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METHODOLOGY FOR EVALUATING POTENTIAL CARCINOGENICITY IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

PREPARED FOR

OFFICE OF EMERGENCY AND REMEDIAL RESPONSE

PREPARED BY

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METHODOLOGY FOR EVALUATING POTENTIAL CARCINOGENITICY IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

Prepared for
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response

Prepared by
Office of Health and Environmental Assessment
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CONTENTS

CONTENTS (continued)

CONTENTS (continued)

TABLES

PREFACE

This report describes the technical methodology the U.S. Environmental Protection Agency (EPA or the Agency) has used in developing a hazard ranking for potential carcinogens in order to adjust reportable quantities (RQs) under Section 102 of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA). The RQ adjustment methodology is based, in part, on the methodology used to establish RQs pursuant to Section 311 of the Clean Water Act. Details of the methodology are given in the document "Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 1," March 1985, and in the final rule published on April 4, 1985 (U.S. EPA, 1985).

In deciding whether to assign primary criteria RQs for potential carcinogens at all five RQ levels, the Agency examined the special properties associated with these substances and evaluated them in light of the Agency's chronic toxicity methodology. The Agency decided not to use the two highest RQ levels, 1000 and 5000 pounds, for several reasons, all of which are explained in the main body of the report "Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102," Volume 3, (U.S. EPA, 1989).

As a consequence of the Agency's decision to adopt a 100-pound maximum RQ for potential carcinogens, the Human Health Assessment Group was request d to rank p tential c rcinogens on a

three-tier scale (high, medium, and low) that corresponds to RQ l vels of 1, 10, and 100 pounds. This document describes the methodology for using the weight of evidence and potency factor (U.S. EPA, 1986) to determine RQs based on the primary criterion of potential carcinogenicity.

ABSTRACT

The Agency's Human Health Assessment Group (HHAG) has developed a methodology for ranking CERCLA hazardous substances for the purpose of establishing reportable quantities (RQs) based on the primary criteria of potential carcinogenicity. The methodology combines the weight of evidence and potency factor to determine a hazard ranking of high, medium, or low which corresponds to an RQ of 1, 10, or 100 pounds respectively.

An appendix is included which lists 194 compounds that were evaluated for potential carcinogenicity along with their respective weight-of-evidence categories, potency factors, and hazard rankings. Profiles for each of these 194 chemicals are available as separate documents.

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1. INTRODUCTION

1.1. BACKGROUND

This report describes the technical methodology the Agency has used in developing a hazard ranking for potential carcinogens in order to adjust reportable quantities (RQs) under Section 102 of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA). Section 103 of CERCLA requires immediate notification to the National Response Center by any person in charge of a vessel or facility who releases an amount of a hazardous substance equal to or greater than its RQ. Under CERCLA Section 102(b), the RQ of any hazardous substance designated in Section 101(14) is 1 pound unless a different RQ has been established pursuant to Section 311(b)(4) of the Federal Water Pollution Control Act. Under Section 102(a) these statutory RQs may be adjusted by regulations establishing different quantities to be reported upon release of a hazardous substance. Section 102(a) also gives the U.S. Environmental Protection Agency (EPA or the Agency) authority to establish a single RQ for each hazardous substance, regardless of the environmental medium into which the substance is released.

The RQ adjustment methodology is one with which the regulated community is familiar and is based, in part, on the methodology used to establish RQs pursuant to Section 311 of the Clean Water Act (CWA). Details of the methodology are given in the technical background document (U.S. EPA, 1985a), and in the

final rule (U.S. EPA, 1985b). The methodology begins with an evaluation of the intrinsic physical, chemical, and toxicological properties associated with each hazardous substance. The intrinsic properties evaluated, called primary criteria, are: aquatic toxicity, mammalian toxicity (oral, dermal, and inhalation), ignitability, reactivity, chronic toxicity, and potential carcinogenicity. The Agency ranks each intrinsic property (other than potential carcinogenicity, which is discussed below) on a five-tier scale, associating a specific range of values on each scale with a particular RQ value. This five-tier scale uses the RQ levels of 1, 10, 100, 1000, and 5000 pounds, which were originally established pursuant to the CWA Section 311. Each hazardous substance receives several tentative RQ values based on its particular properties. The lowest of all of the tentative RQs becomes the primary criteria RQ for that hazardous substance. The primary criteria RQ can then be raised by one level using biodegradability, hydrolysis, and photolysis as secondary criteria. The Agency has determined that no potential carcinogen shall be assigned a primary criteria RQ above 100 pounds. The Agency has always regarded potential carcinogens with special concern and in its regulatory actions has sought to minimize carcinogenic risks. This concern is justified by scientific factors particular to cancer:

- It has not been demonstrated that there is a threshold level of exposure below which potential carcinogens do not present some risk of cancer. Therefore, a release

of any amount of a potential carcinogen represents an increased risk of cancer to the exposed population. This is in contrast with most other toxic effects, for which thresholds can be demonstrated (U.S. EPA, 1987 pp. 8140, 8145).

- Cancer risks are considered to be cumulative. A number of small releases can be as serious as a single large release (U.S. EPA, 1987 pp. 8140, 8146).
- Cancer is not immediately manifested. There is a latent period between exposure to a carcinogen and the manifestation of cancer that makes it impossible to directly observe carcinogenic risks from substances newly released into the environment (U.S. EPA, 1987 pp. 8140, 8146). This is in contrast to acute toxic effects, which are more immediately manifested.

In deciding whether to assign primary criteria RQs for potential carcinogens at all five RQ levels, the Agency examined the special properties associated with these substances and evaluated them in light of the Agency's chronic toxicity methodology. The Agency decided not to use the two highest RQ levels, 1000 and 5000 pounds, for several reasons, all of which are explained in the main body of the report "Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102," Volume 3, (U.S. EPA, 1989).

As a consequence of the Agency's decision to adopt a 100-pound maximum RQ for potential carcinogens, the Human Health

Assessment Group (HHAG) was requested to rank potential carcinogens on a three-tier scale (high, medium, and low) that corresponds to RQ levels of 1, 10, and 100 pounds.

1.2. METHODOLOGY

The HHAG developed a methodology for ranking potential carcinogens based originally on a combination of the International Agency for Research on Cancer's (IARC) w ight-of-evidence scheme and the HHAG's potency factor. This methodology had been reviewed and was described in a previous draft of this report. On September 24, 1986, the Agency published its "Guidelines for Carcinogen Risk Assessment" (U.S. EPA, 1986), which refined the IARC weight-of-evidence criteria. The EPA Reportable Quantity Work Group determined on June 4, 1985, that the ranking methodology should be revised to be consistent with the Agency's final guidelines, and should include the Agency's new weight-of-evidence criteria. This has been done in the methodology described in this report.

The following sections of this report present the objectives and methodology applied in arriving at a carcinogenic hazard assessment for each of the hazardous substances under study. The major findings are summarized in tabular form in a separate, but attached, appendix (Hazard Ranking of Potential Carcinogens). A more detailed discussion of the available studies, weight-of-vidence determinations, potency factor assignments for each potential carcinogen under study, and a bibliography of other pertinent references is contained in a profile for each

ch mical. The profiles, entitled "Evaluation of Potential Carcinogenicity of [substance name] in Support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102," collectively form an additional appendix to, but are not attached as part of, this methodology document. The profiles can be accessed separately in the record that supports CERCLA RQ adjustment rulemakings, which are available in Room M2427 at the U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460 (Docket Number 102 RQ-273C). The docket is available for inspection between the hours of 9:00 a.m. and 4:00 p.m., Monday through Friday, excluding Federal holidays. To review docket materials, you may make an appointment by calling 1-202/382-3046. The public may copy a maximum of 50 pages from any regulatory docket at no cost. Additional copies cost $.20 per page.

