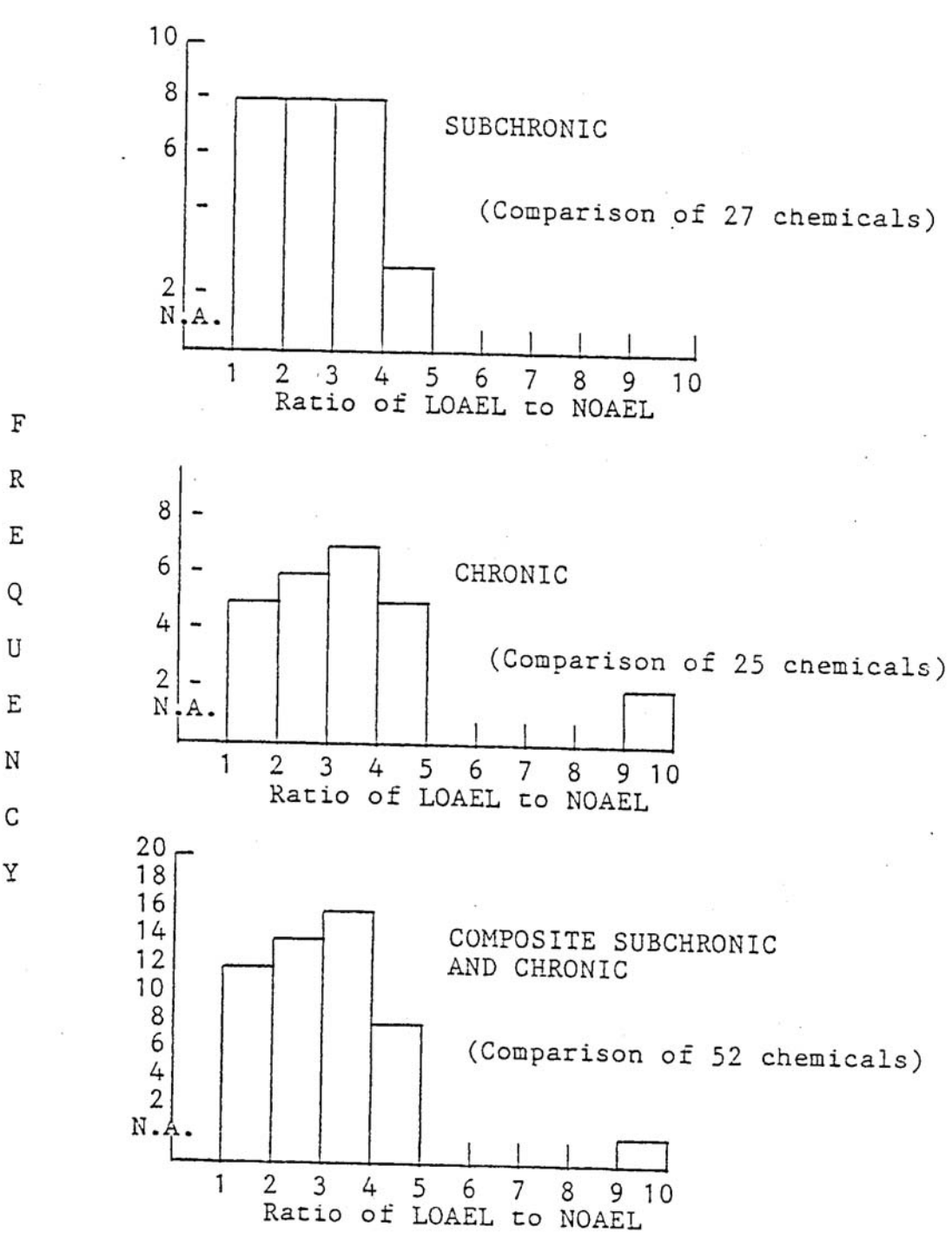
d. Extrapolation from LOAEL to NOAEL

The fourth type of uncertainty factor accounts for adjustments needed when the no-observed adverse effect level cannot be identified and the lowest-observed-adverse effect level must be adjusted. In the study of Weil and McCollister (1963) the ratios of the corresponding LOAEL to NOAEL, for both chronic and subchronic exposures, were determined for a group of chemicals in rat and dog models. Figure III-6 presents the plot of frequency versus the ratios of LOAEL to NOAEL for subchronic or chronic exposure, or both. The derived ratios represent reductions in the LOAEL found after subchronic or chronic exposure, to obtain the corresponding NOAEL. For all chemicals studied, this ratio was less than 10, and for 96% of the chemicals the ratio was five or less.

Based on the above data, it appears that a 10-fold uncertainty factor is adequate to address the uncertainty in extrapolating from lowest-observed adverse effect levels. Indeed, it appears that in most cases a smaller factor would suffice. On that basis, EPA proposed that a variable safety factor, between one and ten, should be used in deriving acceptable exposure levels when a LOAEL is used instead of a NOAEL (USEPA, 1980). The value of the factor would depend on the severity of the adverse health effect.

Since the TEL is based on occupational limits, however, factors for extrapolating from LOAELs to NOAELs do not apply to the Massachusetts system, and are not used in deriving AALs. Instead, the Department assumes that the adjustment and threshold effects uncertainty factors described in

FIGURE III-6 A plot: of Frequency vs Ratio of LOAEL to NOAEL after either subchronic, chronic, or composite subchronic and chronic exposures. A ratio of 1.0 or less is not allowable (N.A.)by definition.



SOURCE: Dourson and Stara, 1983 (from Weil and McCollister, 1963)

section B will provide adequate protection against documented threshold effects.

e. Combined Uncertainty Factors

Uncertainty factors are designed to account for the uncertainties inherent in extrapolating from laboratory animals to humans, from subchronic to chronic exposures, and from LOAELs to NOAELs, for sensitive members of the population. The usual procedure is to apply factors in multiples of ten, depending on the type and extent of toxicity data available. Thus, the uncertainty factor applied to a given chemical could range from 1 to 10,000 using the methods described by Dourson and Stara. For example, an uncertainty factor of 10 for intraspecies variation would be applied when NOAELs from chronic studies in humans were available, whereas an overall factor of 1000 is used when deriving an acceptable exposure level from a subchronic animal study where extrapolation involves intraspecies variability, animal to human variations, and subchronic to chronic exposure (10 x 10 x 10). Table III-4 summarizes the use of, and experimental support for, compounding of uncertainty factors.

3. Use of Uncertainty Factors for Non-Threshold Effects

Several uncertainty factors are generally used by EPA and others in deriving acceptable human exposure levels to toxic pollutants. These factors are 10, 100, 1000, or 10,000 depending on the available human and animal data, and are justified by several studies. The uncertainty factor approach to derivation of acceptable levels of human exposure to pollutants has generally been used for toxic effects where a threshold level is assumed to exist, since nonthreshold effects are assumed to present some degree of

TABLE III-4 GUIDELINES, EXPERIMENTAL SUPPORT, AND REFERENCES FOR THE USE OF UNCERTAINTY (SAFETY) FACTORS

GUIDELINES	EXPERIMENTAL SUPPORT	REFERENCES
(a) Use a 10-fold factor when extrapolating from valid experimental results from studies on prolonged ingestion by man. This 10-fold factor protects the sensitive members of the human population estimated from data garnered on average healthy individuals	Log-probit analysis; Composite human sensitivity	Mantel and Bryan, 1961; Weil, 1972; Krasovskii, 1976
(b) Use a 100-fold factor when extrapolating from valid results of long-term feeding studies on experimental animals with results of studies of human ingestion not available or scanty (e.g., acute exposure only) . This represents an additional 10-fold uncertainty factor in extrapolating data from the average animal to the average man.	Body-surface area dose equivalence; Toxicity comparison between humans and rats; or between humans and rats; or dogs	Rail, 1969; Evans et. al., 1944, Hayeas, 1967; Lehman and Fitzhugh, 1954
(c) Use a 1000-fold factor when extrapolating from less than chronic results on experimental animals with no useful long-term or acute human data. This represents an additional 10-fold uncertainty factor in extrapolating from less than chronic to chronic exposures.	Subchronic/chronic NOEL comparison; Subchronic/chronic NOAEL or LOAEL comparison	Weil and McCollister 1963

continued . . .

TABLE III-4. GUIDELINES, EXPERIMENTAL SUPPORT, AND REFERENCES FOR THE USE OF UNCERTAINTY (SAFETY) FACTORS, continued

GUIDELINES	EXPERIMENTAL SUPPORT	REFERENCES
(d) Use an additional uncertainty factor of between 1 and 10 depending on the sensitivity of the adverse effect when deriving an ADI from a LOAEL. This uncertainty factor drops the LOAEL into the range of a NOAEL.		Weil and McCollister, 1963

a. These factors are to be applied to the highest valid NOAEL or NOEL which does not have a valid LOAEL egual to or below it, in calculating an ADI when no indication of carcinogenicity of a chemical exists.

b. Guidelines 1 and 2 are supported by the FDA and the WHO/FAO deliberations (Lehman and Fitzhugh, 1954; Bigwood, 1973; Vettorazzi, 1976, 1980); Guidelines 1-3 have been established by the NAS (1977) and are used in a similar form by the FDA (Kokoski, 1976); Guidelines 1-4 are recommended by the U.S EPA (1980).

SOURCE: Dourson and Stara, 1983

risk at any exposure level. For carcinogens, the most commonly used approach has been to (i) perform a risk assessment using a mathematical model; (ii) choose a risk level acceptable under the particular set of circumstances; and (iii) set the acceptable level of exposure to pollutants at a concentration which corresponds to that risk value. The advantages of this approach are that it offers a straightforward quantitative approach to regulating carcinogenic substances; it rewards good experimentation in that larger experiments tend to produce narrower confidence limits and consequently higher limits for safe doses; it takes observed portions of dose-response curves into consideration because a mathematical model is fit to all of the dose-response data.

However, there are also several disadvantages to this approach. One is related to choice of mathematic model because different models that fit the observed data equally well can yield different results when extrapolated to doses corresponding to very small risks. A greater disadvantage is that when the approach focuses on quantitative data alone, the qualitative data, and its biological relevance, can be overlooked. Furthermore, reliable quantitative data are often not available, and therefore, approaches based solely on quantitative measures of risk cannot address the problem of inadequate data.

The Department believes that when adequate quantitative data on carcinogenicity are available, this information should be used to determine acceptable exposure levels for humans. However, since it is both unsafe and unscientific to assume that all chemicals without adequate evidence of carcinogenicity or mutagenicity are in fact non-carcinogens or non-mutagens, the Department has the responsibility to evaluate the potential for nonthreshold effects for all

chemicals, and to provide a mechanism for addressing uncertainties and gaps in the data. Thus the Department has developed an alternate methodology using an uncertainty factor approach for chemicals lacking adequate quantitative evidence of carcinogenicity. Uncertainty factors between 1-100 are assigned on a case-by-case basis, depending on a combination of available qualitative evidence of nonthreshold effects, and structure-activity relationship (SAR) analysis. The purpose of the methodology is to develop a Nonthreshold Effects Exposure Limit (NTEL) protective of public health in the absence of direct quantitative measurements of risk.

Recently, in reaction to many of the problems associated with the quantitative risk assessment approach to regulating carcinogenic pollutants, proposals have been made to use safety factors in regulating all systemic toxicants, including carcinogenic substances. One such proposal, advanced by Crump (1984), has received considerable support from experts in the field. During a 2-day workshop on "Approaches to Risk Assessment for Multiple Chemical Exposures" held by EPA on September 29-30, 1982, Dr. Kenny Crump presented three possible options for "utilizing incidence and/or severity-of-effect data in setting allowable exposures", including the one currently used to set Reference Dose values (RfDs) (apply safety factors to NOAEL or LOAEL). The three options are reproduced in Appendix I of this document. As indicated, the effects of concern included both threshold and non-threshold type, and carcinogenicity is specifically mentioned. One option consists of two steps: first, a mathematical model is fit to the dose-response data as is done in quantitative cancer risk assessment, and a lower confidence limit is calculated on the dose corresponding to a risk of 10^{-1} or 10^{-2} (10% or 1%) of incidence, respectively) for both carcinogenic and

noncarcinogenic effects; then, a safety factor is applied to that calculated dose. The safety factor, with values such as 10, 100, 1000, would depend on the severity of the toxic effect (e.g., cancer vs. weight loss) and thoroughness of the study. The advantages of this method are: it takes the shape of the observed portion of the dose-response curve into account; it rewards good experimentation because larger, better designed experiments should yield lower upper confidence limits and thereby higher allowable human exposures; it avoids problems associated with the choice of mathematical models for risk assessment because there is far less disagreement among various models if extrapolation is carried out only to a risk of 10^{-1} or 10^{-2}; it considers qualitative as well as quantitative data, because the safety factors depend on the severity of the effect and the quality of data; and the approach is operationally equivalent to the use of the low-dose linear model to predict doses associated with risk levels of 10^{-5}, or 10^{-6} and lower. At the same time, issues such as the existence or absence of a threshold, acceptability of risks, genotoxic versus epigenetic mechanisms are avoided.

4. Use of Uncertainty Factors in the Massachusetts System

The Department's use of uncertainty factors is in some respects analogous to the approach historically used in developing RfDs. Thus, the Department uses a 10-fold High Risk Group uncertainty factor to account for intraspecies variability (extrapolation of a worker's standard to the general population). The Department also applies an uncertainty factor of 10 for inadequate toxicity data when there are no low-level chronic exposure data for humans.

However, there are some important differences. First, a single uncertainty factor (10) is applied for interspecies variability when chronic human exposure data were not used

to set the MAOL. A separate additional factor of 10 is not applied for subchronic to chronic extrapolation of animal data. The RfD procedure would use two uncertainty factors when using subchronic animal data and thereby apply a total uncertainty factor of 100 (10 x 10) (in addition to the factor of 10 for intraspecies variability).

Thus, while specific gaps in the data are generally considered and accounted for individually, the Massachusetts system considers these data gaps collectively, and uses a single uncertainty factor of 10 to account for inadequate toxicity data. This is because the factors are applied to an occupational limit rather than an experimentally derived LOAEL or NOAEL. The assumption is that since the occupational limits are derived expressly for long-term human exposures, an uncertainty factor of 10 will be adequate to account for gaps in the occupational data pertaining to other potential unknown acute and chronic effects. (NOTE: The Department plans to use EPA inhalation Reference Doses and the traditional uncertainty factor approach described by Dourson and Stara when the RfDs become available, rather than relying on the MAOL).

Second, the Department uses uncertainty factors to account for threshold effects which are identified through CHEM, but not accounted for in the MAOL. In this case, an uncertainty factor of 5 or 10 is applied, depending on score. Finally, for substances lacking adequate quantitative data on nonthreshold effects, as well as a chemical structure indicative of high toxicity, uncertainty factors are applied to account for the lack of data, as illustrated in Table III-3. These uncertainty factors are described in section C (NTEUF). The application of uncertainty factors for serious unknown or unaccounted for nonthreshold effects has no established precedent. The

procedure reflects the Department's response to the inevitable uncertainties and data gaps associated with assessing hazard for humans. The numerical value and use of uncertainty factors represent policy decisions by the Department for reducing risks from potentially irreversible nonthreshold effects.