2. LITERATURE SEARCH AND INFORMATION SOURCES

2.1. SEARCH STRATEGY

The objective of the information search was to identify all relevant published reports concerning the potential carcinogenicity of the chemicals under study. For the most part, only reports published prior to 1985 were considered in this review. Epidemiologic studies and the published results of controlled investigations with experimental laboratory animals were sought from the worldwide biomedical literature. In order that the information search be exhaustive, both on-line and hard-copy sources of bibliographic information were consulted. A list of the data bases searched for this project is presented in Table 2-1. Retrieval of old literature was accomplished through searches of hard-copy sources and through researching bibliographies of relevant publications. Every attempt has been made to rely upon primary publications as opposed to data summaries or abstracts contained in secondary sources such as monographs, surveys, review articles, criteria documents, etc.

Searches were conducted using specific Chemical Abstracts Service (CAS) names, CAS registry numbers, common synonyms, designated substructures, and key words related to carcinogenicity and mutagenicity when appropriate. All of the ch micals included in the study were first searched in the CHEMLINE on-line chemical dictionary to identify proper CAS registry numbers and all available synonyms. On-line

TABLE 2-1. SOURCES OF BIBLIOGRAPHIC AND NUMERICAL INFORMATION FOR SUSPECT CARCINOGENS

On-Line Sources

CHEMLINE (National Library of Medicine)
RTECS (National Library of Medicine)
Hazardous Substances Data Bank (National Library of Medicine)
TOXLINE (National Library of Medicine)
CANCERLINE (National Library of Medicine)
Chemical Abstracts (DIALOG Information Services)

Hard-Copy Sources

"Survey of Compounds Tested for Carcinogenicity," PHS-149 (all volumes)

"International Agency for Research on Cancer--Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans," Volumes 1-29

National Toxicology Program, Carcinogenesis Testing Program, "Chemicals on Standard Protocol" (as of October 7, 1982)

National Cancer Institute--Technical Report Series

"Genetox Carcinogen List" (as of July 9, 1982)

"TOX-TIPS" (National Library of Medicine)

"Chemical Carcinogens," C.E. Searle (ed.), ACS Monograph 173, 1976

"Documentation of the Threshold Limit Values for Substances in Workroom Air," American Conference of Governmental Industrial Hygienists

"Ambient Water Quality Criteria Documents," U.S. EPA, ORD

National Institute for Occupational Safety and Health--Criteria Documents, Technical Reports, Special Occupational Hazard Reviews, Current Intelligence Bulletins, Information Profiles on Potential Occupational Hazards

"Current Contents--Life Sciences," Institute for Scientific Information

bibliographic data bases were then searched by developing a list f key words, translating them into data base specific index terms and searching the file. If the citations retrieved were relevant, they were printed. If these results indicated new key words, the data base was searched again.

In most cases, the decision to obtain an article in hard copy was based upon a review of information contained in abstracts which were obtained from the on-line computer search. For the sake of completeness, many articles were obtained in hard copy even if it was not clear from the title that useful data for assessment of carcinogenic risk would be contained in the report. Thus, a large body of literature relating to the chemicals under study was collected, although no attempt was made to cite all of th articles retrieved.

Only published literature was reviewed for the assessments made in this report. However, the HHAG is now in the process of reviewing unpublished carcinogenicity study data submitted to the Agency. The summary table (Hazard Ranking of Potential Carcinogens), which is attached as an appendix to this report, may be revised upon the completion of that review.

2.2. SELECTION OF APPROPRIATE STUDIES

It is important to recognize that many published studies may be acceptable to provide qualitative evidence of carcinogenicity, yet still may be inappropriate for quantitative estimation of carcinogenic potency.

It is also important to consider the relevance of the route of administration of the test substance in experimental animals to the anticipated route of exposure in humans. For example, the results of animal studies in which test substances are administered by intravenous or intramuscular injection may provide strong qualitative evidence of carcinogenic potential and yet be inappropriate to predict the tumor incidence in humans resulting from ingestion or inhalation of the substance. The problem is often compounded by a lack of data concerning the extent of absorption from different routes of exposure (i.e., oral, inhalation, and dermal contact), thereby leading to inaccurate estimates of actual absorbed doses.

Before a study can be used to support either a qualitative or quantitative assessment of carcinogenicity, several criteria should be met. These general criteria, that are applied by reviewers when evaluating the output of a literature search, are listed as follows.

Factor: Experimental Design

Scoring Elements:

1. What are the objectives of the study?
2. Does the design address the issues?
3. Does the design represent the state-of-the-art?
4. Are there areas which might produce ambiguous results?
5. Were the sampling and handling procedures adequate?

Factor: Experimental Procedure

Scoring Elements:

1. Were standard protocols followed?

2. Were any variations from design noted, explained, and/or considered in reporting results?
3. Were analytical and quantitative parameters provided?

Factor: Results and Conclusions

Scoring Elements:

1. Were sufficient data presented to allow a credible case to be established?
2. Were the results understandable?
3. Were results statistically valid?
4. Were the investigators' conclusions supported by the results?
5. Does the paper allow for additional conclusions to be reached concerning correlation of results with the findings of other investigators?

A publication need not necessarily be rejected from consideration if all of the above criteria are not met, although deficiencies in the study should be indicated by the reviewer if the data are intended to be used for qualitative and quantitative assessment purposes.

3. APPROACH TO DATA EVALUATION

Each primary publication retrieved during the literature search phase of the project is critically evaluated, both with respect to its relevance to an assessment of carcinogenicity and to the quality of the reported data. In developing a hazard ranking methodology, the Agency recognizes that a distinction must be made between the evaluation of the qualitative strength of the case that a substance causes cancer, and the quantitative estimate of the strength of the substance to cause cancer. The qualitative assessments are expressed as an overall weight of evidence of the likelihood that the substance is a human carcinogen (see Section 3.1.). The quantitative assessment, on the other hand, is a numerical estimate of the strength of the substance to cause cancer (see Section 3.2.).

Because of the large number of substances to be evaluated, it is necessary to be as systematic as possible in conducting both the qualitative and quantitative assessments. A two-phase approach was developed that would facilitate the grouping of substances based on the overall weight of evidence of carcinogenicity and on the calculated carcinogenic potency.

A subsequent quality control review, under the direction of the HHAG, has been conducted to assure that all determinations and study interpretations within each profile are consistent with qualitative and quantitative analysis in other Agency risk assessment reports. The risk assessm nt reports reviewed were

Health Effects Assessments (HEAs), Health and Environmental Effects Profiles (HEEPs), Health and Environmental Effects Documents (HEEDs), Health Assessment Documents (HADs), and Drinking Water Criteria Documents (DWCDs).

3.1. QUALITATIVE PHASE: WEIGHT OF EVIDENCE OF CARCINOGENICITY

The first phase of the HHAG ranking procedure is a qualitative evaluation of the strength of the available data. This evaluation is based on the Agency's "Guidelines for Carcinogen Risk Assessment" (U.S. EPA, 1986). The remainder of this section paraphrases the guidelines.