The approach chosen is one of many possible approaches. It is the product of a six-year effort that evolved into the present document. Certainly it is not free of controversy. However, science inevitably involves uncertainty, risk management inevitably involves judgement, and the regulator must account for each (NAS, 1983). Thus, the approach outlined in this document is workable and consistent, can be applied to adequate data, as well as lack of data, and provides a clear framework for regulatory decision-making. The Department believes that, within a reasonable margin of error (an uncertainty necessarily present), the Massachusetts system offers a viable tool for minimizing risks to public health from exposures to toxic air pollutants.

F. Summary of Results

The results of the assessments and AAL derivations for all chemicals are shown in Tables III-5 and III-6. Table III-5 summarizes the information from CHEM for each chemical, the resulting uncertainty factors assigned in the threshold effects evaluation, and the derived Threshold Effects Exposure Limit (TEL). Table III-6 summarizes the results of application of the adjustment and uncertainty factors in the nonthreshold effects evaluation, and the final selection of the AAL.

TABLE III–5
Summary of Results from CHEM and Derivation of Threshold Effects Exposure Limits

and

TABLE III-6
Summary of AAL Derivations

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES				"E.N.A."		MAOL		MAOL SOURCE	TOX
			(1)			(2)		(3)		(4)	(5)
		A/C	C	M	D/R	A/C	D/R	mg/m^3	ppm	(A,N,O)	
ACETALDEHYDE	75070	D	B	B	B		x	179.80	100.00	A	10
ACETONE	67641	E	ND	E	ND			590.00	250.00	N	10
ACRYLONITRILE	107131	A	A	A	A*		x	4.34	2.00	A	1
AMMONIA	7664417	C	ND	ND	ND			17.40	25.00	A	10
ANILINE	62533	A	C	C	E			7.61	2.00	A	10
ASBESTOS	1332214	A	A	ND	ND			0.10	f/cm^3	N	1
BENZENE	71432	A	A	A	C		x	3.19	1.00	N	1
BENZYL CHLORIDE	100447	B	C*	A	ND			5.17	1.00	A	1
BERYLLIUM	7440417	A	A	ND	ND			0.0005	-	N	1
1,3-BUTADIENE	106990	C	A	ND	D		x	22.11	10.00	A	10
n-BUTYL ALCOHOL	71363	C	ND	ND	ND			151.50	50.00	A	1
CADMIUM	7440439	A	A	ND	A		x	0.01	-	A	1
CALCIUM CHROMATE	13765190	A	A	A	ND			0.001	-	N	1
CARBON TETRACHLORIDE	56235	B	B	C	D			31.43	5.00	A	1
CHLORDANE	57749	A	A	D	B*		x	0.50	0.03	A	1
CHLORINE	7782505	B	ND	ND	ND			1.45	0.50	A	1
CHLOROBENZENE	108907	C	C	ND	ND			345.00	75.00	A	10
CHLOROETHANE	75003	E	ND	ND	ND			2637.00	1000.00	A	10
CHLOROFORM	67663	B	B	C	B			48.79	10.00	A	1
CHLOROPRENE	126998	A	ND	C	B		x	3.62	1.00	N	1
CHROMIC ACID	7738945	A	A	ND	ND			0.001	-	N	1
CHROMIUM(METAL)	7440473	B	ND	ND	ND			0.50	-	A	1

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
ACETALDEHYDE	244.63	136.05	1	10	4.89	2.72
ACETONE	802.72	340.14	1	1	160.54	68.03
ACRYLONITRILE	59.01	27.21	1	10	1.18	0.54
AMMONIA	23.67	34.01	1	1	4.73	6.80
ANILINE	10.36	2.72	1	1	2.07	0.54
ASBESTOS	1.36	f/cm^3	1	1	0.27	-
BENZENE	43.46	13.61	1	5	1.74	0.54
BENZYL CHLORIDE	70.38	13.61	1	1	14.08	2.72
BERYLLIUM	0.007		1	1	0.001	-
1,3-BUTADIENE	30.08	13.61	1	5	1.20	0.54
n-BUTYL ALCOHOL	2061.22	680.27	1	1	412.24	136.05
CADMIUM	0.136	-	1	10	0.0027	-
CALCIUM CHROMATE	0.01	-	1	1	0.003	-
CARBON TETRACHLORIDE	427.62	68.03	1	1	85.52	13.61
CHLORDANE	6.80	0.41	1	10	0.14	0.008
CHLORINE	19.73	6.80	1	1	3.95	1.36
CHLOROBENZENE	469.39	102.04	1	1	93.88	20.41
CHLOROETHANE	3587.76	1360.54	1	1	717.55	272.11
CHLOROFORM	663.81	136.05	1	1	132.76	27.21
CHLOROPRENE	49.22	13.61	1	10	0.98	0.27
CHROMIC ACID	0.01	-	1	1	0.003	-
CHROMIUM(METAL)	6.80	-	1	1	1.36	-

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES				"E.N.A."		MAOL		MAOL SOURCE	TOX
			(1)			(2)		(3)		(4)	(5)
		A/C	C	M	D/R	A/C	D/R	mg/m^3	ppm	(A,N,O)	
CHROMIUM (VI) COMPOUNDS		A	A	ND	ND			0.001	-	N	1
p-CRESOL	106445	B	ND	ND	ND			8.84	2.00	N	1
CYCLOHEXANE	110827	E	ND	ND	ND			1032.00	300.00	A	10
o-DICHLOROBENZENE	95501	C	F	ND	ND			300.40	50.00	A	10
p-DICHLOROBENZENE	106467	C	B	D	ND			450.60	75.00	A	10
1,2-DICHLOROETHANE	107062	B	B	A	B		x	40.45	10.00	A	1
1,2-DICHLOROETHYLENE	540590	E	ND	ND	ND			792.40	200.00	A	10
DICHLOROMETHANE	75092	B	B	B	D*		x	173.70	50.00	A	10
1,2-DICHLOROPROPANE	78875	B	C	C	ND			346.30	75.00	A	10
DIETHYLAMINE	109897	B	ND	ND	ND			29.89	10.00	A	10
DI(2-ETHYLHEXYL)-PHTHALATE	117817	A	B	B	B		x	5.00	0.31	A	1
DIMETHYLFORMAMIDE	68122	B	ND	ND	ND			29.87	10.00	A	10
1,4-DIOXANE	123911	B	B	ND	ND			90.01	25.00	A	10
DIPHENYL	92524	A	ND	D	ND			1.26	0.20	A	10
DIPHENYLAMINE	122394	A	ND	C	ND			10.00	1.45	A	10
EPICHLOROHYDRIN	106898	A	B	A	B		x	2.00	0.50	N	1
ETHANOL	64175	C	ND	C	B		x	1883.00	1000.00	A	10
ETHYL ACETATE	141786	E	ND	ND	ND			1440.00	400.00	A	10
ETHYL ACRYLATE	140885	B	B*	ND	B		x	20.46	5.00	A	10
ETHYLBENZENE	100414	D	ND	ND	ND			433.80	100.00	A	10

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
CHROMIUM (VI) COMPOUNDS	0.01	-	1	1	0.003	-
p-CRESOL	120.24	27.21	1	1	24.05	5.44
CYCLOHEXANE	1404.08	408.16	1	1	280.82	81.63
o-DICHLOROBENZENE	408.71	68.03	1	1	81.74	13.61
p-DICHLOROBENZENE	613.06	102.04	1	1	122.61	20.41
1,2-DICHLOROETHANE	550.34	136.05	1	10	11.01	2.72
1,2-DICHLOROETHYLENE	1078.10	272.11	1	1	215.62	54.42
DICHLOROMETHANE	236.33	68.03	1	5	9.45	2.72
1,2-DICHLOROPROPANE	471.16	102.04	1	1	94.23	20.41
DIETHYLAMINE	40.67	13.61	1	1	8.13	2.72
DI(2-ETHYLHEXYL)-PHTHALATE	68.03	4.26	1	10	1.36	0.09
DIMETHYLFORMAMIDE	40.64	13.61	1	1	8.13	2.72
1,4-DIOXANE	122.46	34.01	1	1	24.49	6.80
DIPHENYL	1.71	0.27	1	1	0.34	0.05
DIPHENYLAMINE	13.61	1.97	1	1	2.72	0.39
EPICHLOROHYDRIN	27.21	6.80	1	10	0.54	0.14
ETHANOL	2561.90	1360.54	1	10	51.24	27.21
ETHYL ACETATE	1959.18	544.22	1	1	391.84	108.84
ETHYL ACRYLATE	27.84	6.80	1	10	0.56	0.14
ETHYLBENZENE	590.20	136.05	1	1	118.04	27.21