3.1.1. Assessment of Evidence for Carcinogenicity from Studies in Humans

Evidence of carcinogenicity from human studies comes from three main sources:

- Case reports of individual cancer patients who were exposed to the agent(s);
- Descriptive epidemiologic studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agent(s); and
- Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the agent(s) was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

- There is no identified bias that can explain the association;
- The possibility of confounding variables has been considered and ruled out as explaining the association; and
- The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies show the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

From studies in humans, the evidence for carcinogenicity[1] is classified as:

- Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer;
- Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded;

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[1]For purposes of public health protection, agents associated with life-threatening benign tumors in humans are included in the evaluation.

- Inadequate evidence, which indicates that one of two conditions prevailed: (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, which indicates that data are not available; or
- No evidence, which indicates that no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

3.1.2. Assessment of Evidence for Carcinogenicity from Studies in Experimental Animals

These assessments are classified into five groups:

- Sufficient evidence[2] of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors[3]: (a) in multiple species or strains; (b) in multiple experiments (e.g., with different routes of

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[2]An increased incidence of neoplasms that occurs even with high spontaneous background incidence (e.g., mouse liver tumors and rat pituitary tumors in certain strains) generally constitutes "sufficient" evidence of carcinogenicity, but may be changed to "limited" when warranted by the specific information available on the agent.

[3]Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin.

exposure) or of unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure;

- Limited evidence of carcinogenicity, which means that 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 (U.S. EPA, 1986); (b) the experiments are restricted by adequate 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 evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect;
- No data, which indicates that data are not available; or
- No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies in different species.

The classifications "sufficient evidence" and "limited evidence" refer only to the weight of the experimental evidence that these agents are carcinogenic, and not to the potency of their carcinogenic action.

3.1.3. Categorization of Overall Weight of Evidence for Human Carcinogenicity

The overall scheme for categorizing the weight of evidence of carcinogenicity of a chemical for humans uses a three-step process: (1) the evidence in human studies or animal studies is summarized; (2) these lines of information are combined to yield a tentative assignment to a weight-of-evidence category (Table 3-1); and (3) all relevant supportive information is evaluated to see if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor information from human and animal studies include structure-activity relationships; short-term test findings; results of appropriate physiological, biochemical, and toxicological observations; and comparative metabolism and kinetic studies. The nature of these findings may cause one to adjust the overall categorization of the weight of evidence.

The substances are categorized in the manner shown below.

Group A--Human Carcinogen

An agent is placed in this group only when there is "sufficient" evidence from epidemiologic studies to support a causal association between exposure to the agent(s) and cancer.

Group B--Probable Human Carcinogen

This group includes agents for which the weight of evidence of human carcinogenicity based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two groups. Group B1 is usually reserved for agents for which there is "limited" evidence of carcinogenicity from epidemiologic studies. It is reasonable, for practical purposes, to regard an agent for which there is "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate" evidence or "no data" from epidemiologic studies (human) would usually be categorized under Group B2.

Group C--Possible Human Carcinogen

This group is used for agents with "limited" evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence; for example: (a) a malignant tumor response in a single, well-conducted experiment that does not meet conditions for "sufficient" evidence; (b) tumor responses of marginal, statistical significance in studies having inadequate design or reporting; (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity; and (d) responses of

TABLE 3-1. TENTATIVE WEIGHT OF EVIDENCE BASED ON HUMAN AND ANIMAL EVIDENCE[a]

Human Evidence	Animal Evidence				
	Sufficient	Limited	Inadequate	No Data	No Evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No Data	B2	C	D	D	E
No Evidence	B2	C	D	D	E

[a]The above assignments are presented for illustrative purposes. There maybe instances in the classification of both animal and human data indicating that different categorizations than those given in the table should be assigned. Furthermore, these assignments are tentative and may be modified by ancillary evidence. In this regard all relevant information should be evaluated to determine if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor data from human and animal studies include structure-activity relationships, short-term test findings, results of appropriate physiological, biochemical and toxicological observations, and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause an adjustment of the overall categorization of the weight of evidence

SOURCE: U.S. EPA, 1986.

marginal statistical significance in a tissue known to have a high or variable background rate of cancer.

Group D--Not Classifiable as to Human Carcinogenicity

This group is generally used for agent(s) with "inadequate" human and animal evidence of carcinogenicity or for which "no data" are available.

Group E--Evidence of Non-Carcinogenicity for Humans

This group is used for agent(s) that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of a Group E agent is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

3.2. QUANTITATIVE PHASE: ESTIMATION OF CARCINOGENIC POTENCY

After the qualitative determination that a substance is a potential carcinogen, a quantitative assessment can usually be performed. Such quantitative assessments are most useful for: (1) estimating the cancer risk associated with a particular level of exposure; and (2) making comparisons among potential carcinogens based on their relative potencies. This latter application is the objective of this methodology. More specifically, the objective is to group potential carcinogens according to potency.

3.2.1. Model Selection for Analysis of Dose-Response Data

Given the stated objective of grouping potential carcinogens according to potency, there is a need for consistency and comparability in the evaluation process. In accordance with the Agency's guidelines and with Agency practice in numerous risk assessments, the multistage model is used for estimating carcinogenic potency (U.S. EPA, 1986). Under the multistage model, the lifetime probability of developing cancer with a constant dose (d) is given by:

$$(3\text{-}1) \qquad P(d) = 1 - \exp\left[-(q_o + q_1 d + \ldots + q_k d^k)\right]$$

In accordance with the Agency's "Guidelines for Carcinogen Risk Assessment" (U.S. EPA, 1986), when study results are such that another model would provide adequate estimates of carcinogenic potency, the HHAG may choose to use the more appropriate model. For instance, because of the extraordinary rate of early deaths of animals with tumors, the model used to estimate risks from exposure to ethylene dibromide (EDB) incorporates a time parameter. This time parameter allows the differential risks of less than lifetime exposure to EDB to different age groups to be factored into the risk estimated from a National Cancer Institute (NCI) bioassay. Any variance from the standard multistage model is described in the individual potential carcinogen profiles.

For reportable quantity adjustments pursuant to CERCLA Section 102, the potency factor (F) is defined as the reciprocal of the estimated dose in mg/kg/day, associated with a lifetime cancer risk of 10 percent (ED_{10}). The reciprocal of the ED_{10} is us d because it is the more direct measure of potency. The ED_{10} itself is inversely related to potency.

The potency factor (F) is used in place of the upper bound on the linear coefficient (q^*_1) (U.S. EPA, 1989), that HHAG normally uses to estimate potency because:

- It can be estimated without the use of many assumptions required for q^*_1. This is possible because there is no need for extrapolation below the experimentally observable dose range[4].
- It is relatively insensitive to the choice of the dose-response extrapolation model. Therefore, the potency rankings are not distorted by the selection of any particular dose-response model.
- The point estimate of ED_{10}, which has some optimal statistical properties, can be used to calculate F. Therefore, it is not necessary to use statistical upper bounds, which are needed to ensure stable estimates of q^*_1.

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[4]Extrapolation below the experimentally observable dose range is the whole purpose of thE q^*_1 estimation. It is done because "risk at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies" (U.S. EPA, 1986).

The potency factor (F) is used together with the qualitative weight of evidence of carcinogenicity in ranking the potential carcinogens.