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES (1) A/C	C	M	D/R	"E.N.A." (2) A/C	D/R	MAOL (3) mg/m^3	ppm	MAOL SOURCE (4) (A,N,O)	TOX (5)
ETHYLENE GLYCOL	107211	D	ND	ND	ND			126.80	50.00	A	10
ETHYL ETHER	60297	D	ND	D	ND			1212.00	400.00	A	10
FLUORIDE	16984488	B	ND	ND	ND			2.50	3.22	A	1
FORMALDEHYDE	50000	B	B	B	B*		x	1.23	1.00	A	1
HEPTACHLOR	76448	B	A	D	ND			0.50	0.03	A	10
HEXACHLOROCYCLO-PENTADIENE	77474	A	ND	ND	D*		x	0.11	0.01	A	10
HEXACHLOROETHANE	67721	B	C	ND	D		x	9.68	1.00	N	10
HEXACHLOROPHENE	70304	-	ND	ND	A			-	-	-	-
2-HEXANONE	591786	B	ND	ND	ND			4.00	0.98	N	1
HYDRAZINE	302012	A	B*	C	C*		x	0.13	0.10	A	10
HYDROGEN CHLORIDE	7647010	B	ND	ND	ND			7.45	5.00	A	10
HYDROGEN FLUORIDE	7664393	B	ND	C	ND			2.50	3.06	N	10
HYDROGEN SULFIDE	7783064	B	ND	ND	ND			13.93	10.00	A	10
ISOAMYL ACETATE	123922	D	ND	ND	ND			532.00	100.00	A	10
ISOBUTYL ACETATE	110190	E	ND	ND	ND			712.10	150.00	A	10
ISOBUTYL ALCOHOL	78831	D	ND	ND	ND			151.50	50.00	A	10
ISOPROPYL ACETATE	108214	E	ND	ND	ND			1043.00	250.00	A	10
LEAD	7439921	A	ND	D	A*			0.05	-	O	1
LEAD SUBACETATE	1335326	A	B*	ND	E			0.05	-	O	1
LINDANE	58899	A	B*	C	ND			0.05	0.04	A	1
MALEIC ANHYDRIDE	108316	B	ND	ND	ND			1.00	0.25	A	10

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
ETHYLENE GLYCOL	172.52	68.03	1	1	34.50	13.61
ETHYL ETHER	1648.98	544.22	1	1	329.80	108.84
FLUORIDE	34.01	43.81	1	1	6.80	8.76
FORMALDEHYDE	16.69	13.61	1	10	0.33	0.27
HEPTACHLOR	0.68	0.04	1	1	0.14	0.009
HEXACHLOROCYCLO-PENTADIENE	0.15	0.01	1	5	0.006	0.0005
HEXACHLOROETHANE	13.17	1.36	1	5	0.53	0.05
HEXACHLOROPHENE			-	-		
2-HEXANONE	54.42	13.30	1	1	10.88	2.66
HYDRAZINE	0.18	0.14	1	5	0.007	0.005
HYDROGEN CHLORIDE	10.14	6.80	1	1	2.03	1.36
HYDROGEN FLUORIDE	3.40	4.16	1	1	0.68	0.83
HYDROGEN SULFIDE	18.95	13.61	1	1	3.79	2.72
ISOAMYL ACETATE	723.81	136.05	1	1	144.76	27.21
ISOBUTYL ACETATE	968.84	204.08	1	1	193.77	40.82
ISOBUTYL ALCOHOL	206.12	68.03	1	1	41.22	13.61
ISOPROPYL ACETATE	1419.05	340.14	1	1	283.81	68.03
LEAD	0.68	-	1	1	0.14	-
LEAD SUBACETATE	0.68	-	1	1	0.14	-
LINDANE	0.68	0.57	1	1	0.14	0.11
MALEIC ANHYDRIDE	1.36	0.34	1	1	0.27	0.07

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES				"E.N.A."		MAOL		MAOL SOURCE	TOX
			(1)			(2)		(3)		(4)	(5)
		A/C	C	M	D/R	A/C	D/R	mg/m^3	ppm	(A,N,O)	
METHANOL	67561	C	ND	E	B		x	261.90	200.00	A	10
2-METHOXY ETHANOL	109864	B	ND	ND	B*			15.55	5.00	A	10
METHYL ACRYLATE	96333	C	ND	ND	ND			35.18	10.00	A	10
METHYL BROMIDE	74839	B	ND	ND	ND			19.40	5.00	A	10
METHYL ETHYL KETONE (MEK)	78933	C	ND	ND	D		x	589.30	200.00	A	10
METHYL ISOBUTYL KETONE (MIBK)	108101	B	ND	ND	ND			204.70	50.00	A	10
METHYL METHACRYLATE	80626	D	F	ND	D*		x	409.20	100.00	A	10
MIREX	2385855	-	B*	ND	ND			-	-	-	-
NAPHTHALENE	91203	B	ND	ND	ND			52.37	10.00	A	10
NICKEL (METAL)	7440020	B	C*	ND	B		x	1.00	-	A	1
NICKEL OXIDE	1313991	B	B*	ND	ND			1.00	-	A	10
NITROBENZENE	98953	B	ND	ND	ND			5.03	1.00	A	1
PENTACHLOROPHENOL	87865	A	ND	D	B		x	0.50	0.05	A	10
PHENOL	108952	B	E	ND	ND			19.23	5.00	A	1
PHOSPHORIC ACID	7664382	B	ND	ND	ND			1.00	0.25	A	10
PHTHALIC ANHYDRIDE	85449	B	E	ND	ND			6.05	1.00	A	10
PCBs	1336363	A	A	ND	A			0.001		N	1
PROPYL ALCOHOL	71238	E	ND	ND	ND			491.10	200.00	A	10
PROPYLENE OXIDE	75569	B	C	C	ND			47.47	20.00	A	10
RESORCINOL	108463	C	ND	D	ND			45.00	10.00	A	10
SELENIUM	7782492	A	ND	ND	ND			0.20	-	A	1

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
METHANOL	356.33	272.11	1	10	7.13	5.44
2-METHOXY ETHANOL	21.16	6.80	1	1	4.23	1.36
METHYL ACRYLATE	47.86	13.61	1	1	9.57	2.72
METHYL BROMIDE	26.39	6.80	1	1	5.28	1.36
METHYL ETHYL KETONE (MEK)	801.77	272.11	1	5	32.07	10.88
METHYL ISOBUTYL KETONE (MIBK)	278.50	68.03	1	1	55.70	13.61
METHYL METHACRYLATE	556.73	136.05	1	5	22.27	5.44
MIREX			-	-		
NAPHTHALENE	71.25	13.61	1	1	14.25	2.72
NICKEL (METAL)	13.61	-	1	10	0.27	-
NICKEL OXIDE	1.36	-	1	1	0.27	-
NITROBENZENE	68.45	13.61	1	1	13.69	2.72
PENTACHLOROPHENOL	0.68	0.06	1	10	0.01	0.001
PHENOL	261.63	68.03	1	1	52.33	13.61
PHOSPHORIC ACID	1.36	0.34	1	1	0.27	0.07
PHTHALIC ANHYDRIDE	8.24	1.36	1	1	1.65	0.27
PCBs	0.01	-	1	1	0.003	-
PROPYL ALCOHOL	668.16	272.11	1	1	133.63	54.42
PROPYLENE OXIDE	64.59	27.21	1	1	12.92	5.44
RESORCINOL	61.22	13.61	1	1	12.24	2.72
SELENIUM	2.72		1	1	0.54	