3.2.2. Selection of Bioassay Response Data to be Used in the Model to Calculate Potency

This section covers the selection of animal study response data for use in the multistage model and estimation of $1/ED_{10}$. Human epidemiologic data must be reviewed and used on a case-by-case basis. Hence, if epidemiologic studies are selected as suitable for derivation of a potency estimate, their use is described separately in the individual potential carcinogen profile. In general, the data selection criteria are those described in EPA's guidelines (U.S. EPA, 1986).

The following approach to selecting the data sets for calculating a potency factor is used where several studies on a particular substance might involve different animal species, strains, and sexes, at several doses and by different routes of exposure, and may result in different tumor sites and types.

The tumor incidence data are separated according to organ site and tumor type. All biologically and statistically acceptable data sets are presented in the potential carcinogen profiles. Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest

sensitivity is generally used, with due regard to biological and statistical considerations.

All assumptions are presented in the profile along with a discussion of any uncertainties in the extrapolation. Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections are made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence are pooled and used for extrapolation. The pooled estimates are generally used in preference to potency estimates based on single sites or types. Quantitative risk extrapolations are generally not performed on the basis of totals that include tumor sites without statistically significant elevations.

Benign tumors are generally combined with malignant tumors for potency estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin.

3.2.3. Adjustment (Transformation) of Dose Data

Before a potency factor can be calculated all dose information must be transformed to standard units of milligram (mg) (substance) per kilogram (kg) (animal weight) per day, administered over the entire length of the study. If doses are given in units other than mg/kg/day, or if animals are dosed in a non-continuous manner, or if the reviewer has evidence that the absorbed or metabolized dose is significantly less than the

administered dose, then the dose data must be converted to a "transformed dose."

The next three subsections discuss how this is done for three exposure routes: diet, water, and air. The assumptions and procedures used parallel those described in the Agency's "Guidelines and Methodology for the Preparation of Health Effects Assessment Chapters of the Ambient Water Quality Criteria Documents" (U.S. EPA, 1980).

3.2.3.1. Calculation of Dose in mg/kg/day from Doses Expressed as Dietary Concentrations--If the authors provide information on body weight and food consumption, then the dietary dose (d) is calculated directly. If these data are not provided, then the d se may be estimated by using standard food consumption estimates based on the fraction of body weight that is consumed each day as food (f) (U.S. EPA, 1980):

Species	f
Mouse	0.13
Rat	0.05
Human	0.028

In order to obtain the dietary dose (d) from the data given in parts per million (ppm), the daily experimental dose in ppm is multiplied by f:

(3-2) $$d = ppm \times f$$

Note that ppm in food has units of mg toxicant per kg food, and the fraction f has units of kg food per kg body weight per day. Thus, the product has units of mg of toxicant per kg body weight per day.

3.2.3.2. Calculation of Dose in mg/kg/day from Doses Expressed as Water Concentrations--If the authors of the studies provide information on body weight and water consumption, then the dietary dose d is calculated directly. If these data are not available then d may be estimated by using standard water consumption estimates based on the fraction of the body weight consumed as water per day (fw) (U.S. EPA, 1980). The assumptions and the procedure for making this estimation are the same as for dietary concentrations (Section 3.2.3.1.) but the following rates for fw apply:

Species	fw
Mouse	0.17
Rat	0.078
Human	0.029

The dietary dose (d) in mg/kg/day is calculated by multiplying the daily dose in ppm by the appropriate fw:

(3-3) $$d = ppm \times fw$$

Note that ppm in water has units of mg toxicant per liter water and that fw has units of liters of water per kg body weight per day. Thus the product has units of mg toxicant per kg body weight per day.

3.2.3.3. Calculation of Dose in mg/kg/day from Doses Expressed as Air Concentrations--When exposure is via inhalation, the calculation of dose can be considered for two cases where: (1) th carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed in proportion to the amount of air breathed in; and (2) where the carcinogen is a poorly water-soluble gas that reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which is proportional to the rate of oxygen consumption, which in turn is a function of surface area (U.S. EPA, 1980).

For Case 1, agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportional to the inhalation rate. The inhalation rate (I) for various species can be calculated from the observations (FASEB, 1974) that 25-g mice breathe 0.0345 cubic meters (m^3) per day and 113-g rats breathe 0.105 m^3/day. For mice and rats of other weights in kilograms (w), the surface-area proportionality can be used to find breathing rates in m^3/day as follows:

(3-4) for mice, $I = 0.0345\ (W/0.025)^{2/3}\ m^3/day$; and

(3-5) for rats, $I = 0.105\ (W/0.113)^{2/3}\ m^3/day$.

The weight ratio is raised to the two-thirds power because, to a close approximation, the surface area is proportional to the two-thirds power of the weight as would be the case for a perfect sphere.

For humans, the value of $I = 20\ m^3/day$ is adopted as the standard breathing rate. This is calculated from the observation (ICRP, 1977) that the average breathing rate is 10^7 cubic centimeters (cm^3) per 8-hour workday and $2 \times 10^7\ cm^3$ in 24 hours.

The empirical factors for the air intake per kg per day, $i = I/W$, calculated from the previously stated relationships for standard weight animals, are tabulated as follows:

Species	W	i = I/W
Mouse	0.03	1.3
Rat	0.35	0.64
Human	70	0.29

The inhalation dose (d) in mg/kg/day is calculated by multiplying the substance's air concentration (v) by the appropriate intake factor (i) and the absorption fraction (r):

(3-6) $$d = v \times i \times r$$

Note that v has units of mg toxicant per m^3, i has units of m^3 per kg body weight per day, and r is dimensionless. Thus the product has units of mg toxicant per kg body weight per day.

In the absence of experimental information or a sound theoretical argument to the contrary, r is assumed to be the same for all species and therefore drops out of the calculations.

For Case 2, the dose in mg/day of partially soluble vapors is proportional to O_2 consumption, which in turn is proportional to $W^{2/3}$. The dose is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient (r) for the gas.

Therefore, by expressing the O_2 consumption as $O_2 = k \times W^{2/3}$, where k is a constant independent of species, it follows that the average dose per day in mg during administration of the agent (n) can be expressed as:

$$n = k \times W^{2/3} \times v \times r \qquad (3\text{-}7)$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction (r) is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or mg/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps

et al., 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice-versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

In this case, the dose (d) in mg/kg/day is:

(3-8) $$d = n/kg \text{ (animal)}$$

For either inhalation case, exposures given in terms of ppm (by volume) in air can be converted to units of mg/m^3 (v) by the following formula:

(3-9) $$v = 0.041 \times \text{molecular weight (gas)} \times ppm$$

(Note that 1 ml in 1 cm^3 is 1 ppm (by volume); therefore, 0.041 x molecular weight (MW) is the weight in mg of 1 ml of a gas.)

3.2.3.4. Adjustment for Non-Continuous Exposure -- To this point the dose (d) calculated reflects the daily dose given over the experimental treatment period. To derive the final "transformed dose," the dose must be multiplied by the fraction of the study over which the animal was actively dosed. If the animal was dosed continuously over an entire treatment period (e.g., not 5 times per week or, for inhalation studies, 6 hours per day) then the transformed dose is:

(3-10) $$\text{transformed dose} = d \times \frac{le}{Le}$$

where le = duration of the treatment and Le = duration of the study.

If the animal was dosed for a fraction of a week (e.g., 5/7) r a fraction of a day (e.g., 6/24), then the transformed dose becomes, for example:

(3-11) $$\text{transformed dose} = d \times \frac{le}{Le} \times \frac{5}{7} \times \frac{6}{24}$$

3.2.3.5. Adjustment for Absorption, Distribution, Metabolism, and Excretion--Whenever there is usable information on the absorption, distribution, metabolism, or excretion of the substance, the potency factor is adjusted to reflect this information. For example, if the effective dose to the target organ in an animal, due to any of these four factors, is known to be a fraction of the administered dose, then the effective dose is used to estimate the potency factor. However, in the absence of information or differences in absorption, distribution, metabolism, or excretion between animals and humans, no such adjustments are made.

3.2.4. Calculation of the Human Potency Factor (F)

The information needed for calculating a human potency factor (F) can be found in the profiles entitled "Evaluation of the Potential Carcinogenicity of [substance name] in Support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102." A sample potency factor derivation table from the profile for chloroform is presented in Table 3-2.

TABLE 3-2. SAMPLE TABLE FOR THE DERIVATION OF POTENCY FACTOR (F)

Agent: Chloroform

Reference:	NCI (1976)		
Exposure route:	oral (gavage)		
Species:	mice		
Strain:	B6C3F1		
Sex:	F		
Vehicle or physical state:	corn oil		
Body weight:	0.03 kg[a]		
Duration of treatment (le):	546 days		
Duration of study (Le):	644 - 651 days		
Lifespan of animal:	730 days[b]		
Target organ:	Liver		
Tumor type:	hepatocellular carcinoma		
Experimental doses/exposure[c] (mg/kg):	477	238	0
Transformed doses[d] (mg/kg/day):	288	143	0
Tumor incidence:	39/41	36/45	0/20
Lifetime animal potency :	0.104		
Human potency factor (f):	1.97		

[a]Reported.
[b]Assumed.
[c]Exposures were 5 days/week. Duration of study was assumed to be 647 days.
[d]To derive the transformed dose from the experimental dose data: experimental dose (mg/kg/day) x 5(treatment days/week)/ 7(days/week) x duration.

3.2.4.1. Animal Potency--The first step in the derivation of F is the calculation of the animal potency from the transformed dose and response (tumor incidence) data.

The animal potency is estimated by fitting a multistage dose-response model to the transformed dose-response data, as described in EPA's Notice of Availability of Water Quality Criteria Documents (U.S. EPA, 1980). The mathematical assumptions made for the model used are described in a separate appendix to the technical background document (U.S. EPA, 1989) for the reportable quantity rule. For chloroform, the dose causing an increased cancer risk of 10 percent of the population is calculated to be ED_{10} = 9.62 mg/kg/day. The animal potency is the reciprocal of this dose, 0.104 $(mg/kg/day)^{-1}$.

3.2.4.2. Adjustment for Less Than Lifetime Studies--Under the current procedures used by HHAG, the risk levels are derived only for full lifetime experiments. In dealing with experimental data in which the observation period (Le) is less than the lifespan (L) of the experimental animal, the potency factor derived from the experimental data, which would give a risk estimate over the fraction Le/L of the animal's lifespan, is increased by a factor of $(L/Le)^3$ to obtain an estimated potency for full lifetime risk. As explained by the EPA (1980):

> We assume that if the average dose (d) is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the second power of the age and often by a considerably higher power, as demonstrated by Doll (1971). Thus we would expect the cumulative tumor rate to increase by at least the third power of age...

(3-12) Lifetime Animal Potency = Observed Animal Potency x $(L/Le)^3$

This adjustment is conceptually consistent with the proportional hazard model considered by Crump and Watson (1982).

For chloroform, the lifetime animal potency is:

(3-13) Lifetime Animal Potency = $0.104 \times (730/648)^3 = 0.149$

3.2.4.3. Human Potency (F) -- Finally, the potency must be adjusted for humans (if derived from animal data). The human potency adjustment is made using the following surface-area correction:

(3-14) Human Potency (F) = Lifetime Animal Potency x $(70\ kg/W_a)^{1/3}$;

where W_a is the weight of the animal and 70 kg is the assumed average weight of humans. This is in accordance with the Agency's cancer guidelines (U.S. EPA, 1986)[5].

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[5]The Agency's guidelines reflect that animal potency is converted to human potency by first multiplying the animal ED_{10} by the ratio of the the weight of the animal to the weight of man, and dividing the entire ED_{10} by the ratio of the surface area of the animal to man.

$$\text{Human } ED_{10} = \frac{\text{animal } ED_{10} \times (W_a/W_{man})}{(W_a/W_{man})^{2/3}} = \text{animal } ED_{10}\ (W_a/W_{man})^{1/3}$$

Then, the reciprocal of the Human ED_{10} is the adjusted human potency.

For chloroform, the human potency (F) is:

(3-15) Human Potency (F) = $0.149 \times (70/0.03)^{1/3} = 1.97$.

3.2.5. Grouping of Chemicals Based on Carcinogenic Potency

After the potency factors are estimated, the substances are placed into three potency groups. The most potent substances, those with potency factors above 100, are placed in Potency Group 1; substances with potency factors between 1 and 100 are placed in Potency Group 2; and substances with potency factors below 1 are placed in Potency Group 3. The Potency Group will be used along with the weight-of-evidence group in assigning tentative RQs for potential carcinogenicity.

In the case where available data are inadequate for estimating a potency factor, the HHAG has identified three possible alternatives:

- If the best available data suggest that the substance is a possible strong carcinogen, but there is no basis for assigning a specific ED_{10} dose (e.g., all treated animals at every dose developed tumors), then the substance is assigned to the highest potency group (i.e., Potency Group 1).
- If the best available data are inadequate for calculating a potency factor and no quantitative inferences can be made (e.g., in animal studies where

control groups were not used or number of animals treated were not specified), then the substance is assigned to the mid-range potency group (i.e., Potency Group 2).

- If the best available data suggest that the substance is a possible weak carcinogen, but there is no basis for assigning a specific ED_{10} dose (e.g., due to uncertainties associated with the pharmacokinetics of the substance), then the substance is assigned to the lowest potency group (i.e., Potency Group 3).

Hazard rankings can then be assigned by following the standard procedure for combining the weight-of-evidence group and the assigned potency group.

3.3. OVERALL HAZARD RANKING BASED ON COMBINED QUALITATIVE AND QUANTITATIVE ASSESSMENTS

The culmination of the hazard ranking process performed in this study is accomplished by combining the qualitative weight of evidence for carcinogenicity (Section 3.1.) with the potency group (Section 3.2.) to arrive at a final hazard ranking for each substance. Substances are ranked as "high," "medium," or "low" hazard according to the scheme shown in Table 3-3.

Hazard rankings are based jointly on two factors--weight of evidence and potency--that the Agency believes are important in describing carcinogenic hazards. Hazard rankings of high, medium, and low are assigned so that the hazard ranking

TABLE 3-3. HAZARD RANKING SCHEME FOR REPORTABLE QUANTITIES UNDER CERCLA

W ight-of-Evidence Group	Potency Group : 1 Potency Factor : F > 100	2 F = 1 to 100	3 F < 1
A - Carcinogenic to humans	High	High	Medium
B - Probably carcinogenic to humans[a]	High	Medium	Low
C - Possibly carcinog nic to humans	Medium	Low	Low
D - Not classifiable as to human carcinogenicity	No hazard ranking		
E - Evidence of non-carcinogenicity for humans	No hazard ranking		

[a]Includes weight-of-evidence Groups B1 and B2.

increases as either the weight of evidence or the potency increases.