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES (1)				"E.N.A." (2)		MAOL (3)		MAOL SOURCE (4)	TOX (5)
		A/C	C	M	D/R	A/C	D/R	mg/m^3	ppm	(A,N,O)	
SELENIUM SULFIDE	7446346	A	B	ND	ND			0.20	-	A	1
STYRENE	100425	B	C	A	C*		x	212.80	50.00	N	1
SULFURIC ACID	7664939	B	ND	ND	ND			1.00	0.25	A	1
1,1,2,2-TETRACHLORO-1,2-DIFLUOROETHANE	76120	D	ND	ND	ND			4165.00	500.00	A	10
1,1,2,2-TETRACHLORO-ETHANE	79345	A	C	C	ND			6.86	1.00	A	1
TETRACHLOROETHYLENE	127184	B	B	C	ND			338.90	50.00	A	1
TETRAHYDROFURAN	109999	D	ND	ND	ND			589.30	200.00	A	10
TOLUENE	108883	C	ND	E	B		x	376.50	100.00	A	10
TOLUENE DIISOCYANATE	584849	A	B	ND	ND			0.04	0.005	A	1
o-TOLUIDINE	95534	B	B	C	ND			8.76	2.00	A	10
1,1,1-TRICHLORO-ETHANE	71556	D	E	C	D*		x	1908.00	350.00	A	1
1,1,2-TRICHLORO-ETHANE	79005	B	C	ND	ND			54.52	10.00	A	10
TRICHLOROETHYLENE	79016	B	B	A	A		x	134.20	25.00	N	1
2,4,6-TRICHLORO-PHENOL	88062	-	B	D	ND			-	-	-	-
TRIETHYLAMINE	121448	B	ND	ND	A		x	41.35	10.00	A	10
VANADIUM	1314621	B	ND	ND	ND			1.00	-	N	10
VANADIUM PENTOXIDE	1314621	B	ND	C	ND			0.05	0.0067	A	1
VINYL ACETATE	108054	B	ND	C	ND			14.07	4.00	N	1
VINYL CHLORIDE	75014	B	A	B	B*		x	12.77	5.00	A	1

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
SELENIUM SULFIDE	2.72		1	1	0.54	
STYRENE	2895.24	680.27	1	5	115.81	27.21
SULFURIC ACID	13.61	3.39	1	1	2.72	0.68
1,1,2,2-TETRACHLORO-1,2-DIFLUOROETHANE	5666.67	680.27	1	1	1133.33	136.05
1,1,2,2-TETRACHLORO-ETHANE	93.36	13.61	1	1	18.67	2.72
TETRACHLOROETHYLENE	4610.88	680.27	1	1	922.18	136.05
TETRAHYDROFURAN	801.77	272.11	1	1	160.35	54.42
TOLUENE	512.24	136.05	1	10	10.24	2.72
TOLUENE DIISOCYANATE	0.48	0.07	1	1	0.10	0.01
o-TOLUIDINE	11.92	2.72	1	1	2.38	0.54
1,1,1-TRICHLORO-ETHANE	25959.18	4761.90	1	5	1038.37	190.48
1,1,2-TRICHLORO-ETHANE	74.18	13.61	1	1	14.84	2.72
TRICHLOROETHYLENE	1825.85	340.14	1	10	36.52	6.80
2,4,6-TRICHLORO-PHENOL	-	-	-	-	-	-
TRIETHYLAMINE	56.26	13.61	1	10	1.13	0.27
VANADIUM	1.36		1	1	0.27	
VANADIUM PENTOXIDE	0.68	0.09	1	1	0.14	0.02
VINYL ACETATE	191.43	54.42	1	1	38.29	10.88
VINYL CHLORIDE	173.74	68.03	1	10	3.47	1.36

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	CAS NUMBER	LETTER CODE SCORES (1)				"E.N.A." (2)		MAOL (3)		MAOL SOURCE (4)	TOX (5)
		A/C	C	M	D/R	A/C	D/R	mg/m^3	ppm	(A,N,O)	
VINYLIDENE CHLORIDE	75354	B	C	C	D		x	19.81	5.00	A	10
XYLENES (m-,o-,p-,ISOMERS)	1330207	C	F	ND	B		x	433.80	100.00	A	10

1. A/C = Acute/Chronic Toxicity; C = Carcinogenicity; M = Mutagenicity; D/R = Developmental/Reproductive Toxicity; (See Part II,Reproductive Toxicity; (See Part II, Sections C - F.)
2. Effects Not Accounted for in MAOL (Acute/Chronic or Developmental/Reproductive Toxicity; (See Part III, Section B(4).)
3. Most Appropriate Occupational Limit (MAOL); See Part II, Section B.
4. A = ACGIH; N = NIOSH; O = OSHA (See Part II, Section B.)
5. TOX = Uncertainty Factor for Inadequate Toxicity Data (See Part III, Section B(2))
6. MAOL/(73.5)(TOX Factor) (See Part III, Sections B(2) and B(3).)
7. Threshold Effects Uncertainty Factor (TEUF); See Part III, Section B(4).
8. TEL = Adjusted MAOL/(TEUF)x(0.2 exposure adjustment); See Part III, Sections A and B.

TABLE III-5. SUMMARY OF RESULTS FROM CHEM AND DERIVATION OF THRESHOLD EFFECTS EXPOSURE LIMITS

CHEMICAL	ADJUSTED MAOL (6)		TEUF (7)		THRESHOLD EFFECTS EXPOSURE LIMIT (TEL) (8)	
	$\mu g/m^3$	ppb	A/C	D/R	$\mu g/m^3$	ppb
VINYLIDENE CHLORIDE	26.95	6.80	1	5	1.08	0.27
XYLENES (m-,o-,p-,ISOMERS)	590.20	136.05	1	10	11.80	2.72

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		µg/m^3	ppm	µg/m^3	ppb		C	M	(µg/m^3)
ACETALDEHYDE	75070	179.80	100.00	244.63	136.05	SUBST 2	B	B	2.26E-06
ACETONE	67641	590.00	250.00	802.72	340.14	ND	ND	E	
ACRYLONITRILE	107131	4.34	2.00	59.01	27.21	SUFF	A	A	6.80E-05
AMMONIA	7664417	17.40	25.00	23.67	34.01	ND	ND	ND	
ANILINE	62533	7.61	2.00	10.36	2.72	SUBST 2	C	C	7.09E-06
ASBESTOS	1332214	0.10	f/cm3	0.001	f/cm3	SUFF	A	ND	7.60E-03
BENZENE	71432	3.19	1.00	43.46	13.61	SUFF	A	A	8.10E-06
BENZYL CHLORIDE	100447	5.17	1.00	70.38	13.61	SUBST 2	C*	A	
BERYLLIUM	7440417	0.0005	-	0.007	-	SUBST 1	A	ND	2.40E-03
1,3-BUTADIENE	106990	22.11	10.00	30.08	13.61	SUBST 2	A	ND	2.90E-04
n-BUTYL ALCOHOL	71363	151.50	50.00	2061.22	680.27	ND	ND	ND	
CADMIUM	7440439	0.01	-	0.136	-	SUFF	A	ND	1.80E-03
CALCIUM CHROMATE	13765190	0.001	-	0.01	-	SUFF	A	A	1.20E-02
CARBON TETRACHLORIDE	56235	31.43	5.00	427.62	68.03	SUBST 2	B	C	1.50E-05
CHLORDANE	57749	0.50	0.03	6.80	0.41	SUGG	A	D	3.70E-05
CHLORINE	7782505	1.45	0.50	19.73	6.80	ND	ND	ND	
CHLOROBENZENE	108907	345.00	75.00	469.39	102.04	SUGG	C	ND	
CHLOROETHANE	75003	2637.00	1000.00	3587.76	1360.54	ND	ND	ND	
CHLOROFORM	67663	48.79	10.00	663.81	136.05	SUBST 2	B	C	2.35E-05
CHLOROPRENE	126998	3.62	1.00	49.22	13.61	ND	ND	C	
CHROMIC ACID	7738945	0.001	-	0.01	-	SUFF	A	ND	1.20E-02
CHROMIUM(METAL)	7440473	0.50	-	6.80	-	ND	ND	ND	