Depending on whether a substance falls into Potency Groups 1, 2, or 3, a hazard ranking of high, medium, or low is assigned to Group B carcinogens. Hazard rankings are one level higher (high, high, or medium) for Group A carcinogens. This increased concern is justified because there is direct human evidence establishing that Group A substances cause cancer. Hazard rankings are one level lower (medium, low, or no hazard ranking is assigned at this time) for Group C carcinogens. This reduced concern is justified because the evidence implicating Group C substances either is unreplicated or is of marginal biological or statistical significance. Before settling on these hazard ranking assignments, alternative ranking schemes were considered. Proposals that all Group A substances be ranked high or that all Group C substances be ranked low were rejected because the Agency believes strongly that potency, too, is important in describing a carcinogenic hazard. Similarly, a proposal to base hazard rankings on potency alone was rejected because the Agency believes that the weight of evidence must be considered as well. It is the Agency's judgment that the hazard scheme finally selected gives proper consideration to both weight of evidence and potency.

For substances placed in weight-of-evidence Groups D or E, primary criteria other than potential carcinogenicity must be used to assign an adjust d RQ.

3.3.1. Use of Chemical and Environmental Fate and Transformation Data in Hazard Ranking of Metals and Their Salts

The chemical and environmental specification, oxidation state, solubility, chemical and environmental fate and half-life, and disproportionation reactions are important determinants of the toxicity of inorganic compounds. Furthermore, toxicity data relevant to potential carcinogenicity and other chronic effects ar lacking for many of the metals and their salts. Therefore, in cases where toxicity data are not available on a particular metal salt, and an evaluation of the above parameters indicates its convertibility to the toxic (i.e., carcinogenic) species under realistic human exposure conditions, then an appropriate hazard ranking assignment will be performed based on this evidence.

3.3.2. Special Problems in Hazard Ranking of Chemicals Associated with Multimedia Exposure in Humans

Carcinogenic hazard ranking in the present study must take into account the potential for multimedia exposure. Thus, all routes of human exposure (oral, inhalation, and dermal) must be considered in the hazard ranking scheme. The final hazard ranking is based on the route that gives the highest potency factor.

4. SUMMARY

The Agency's Human Health Assessment Group (HHAG) has developed a unique method for ranking CERCLA hazardous substances for potential carcinogenicity. This methodology is not a risk assessment and it does not yield an absolute measure of harm. Rather, the methodology simply represents a means of sorting potentially carcinogenic substances into categories, which may then be equated to RQ levels.

The methodology for ranking potential carcinogens begins by reviewing all information available in the scientific literature on each substance identified as a potential carcinogen. This information is then evaluated using a two-stage process. The first stage is a qualitative assessment of the likelihood that a particular hazardous substance is a human carcinogen. During this stage, the available data is evaluated using EPA's weight-of-evidence classification system, developed in the September 24, 1986, "Guidelines for Carcinogen Risk Assessment" (U.S. EPA, 1986). The second stage is a quantitative assessment designed to estimate the relative strength of a hazardous substance to elicit a carcinogenic response (potency factor). The quantitative stage allows the Agency to rank potential carcinogens on a numerical scale. The results of the qualitative and quantitative assessments are then combined to arrive at a hazard ranking for each hazardous substance evaluated for potential carcinogenicity.

There are two separate appendices to this methodology document. The first is a summary table of the hazard ranking results. The second consists of all of the individual chemical profiles prepared to support these results. The profiles are not attached but are available in Room M2427 at the U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460 (Docket Number 102 RQ-273C). The docket is available for inspection between the hours of 9:00 a.m. and 4:00 p.m., Monday through Friday, excluding Federal holidays. To review docket materials, you may make an appointment by calling 1-202/382-3046. The public may copy a maximum of 50 pages from any regulatory docket at no cost. Additional copies cost $.20 per page.

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APPENDIX

HAZARD RANKING OF POTENTIAL CARCINOGENS

HAZARD RANKING OF POTENTIAL CARCIN[redacted]S

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
1	Acetamide, N-fluoren-2-yl	00053963	No Data	Sufficient	B2	148	1	HIGH
2	Acrylonitrile	00107131	Limited	Sufficient	B1	2.28[f]	2	MED
3	Aldrin	00309002	Inadequate	Sufficient	B2	239	1	HIGH
4	Amitrole	00061825	Inadequate	Sufficient	B2	3.30	2	MED
5	Arsenic	07440382	Sufficient	Inadequate	A	142	1	HIGH
6	Arsenic acid	01327522 07778394	d	No Data	d	d	1	HIGH
7	Arsenic disulfide	01303328	d	No Data	d	d	1	HIGH
8	Arsenic pentoxide	01303282	d	No Data	d	d	1	HIGH
9	Arsenic trichloride	07784341	d	No Data	d	d	1	HIGH
10	Arsenic trioxide	01327533	Sufficient	Inadequate	A[d]	d	1	HIGH
11	Arsenic trisulfide	01303339	d	No Data	d	d	1	HIGH
12	Cacodylic acid	00075605	No Data	Inadequate	D[z9]	None	None	None[b]
13	Calcium arsenate	07778441	d	No Data	d	d	1	HIGH
14	Calcium arsenite	52740166	d	No Data	d	d	1	HIGH
15	Cupric acetoarsenite	12002038	d	Inadequate	d	d	1	HIGH
16	Dichlorophenylarsine	00696286	No Data	No Data	D[z9]	None	None	None[b]
17	Diethylarsine	00692422	No Data	No Data	D[z9]	None	None	None[b]
18	Lead arsenate	07784409	d	Inadequate	d	d	1	HIGH
19	Potassium arsenate	07784410	d	No Data	d	d	1	HIGH
20	Potassium arsenite	10124502	Sufficient	Inadequate	A[d]	1	1	HIGH
21	Sodium arsenate	07631892	d	No Data	d	d	1	HIGH
22	Sodium arsenite	07784465	d	No Data	d	d	1	HIGH
23	Asbestos	01332214	Sufficient	Sufficient	A	p	p	HIGH
24	Auramine	00492808	Inadequate	Sufficient	B2	0.48	3	LOW
25	Azaserine	00115026	No Data	Sufficient	B2	169	1	HIGH
26	Aziridine	00151564	No Data	Sufficient	B2	336	1	HIGH
27	Benz(c)acridine	00225514	No Data	Limited	C	a	2	LOW
28	Benz(a)anthracene	00056553	No Data	Sufficient	B2	21.1	2	MED
29	Benzene	00071432	Sufficient	Sufficient	A	0.27[f]	3	MED
30	Benzidine and its salts	00092875	Sufficient	Sufficient	A	2220[f]	1	HIGH
31	Benzo(b)fluoranthene	00205992	No Data	Sufficient	B2	248	1	HIGH
32	Benzo(k)fluoranthene	00207089	No Data	Inadequate	D	None	None	None[b]
33	Benzo(a)pyrene	00050328	Inadequate	Sufficient	B2	248	1	HIGH

HAZARD RANKING OF POTENTIAL CARCINOGEN[illegible]ontinued)

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
34	Benzotrichloride	00098077	Limited	Sufficient	B1	58.0	2	MED
35	Benzyl chloride	00100447	Inadequate	Sufficient	B2	0.66	3	LOW
36	Beryllium	07440417	Inadequate	Sufficient	B2[u]	79.70[u]	2	MED
37	Beryllium chloride	07787475	No Data	No Data	u	ab	1	HIGH
38	Beryllium fluoride	07787497	No Data	Sufficient	u	ab	1	HIGH
39	Beryllium nitrate	13597994	No Data	No Data	u	ab	1	HIGH
40	alpha - BHC	00319846	No Data	Sufficient	B2	51.48	2	MED
41	beta - BHC	00319857	No Data	Limited	C	10.67	2	LOW
42	gamma - BHC (Lindane)	00058899	Inadequate	Sufficient/ Limited	B2/C[m]	7.39	2	MED
43	Bis(2-chloroethyl) ether	00111444	No Data	Sufficient	B2	13.29	2	MED
44	Bis(chloromethyl) ether	00542881	Sufficient	Sufficient	A	10377	1	HIGH
45	Bis(2-ethylhexyl) phthalate	00117817	No Data	Sufficient	B2	0.194	3	LOW
46	Cadmium	07740439	Limited	Sufficient	B1	57.9[k]	2	MED
47	Cadmium acetate	00543908	k	No Data	k	k	2	MED
48	Cadmium bromide	07789426	k	No Data	k	k	2	MED
49	Cadmium chloride	10108642	k	Sufficient	k	k	2	MED
50	Carbon tetrachloride	00056235	Inadequate	Sufficient	B2	59.9	2	MED
51	Chlorambucil	00305033	Limited	Sufficient	B1	a	2	MED
52	Chlordane	00057749	Inadequate	Sufficient	B2	15.13	2	MED
53	Chlornaphazine	00494031	Inadequate	Limited	C	a	2	LOW
54	Chloroform	00067663	Inadequate	Sufficient	B2	1.97	2	MED
55	Chloromethyl methyl ether (technical grade)	00107302	Sufficient	Inadequate	A	n	1	HIGH
56	4-Chloro-o-toluidine, hydrochloride	03165933	No Data	Sufficient	B2	0.40	3	LOW
57	Chromium[g]	07440473	No Data	No Data	D	None	None	None[b]
58	Ammonium bichromate	07789095	h	No Data	A[h]	h	1	HIGH
59	Ammonium chromate	07788989	h	No Data	A[h]	h	1	HIGH
60	Calcium chromate	13765190	h	Inadequate	A[h]	h	1	HIGH
61	Chromic acid	11115745	h	Inadequate	A[h]	h	1	HIGH
62	Lithium chromate	14307358	h	No Data	A[h]	h	1	HIGH
63	Potassium bichromate	07778509	h	Inadequate	A[h]	h	1	HIGH
64	Potassium chromate	07789006	h	Inadequate	A[h]	h	1	HIGH
65	Sodium bichromate	10588019	h	Inadequate	A[h]	h	1	HIGH
66	Sodium chromate	07775113	h	Inadequate	A[h]	h	1	HIGH

HAZARD RANKING OF POTENTIAL CARCINOGENS (continued)

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
67	Strontium chromate	07789062	h	Sufficient	A[h]	h	1	HIGH
68	Chrysene	00218019	No Data	Limited	C	a	2	LOW
69	Coke Oven Emissions	N.A.	Sufficient	Sufficient	A	1.53[f]	2	HIGH
70	Creosote	08001589	Limited	Sufficient	B1[x]	ab	1	HIGH
71	Cyclophosphamide	00050180	Limited	Sufficient	B1	17.5	2	MED
72	Daunomycin	20830813	No Data	Sufficient	B2	a	2	MED
73	DDD	00072548	Inadequate	Sufficient	B2	1.30	2	MED
74	DDE	00072559	Inadequate	Sufficient	B2	3.82	2	MED
75	DDT	00050293	Inadequate	Sufficient	B2	5.58	2	MED
76	Diallate	02303164	No Data	Limited	C	4.28	2	LOW
77	Diaminotoluene (mixed)	00095807	No Data	Sufficient	B2	23.2	2	MED
78	Dibenz(a,h)anthracene	00053703	No Data	Sufficient	B2	ab	1	HIGH
79	1,2:7,8-Dibenzopyrene	00189559	No Data	Sufficient	B2	a	2	MED
80	1,2-Dibromo-3-chloropropane	00096128	No Data	Sufficient	B2	1240	1	HIGH
81	3,3'-Dichlorobenzidine	00091941	No Data	Sufficient	B2	7.49	2	MED
82	1,2-Dichloroethane	00107062	No Data	Sufficient	B2	0.13	3	LOW
83	1,1-Dichloroethylene (Vinylidene chloride)	00075354	No Data	Limited	C	5.19	2	LOW
84	Dieldrin	00060571	Inadequate	Sufficient	B2	236	1	HIGH
85	1,2:3,4-Diepoxybutane	01464535	No Data	Sufficient	B2	28.0	2	MED
86	1,2-Diethylhydrazine	01615801	No Data	Sufficient	B2	a	2	MED
87	Diethylstilbestrol	00056531	Sufficient	Sufficient	A	4740	1	HIGH
88	Dihydrosafrole	00094586	No Data	Sufficient	B2	1.08	2	MED
89	3,3'-Dimethoxybenzidine	00119904	No Data	Sufficient	B2	3.07	2	MED
90	Dimethyl sulfate	00077781	Inadequate	Sufficient	B2	a	2	MED
91	Dimethylaminoazobenzene	00060117	No Data	Sufficient	B2	a	2	MED
92	7,12-Dimethylbenz(a)anthracene	00057976	No Data	Sufficient	B2	540	1	HIGH
93	3,3'-Dimethylbenzidine	00119937	No Data	Sufficient	B2	27.4	2	MED
94	Dimethylcarbamoyl chloride	00079447	Inadequate	Sufficient	B2	505	1	HIGH
95	1,1-Dimethylhydrazine	00057147	No Data	Sufficient	B2	82.5	2	MED
96	1,2-Dimethylhydrazine	00540738	No Data	Sufficient	B2	4210	1	HIGH
97	Dinitrotoluene (mixed)	25321146	No Data	Sufficient	B2[z]3	3.82[z3]	2	MED
98	2,4-Dinitrotoluene	00121142	No Data	Sufficient	B2	3.82	2	MED
99	2,6-Dinitrotoluene	00606202	No Data	Limited	C	a	2	LOW
100	1,4-Dioxane	00123911	Inadequate	Sufficient	B2	0.034	3	LOW

HAZARD RANKING OF POTENTIAL CARCINOGEN[redacted]ntinued)