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) µg/m³	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) µg/m³	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) µg/m³	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
ACETALDEHYDE	D			0.44	0.18	UR	4.89	2.72	0.44	0.18
ACETONE		-	1	802.72	340.14	UF	160.54	68.03	160.54	68.03
ACRYLONITRILE	C			0.01	0.01	UR	1.18	0.54	0.01	0.01
AMMONIA		-	1	23.67	34.01	UF	4.73	6.80	4.73	6.80
ANILINE	D			0.14	0.04	UR	2.07	0.54	0.14	0.04
ASBESTOS	C			0.0001	f/cm3	UR	0.0002	f/cm3	0.0001	f/cm3
BENZENE	C			0.12	0.04	UR	1.74	0.54	0.12	0.04
BENZYL CHLORIDE		+	75	0.94	0.18	UF	14.08	2.72	0.94	0.18
BERYLLIUM	C			0.0004		UR	0.001	-	0.0004	-
1,3-BUTADIENE	C			0.003	0.002	UR	1.20	0.54	0.003	0.002
n-BUTYL ALCOHOL		-	1	2061.22	680.27	UF	412.24	136.05	412.24	136.05
CADMIUM	C			0.001		UR	0.003	-	0.001	-
CALCIUM CHROMATE	C			0.0001		UR	0.003	-	0.0001	-
CARBON TETRACHLORIDE	C			0.07	0.01	UR	85.52	13.61	0.07	0.01
CHLORDANE	C			0.03	0.002	UR	0.14	0.008	0.03	0.002
CHLORINE		-	1	19.73	6.80	UF	3.95	1.36	3.95	1.36
CHLOROBENZENE		+	75	6.26	1.36	UF	93.88	20.41	6.26	1.36
CHLOROETHANE		+	10	358.78	136.05	UF	717.55	272.11	358.78	136.05
CHLOROFORM	C			0.04	0.01	UR	132.76	27.21	0.04	0.01
CHLOROPRENE		+	20	2.46	0.68	UF	0.98	0.27	0.98	0.27
CHROMIC ACID	C			0.0001		UR	0.003	-	0.0001	-
CHROMIUM(METAL)		+	10	0.68		UF	1.36	-	0.68	-

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		$\mu g/m^3$	ppm	$\mu g/m^3$	ppb		C	M	($\mu g/m^3$)
CHROMIUM (VI) COMPOUNDS		0.001	-	0.01	-	SUFF	A	ND	1.20E-02
p-CRESOL	106445	8.84	2.00	120.24	27.21	ND	ND	ND	
CYCLOHEXANE	110827	1032.00	300.00	1404.08	408.16	ND	ND	ND	
o-DICHLOROBENZENE	95501	300.40	50.00	408.71	68.03	NULL	F	ND	
p-DICHLOROBENZENE	106467	450.60	75.00	613.06	102.04	SUBST 1	B	D	5.70E-06
1,2-DICHLOROETHANE	107062	40.45	10.00	550.34	136.05	SUBST 2	B	A	2.60E-05
1,2-DICHLOROETHYLENE	540590	792.40	200.00	1078.10	272.11	ND	ND	ND	
DICHLOROMETHANE	75092	173.70	50.00	236.33	68.03	SUBST 2	B	B	4.10E-06
1,2-DICHLOROPROPANE	78875	346.30	75.00	471.16	102.04	SUBST 2	C	C	1.87E-05
DIETHYLAMINE	109897	29.89	10.00	40.67	13.61	ND	ND	ND	
DI(2-ETHYLHEXYL)-PHTHALATE	117817	5.00	0.31	68.03	4.26	SUBST 2	B	B	1.30E-06
DIMETHYLFORMAMIDE	68122	29.87	10.00	40.64	13.61	ND	ND	ND	
1,4-DIOXANE	123911	90.01	25.00	122.46	34.01	SUBST 2	B	ND	4.10E-06
DIPHENYL	92524	1.26	0.20	1.71	0.27	ND	ND	D	
DIPHENYLAMINE	122394	10.00	1.45	13.61	1.97	ND	ND	C	
EPICHLOROHYDRIN	106898	2.00	0.50	27.21	6.80	SUBST 1	B	A	1.20E-06
ETHANOL	64175	1883.00	1000.00	2561.90	1360.54	ND	ND	C	
ETHYL ACETATE	141786	1440.00	400.00	1959.18	544.22	ND	ND	ND	
ETHYL ACRYLATE	140885	20.46	5.00	27.84	6.80	SUBST 2	B*	ND	
ETHYLBENZENE	100414	433.80	100.00	590.20	136.05	ND	ND	ND	

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) µg/m³	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) µg/m³	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) µg/m³	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
CHROMIUM (VI) COMPOUNDS	C			0.0001		UR	0.003	-	0.0001	-
p-CRESOL		+	10	12.02	2.72	UF	24.05	5.44	12.02	2.72
CYCLOHEXANE		-	1	1404.08	408.16	UF	280.82	81.63	280.82	81.63
o-DICHLOROBENZENE		+	5	81.74	13.61	UF	81.74	13.61	81.74	13.61
p-DICHLOROBENZENE	C			0.18	0.03	UR	122.61	20.41	0.18	0.03
1,2-DICHLOROETHANE	C			0.04	0.01	UR	11.01	2.72	0.04	0.01
1,2-DICHLOROETHYLENE		+	10	107.81	27.21	UF	215.62	54.42	107.81	27.21
DICHLOROMETHANE	C			0.24	0.07	UR	9.45	2.72	0.24	0.07
1,2-DICHLOROPROPANE	D			0.05	0.01	UR	94.23	20.41	0.05	0.01
DIETHYLAMINE		+	10	4.07	1.36	UF	8.13	2.72	4.07	1.36
DI(2-ETHYLHEXYL)-PHTHALATE	D			0.77	0.05	UR	1.36	0.09	0.77	0.05
DIMETHYLFORMAMIDE		+	5	8.13	2.72	UF	8.13	2.72	8.13	2.72
1,4-DIOXANE	D			0.24	0.07	UR	24.49	6.80	0.24	0.07
DIPHENYL		+	20	0.09	0.01	UF	0.34	0.05	0.09	0.01
DIPHENYLAMINE		+	20	0.68	0.10	UF	2.72	0.39	0.68	0.10
EPICHLOROHYDRIN	C			0.83	0.22	UR	0.54	0.14	0.54	0.14
ETHANOL		-	10	256.19	136.05	UF	51.24	27.21	51.24	27.21
ETHYL ACETATE		-	1	1959.18	544.22	UF	391.84	108.84	391.84	108.84
ETHYL ACRYLATE		+	100	0.28	0.07	UF	0.56	0.14	0.28	0.07
ETHYLBENZENE		+	5	118.04	27.21	UF	118.04	27.21	118.04	27.21

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		$\mu g/m^3$	ppm	$\mu g/m^3$	ppb		C	M	($\mu g/m^3$)
ETHYLENE GLYCOL	107211	126.80	50.00	172.52	68.03	ND	ND	ND	
ETHYL ETHER	60297	1212.00	400.00	1648.98	544.22	ND	ND	D	
FLUORIDE	16984488	2.50	3.22	34.01	43.81	ND	ND	ND	
FORMALDEHYDE	50000	1.23	1.00	16.69	13.61	SUBST 1	B	B	1.30E-05
HEPTACHLOR	76448	0.50	0.03	0.68	0.04	SUGG	A	D	1.30E-03
HEXACHLOROCYCLO-PENTADIENE	77474	0.11	0.01	0.15	0.01	ND	ND	ND	
HEXACHLOROETHANE	67721	9.68	1.00	13.17	1.36	SUGG	C	ND	4.00E-06
HEXACHLOROPHENE	70304	-	-	-	-	ND	ND	ND	
2-HEXANONE	591786	4.00	0.98	54.42	13.30	ND	ND	ND	
HYDRAZINE	302012	0.13	0.10	0.18	0.14	SUBST 2	B*	C	
HYDROGEN CHLORIDE	7647010	7.45	5.00	10.14	6.80	ND	ND	ND	
HYDROGEN FLUORIDE	7664393	2.50	3.06	3.40	4.16	ND	ND	C	
HYDROGEN SULFIDE	7783064	13.93	10.00	18.95	13.61	ND	ND	ND	
ISOAMYL ACETATE	123922	532.00	100.00	723.81	136.05	ND	ND	ND	
ISOBUTYL ACETATE	110190	712.10	150.00	968.84	204.08	ND	ND	ND	
ISOBUTYL ALCOHOL	78831	151.50	50.00	206.12	68.03	ND	ND	ND	
ISOPROPYL ACETATE	108214	1043.00	250.00	1419.05	340.14	ND	ND	ND	
LEAD	7439921	0.05	-	0.68	-	ND	ND	D	
LEAD SUBACETATE	1335326	0.05	-	0.68	-	SUBST 2	B*	ND	
LINDANE	58899	0.05	0.04	0.68	0.57	SUGG	B*	C	3.80E-04
MALEIC ANHYDRIDE	108316	1.00	0.25	1.36	0.34	ND	ND	ND	

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) $\mu g/m^3$	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) $\mu g/m^3$	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) $\mu g/m^3$	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
ETHYLENE GLYCOL		+	5	34.50	13.61	UF	34.50	13.61	34.50	13.61
ETHYL ETHER		-	10	164.90	54.42	UF	329.80	108.84	164.90	54.42
FLUORIDE		-	1	34.01	43.81	UF	6.80	8.76	6.80	8.76
FORMALDEHYDE	C			0.08	0.06	UR	0.33	0.27	0.08	0.06
HEPTACHLOR	C			0.001	0.00	UR	0.14	0.009	0.001	0.0001
HEXACHLOROCYCLO-PENTADIENE		+	10	0.01	0.001	UF	0.006	0.0005	0.006	0.0005
HEXACHLOROETHANE	C			0.25	0.03	UR	0.53	0.05	0.25	0.03
HEXACHLOROPHENE		+	10			UF	-	-		-
2-HEXANONE		-	1	54.42	13.30	UF	10.88	2.66	10.88	2.66
HYDRAZINE		+	100	0.00	0.001	UF	0.007	0.005	0.002	0.001
HYDROGEN CHLORIDE		-	1	10.14	6.80	UF	2.03	1.36	2.03	1.36
HYDROGEN FLUORIDE		-	10	0.34	0.42	UF	0.68	0.83	0.34	0.42
HYDROGEN SULFIDE		-	1	18.95	13.61	UF	3.79	2.72	3.79	2.72
ISOAMYL ACETATE		-	1	723.81	136.05	UF	144.76	27.21	144.76	27.21
ISOBUTYL ACETATE		-	1	968.84	204.08	UF	193.77	40.82	193.77	40.82
ISOBUTYL ALCOHOL		-	1	206.12	68.03	UF	41.22	13.61	41.22	13.61
ISOPROPYL ACETATE		-	1	1419.05	340.14	UF	283.81	68.03	283.81	68.03
LEAD		-	10	0.07		UF	0.14	-	0.07	-
LEAD SUBACETATE		-	100	0.01		UF	0.14	-	0.01	-
LINDANE	C			0.003	0.0002	UR	0.14	0.11	0.003	0.0002
MALEIC ANHYDRIDE		+	10	0.14	0.03	UF	0.27	0.07	0.14	0.03

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		$\mu g/m^3$	ppm	$\mu g/m^3$	ppb		C	M	($\mu g/m^3$)
METHANOL	67561	261.90	200.00	356.33	272.11	ND	ND	E	
2-METHOXY ETHANOL	109864	15.55	5.00	21.16	6.80	ND	ND	ND	
METHYL ACRYLATE	96333	35.18	10.00	47.86	13.61	ND	ND	ND	
METHYL BROMIDE	74839	19.40	5.00	26.39	6.80	ND	ND	ND	
METHYL ETHYL KETONE (MEK)	78933	589.30	200.00	801.77	272.11	ND	ND	ND	
METHYL ISOBUTYL KETONE (MIBK)	108101	204.70	50.00	278.50	68.03	ND	ND	ND	
METHYL METHACRYLATE	80626	409.20	100.00	556.73	136.05	NULL	F	ND	
MIREX	2385855	-	-			SUBST 2	B*	ND	
NAPHTHALENE	91203	52.37	10.00	71.25	13.61	ND	ND	ND	
NICKEL (METAL)	7440020	1.00	-	13.61	-	SUGG	C*	ND	
NICKEL OXIDE	1313991	1.00	-	1.36	-	SUBST 1	B*	ND	
NITROBENZENE	98953	5.03	1.00	68.45	13.61	ND	ND	ND	
PENTACHLOROPHENOL	87865	0.50	0.05	0.68	0.06	ND	ND	D	
PHENOL	108952	19.23	5.00	261.63	68.03	INC	E	ND	
PHOSPHORIC ACID	7664382	1.00	0.25	1.36	0.34	ND	ND	ND	
PHTHALIC ANHYDRIDE	85449	6.05	1.00	8.24	1.36	INC	E	ND	
PCBs	1336363	0.001	-	0.01	-	SUBST 2	A	ND	2.20E-03
PROPYL ALCOHOL	71238	491.10	200.00	668.16	272.11	ND	ND	ND	
PROPYLENE OXIDE	75569	47.47	20.00	64.59	27.21	SUBST 2	C	C	6.67E-07
RESORCINOL	108463	45.00	10.00	61.22	13.61	ND	ND	D	
SELENIUM	7782492	0.20	-	2.72	-	ND	ND	ND	

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) µg/m³	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) µg/m³	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) µg/m³	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
METHANOL		-	1	356.33	272.11	UF	7.13	5.44	7.13	5.44
2-METHOXY ETHANOL		+	10	2.12	0.68	UF	4.23	1.36	2.12	0.68
METHYL ACRYLATE		+	10	4.79	1.36	UF	9.57	2.72	4.79	1.36
METHYL BROMIDE		+	10	2.64	0.68	UF	5.28	1.36	2.64	0.68
METHYL ETHYL KETONE (MEK)		-	1	801.77	272.11	UF	32.07	10.88	32.07	10.88
METHYL ISOBUTYL KETONE (MIBK)		-	1	278.50	68.03	UF	55.70	13.61	55.70	13.61
METHYL METHACRYLATE		+	5	111.35	27.21	UF	22.27	5.44	22.27	5.44
MIREX		+	100			UF				
NAPHTHALENE		+	5	14.25	2.72	UF	14.25	2.72	14.25	2.72
NICKEL (METAL)		+	75	0.18		UF	0.27	-	0.18	-
NICKEL OXIDE		+	100	0.01		UF	0.27	-	0.01	-
NITROBENZENE		+	10	6.84	1.36	UF	13.69	2.72	6.84	1.36
PENTACHLOROPHENOL		+	20	0.03	0.003	UF	0.01	0.001	0.01	0.001
PHENOL		+	5	52.33	13.61	UF	52.33	13.61	52.33	13.61
PHOSPHORIC ACID		-	1	1.36	0.34	UF	0.27	0.07	0.27	0.07
PHTHALIC ANHYDRIDE		+	10	0.82	0.14	UF	1.65	0.27	0.82	0.14
PCBs	C			0.0005		UR	0.003	-	0.0005	-
PROPYL ALCOHOL		-	1	668.16	272.11	UF	133.63	54.42	133.63	54.42
PROPYLENE OXIDE	D			1.50	0.63	UR	12.92	5.44	1.50	0.63
RESORCINOL		+	20	3.06	0.68	UF	12.24	2.72	3.06	0.68
SELENIUM		-	1	2.72		UF	0.54	-	0.54	-

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		$\mu g/m^3$	ppm	$\mu g/m^3$	ppb		C	M	($\mu g/m^3$)
SELENIUM SULFIDE	7446346	0.20	-	2.72	-	SUBST 2	B	ND	2.02E-05
STYRENE	100425	212.80	50.00	2895.24	680.27	SUGG	C	A	5.70E-07
SULFURIC ACID	7664939	1.00	0.25	13.61	3.39	ND	ND	ND	
1,1,2,2-TETRACHLORO-1,2-DIFLUOROETHANE	76120	4165.00	500.00	5666.67	680.27	ND	ND	ND	
1,1,2,2-TETRACHLORO-ETHANE	79345	6.86	1.00	93.36	13.61	SUGG	C	C	5.80E-05
TETRACHLOROETHYLENE	127184	338.90	50.00	4610.88	680.27	SUBST 2	B	C	5.52E-05
TETRAHYDROFURAN	109999	589.30	200.00	801.77	272.11	ND	ND	ND	
TOLUENE	108883	376.50	100.00	512.24	136.05	ND	ND	E	
TOLUENE DIISOCYANATE	584849	0.04	0.005	0.48	0.07	SUBST 2	B	ND	6.79E-06
o-TOLUIDINE	95534	8.76	2.00	11.92	2.72	SUBST 2	B	C	5.72E-06
1,1,1-TRICHLORO-ETHANE	71556	1908.00	350.00	25959.18	4761.90	INC	E	C	
1,1,2-TRICHLORO-ETHANE	79005	54.52	10.00	74.18	13.61	SUGG	C	ND	1.60E-05
TRICHLOROETHYLENE	79016	134.20	25.00	1825.85	340.14	SUBST 2	B	A	1.63E-06
2,4,6-TRICHLORO-PHENOL	88062	-	-	-	-	SUBST 2	B	D	6.20E-06
TRIETHYLAMINE	121448	41.35	10.00	56.26	13.61	ND	ND	ND	
VANADIUM	1314621	1.00	-	1.36	-	ND	ND	ND	
VANADIUM PENTOXIDE	1314621	0.05	0.0067	0.68	0.09	ND	ND	C	
VINYL ACETATE	108054	14.07	4.00	191.43	54.42	ND	ND	C	
VINYL CHLORIDE	75014	12.77	5.00	173.74	68.03	SUFF	A	B	2.60E-06

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) µg/m³	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) µg/m³	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) µg/m³	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
SELENIUM SULFIDE	D			0.05		UR	0.54	-	0.05	-
STYRENE	C			1.75	0.41	UR	115.81	27.21	1.75	0.41
SULFURIC ACID		-	1	13.61	3.39	UF	2.72	0.68	2.72	0.68
1,1,2,2-TETRACHLORO-1,2-DIFLUOROETHANE		+	10	566.67	68.03	UF	1133.33	136.05	566.67	68.03
1,1,2,2-TETRACHLORO-ETHANE	C			0.02	0.003	UR	18.67	2.72	0.02	0.003
TETRACHLOROETHYLENE	D			0.02	0.003	UR	922.18	136.05	0.02	0.003
TETRAHYDROFURAN		+	10		27.21	UF	160.35	54.42	80.18	27.21
TOLUENE		+	5	102.45	27.21	UF	10.24	2.72	10.24	2.72
TOLUENE DIISOCYANATE	D			0.15	0.02	UR	0.10	0.01	0.10	0.01
o-TOLUIDINE	D			0.17	0.04	UR	2.38	0.54	0.17	0.04
1,1,1-TRICHLORO-ETHANE		+	20	1297.96	238.10	UF	1038.37	190.48	1038.37	190.48
1,1,2-TRICHLORO-ETHANE	C			0.06	0.01	UR	14.84	2.72	0.06	0.01
TRICHLOROETHYLENE	D			0.61	0.11	UR	36.52	6.80	0.61	0.11
2,4,6-TRICHLORO-PHENOL	D			0.16	0.02	UR	-	-	0.16	-
TRIETHYLAMINE		+	10	5.63	1.36	UF	1.13	0.27	1.13	0.27
VANADIUM		-	1	1.36		UF	0.27	-	0.27	-
VANADIUM PENTOXIDE		+	20	0.03	0.005	UF	0.14	0.02	0.03	0.005
VINYL ACETATE		+	20	9.57	2.72	UF	38.29	10.88	9.57	2.72
VINYL CHLORIDE	C			0.38	0.15	UR	3.47	1.36	0.38	0.15

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	CAS NUMBER	MAOL (1)		ADJUSTED MAOL (2)		CANCER WEIGHT OF EVIDENCE (3)	CHEM SCORE (4)		CANCER UNIT RISK (5)
		$\mu g/m^3$	ppm	$\mu g/m^3$	ppb		C	M	($\mu g/m^3$)
VINYLIDENE CHLORIDE	75354	19.81	5.00	26.95	6.80	SUGG	C	C	5.00E-05
XYLENES (m-,o-,p-,ISOMERS)	1330207	433.80	100.00	590.20	136.05	NULL	F	ND	

1. See Part II, Section B.
2. MAOL/(73.5 or 735) (See Part III, Sections B(2) and B(3).)
3. See Table II-7A.
4. See Tables II-9 and II-18.
5. See Part II, Section D; excess cancer risk assuming 70 kg. person exposed continuously throughout 70 year lifetime to 1 ug/m3 of the substance.
6. Source of Unit Risk Calculation: C = USEPA Carcinogen Assessment Group; D = DEQE (the Department.)
7. Structure-Activity Relationship Analysis (see Part III, Section C(3); Appendix H.)
8. See Part III, Section C(3).
9. See Part III, Section C; value corresponds to an excess lifetime cancer risk of 1.00E-5.
10. Basis of NTEL derivation: Procedure One, based on Unit Risk (UR) or Procedure Two, based on Uncertainty Factor (UF). See Part III, Section C.
11. See Part III, Sections A + B; Table III-5.
12. Maximum allowable concentration, corresponding to an excess lifetime cancer risk of 1.00E-5. AAL = TEL or NTEL, whichever is lower.
13. Ambient concentration corresponding to an excess lifetime cancer risk of 1.00E-6, symbolizing Department goal to reduce exposures to the extent feasible.

TABLE III-6. SUMMARY OF AAL DERIVATIONS

CHEMICAL	UNIT RISK SOURCE (6) (C,D)	SAR (7) (+,-)	NTEUF (8)	NTEL (9) $\mu g/m^3$	NTEL (9) ppb	NTEL BASIS (10) (UR,UF)	TEL (11) $\mu g/m^3$	TEL (11) ppb	ALLOWABLE AMBIENT LIMIT (AAL) (12) $\mu g/m^3$	ALLOWABLE AMBIENT LIMIT (AAL) (12) ppb
VINYLIDENE CHLORIDE	C			0.02	0.01	UR	1.08	0.27	0.02	0.01
XYLENES (m-,o-,p-,ISOMERS)		+	5	118.04	27.21	UF	11.80	2.72	11.80	2.72

G. References for the Method to Derive Allowable Ambient Limits (AALs)

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LIST OF APPENDICES