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
101	1,2-Diphenylhydrazine	00122667	No Data	Sufficient	B1	4.31	2	MED
102	Epichlorohydrin	00106898	Inadequate	Sufficient	B2	0.37	3	LOW
103	Ethyl carbamate (urethane)	00051796	No Data	Sufficient	B2	0.64	3	LOW
104	Ethyl 4,4'-dichlorobenzilate	00510156	Inadequate	Sufficient	B2	1.79	2	MED
105	Ethylene dibromide	00106934	Inadequate	Sufficient	B2	390	1	HIGH
106	Ethylene oxide	00075218	Limited/ Inadequate	Sufficient	B1/B2[M]	1.34	2	MED
107	Ethylenethiourea	00096457	No Data	Sufficient	B2	1.30	2	MED
108	Ethyl methanesulfonate	00062500	No Data	Sufficient	B2	295	1	HIGH
109	Formaldehyde	00050000	Limited	Sufficient	B1	2.96	2	MED
110	Glycidylaldehyde	00765344	No Data	Sufficient	B2	2.90	2	MED
111	Heptachlor	00076448	Inadequate	Sufficient	B2	117	1	HIGH
112	Heptachlor epoxide	01024573	No Data	Sufficient	B2	298	1	HIGH
113	Hexachlorobenzene	00118741	No Data	Sufficient	B2	39.0	2	MED
114	Hexachlorobutadiene	00087683	No Data	Limited	C	0.59	3	*
115	Hexachloroethane	00067721	No Data	Limited	C	0.077	3	*
116	Hydrazine	00302012	Inadequate	Sufficient	B2	107	1	HIGH
117	Indeno(1,2,3-cd)pyrene	00193395	No Data	Limited	C	a	2	LOW
118	Isosafrole	00120581	No Data	Sufficient	B2	0.54	3	LOW
119	Kepone	00143500	No Data	Sufficient	B2	48.0	2	MED
120	Lasiocarpine	00303344	No Data	Sufficient	B2	48.9	2	MED
121	Lead	07439921						##
122	Lead acetate	00301042						##
123	Lead phosphate	07446277						##
124	Lead stearate	07428480						##
125	Lead subacetate	01335326						##
126	Lead sulfide	01314870						##
127	Melphalan	00148823	Limited	Sufficient	B1[Z2]	810	1	HIGH
128	Methyl chloride	00074873	No Data	Limited	C	0.050	3	LOW
129	3-Methylcholanthrene	00056495	No Data	Sufficient	B2	25.5	2	MED
130	4,4'-Methylenebis(2-chloroaniline)	00101144	Inadequate	Sufficient	B2	1.52	2	MED
131	Methyl iodide	00074884	No Data	Limited	C	a	2	LOW
132	N-Methyl-N'-nitro-N-nitrosoguanidine	00070257	No Data	Sufficient	B2	54.7	2	MED
133	Methylthiouracil	00056042	Inadequate	Sufficient	B2	a	2	MED

HAZARD RANKING OF POTENTIAL CARCINOGENS (continued)

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
134	Mitomycin C	00050077	No Data	Sufficient	B2	a	2	MED
135	1-Naphthylamine	00134327	Inadequate	Limited	C	None	2	LOW
136	2-Naphthylamine	00091598	Sufficient	Sufficient	A	4.77	2	HIGH
137	Nickel	07440020	Inadequate	Limited	C	z[7]	z[7]	LOW
138	Nickel ammonium sulfate	15699180	No Data	No Data	z7	z7	z7	LOW
139	Nickel carbonyl	13463393	Inadequate	Sufficient	B2	z[7]	z[7]	MED
140	Nickel chloride	07718549	Inadequate	Limited	z7	z7	z7	LOW
141	Nickel cyanide	00557197	No Data	No Data	z7	z7	z7	LOW
142	Nickel hydroxide	12054487	No Data	Limited	z7	z7	z7	LOW
143	Nickel nitrate	14216752	No Data	No Data	z7	z7	z7	LOW
144	Nickel sulfate	07786814	Inadequate	Limited	z7	z7	z7	LOW
145	2-Nitropropane	00079469	Inadequate	Sufficient	B2	a	2	MED
146	N-Nitrosodi-n-butylamine	00924163	No Data	Sufficient	B2	43.70	2	MED
147	N-Nitrosodiethanolamine	01116547	No Data	Sufficient	B2	ab	1	HIGH
148	N-Nitrosodiethylamine	00055185	No Data	Sufficient	B2	969	1	HIGH
149	N-Nitrosodimethylamine	00062759	No Data	Sufficient	B2	61.2	2	MED
150	N-Nitrosodi-n-propylamine	00621647	No Data	Sufficient	B2	a	2	MED
151	N-Nitroso-N-ethylurea	00759739	No Data	Sufficient	B2	137	1	HIGH
152	N-Nitroso-N-methylurea	00684935	No Data	Sufficient	B2	2100	1	HIGH
153	N-Nitroso-N-methylurethane	00615532	No Data	Sufficient	B2	ab	1	HIGH
154	N-Nitrosomethylvinylamine	04549400	No Data	Sufficient	B2[z]	a	2	MED
155	N-Nitrosopiperidine	00100754	No Data	Sufficient	B2	37.5	2	MED
156	N-Nitrosopyrrolidine	00930552	Inadequate	Sufficient	B2	279	1	HIGH
157	5-Nitro-o-toluidine	00099558	No Data	Limited	C	0.17	3	LOW
158	Pentachloroethane	00076017	No Data	Limited	C	1.26	2	LOW
159	Pentachloronitrobenzene	00082688	No Data	Limited	C	1.42[210]	2	LOW
160	Pentachlorophenol	00087865	Inadequate	No Data	D	None	None	None[b]
161	Phenacetin	00062442	Inadequate	Sufficient	B2	0.028	3	LOW
162	Polychlorinated biphenyls (PCBs)	01336363	Inadequate	Sufficient	B2	50.47[t]	2	MED
163	Aroclor 1016	12674112	Inadequate	No Data	t	t	2	MED
164	Aroclor 1221	11104282	Inadequate	No Data	t	t	2	MED
165	Aroclor 1232	11141165	Inadequate	No Data	t	t	2	MED
166	Aroclor 1242	53469219	Inadequate	No Data	t	t	2	MED

HAZARD RANKING OF POTENTIAL CARCINOGEN[redacted]ontinued)

	Substance	CASRN	Degree of Evidence Humans	Degree of Evidence Animals	Weight-of-Evidence Group	Potency Factor	Potency Group	Hazard Ranking
167	Aroclor 1248	12672296	Inadequate	No Data	t	t	2	MED
168	Aroclor 1254	11097691	Inadequate	Sufficient	B2	t	2	MED
169	Aroclor 1260	11096825	Inadequate	Sufficient	B2	50.5	2	MED
170	1,3-Propane sultone	01120714	No Data	Sufficient	B2	10.0	2	MED
171	1,2-Propylenimine	00075558	No Data	Sufficient	B2	259	1	HIGH
172	Saccharin	00081072	Inadequate	Limited	C	0.007	3	LOW
173	Safrole	00094597	No Data	Sufficient	B2	0.18	3	LOW
174	Selenium sulfide	07488564	Inadequate	Sufficient	B2	0.93	3	LOW
175	Streptozotocin	18883664	No Data	Sufficient	B2	109	1	HIGH
176	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	01746016	Inadequate	Sufficient	B2	659,000	1	HIGH
177	1,1,1,2-Tetrachloroethane	00630206	Inadequate	Limited	C	0.85	3	LOW
178	1,1,2,2-Tetrachloroethane	00079345	Inadequate	Limited	C	1.66	2	LOW
179	Tetrachloroethylene	00127184	Inadequate	Sufficient	B2/C[m]	0.29	3	LOW
180	Thioacetamide	00062555	No Data	Sufficient	B2	24.8	2	MED
181	Thiourea	00062566	No Data	Sufficient	B2	1.05	2	MED
182	o-Toluidine	00095534	Inadequate	Sufficient	B2	0.069	3	LOW
183	p-Toluidine	00106490	No Data	Limited	C	0.94	3	LOW
184	o-Toluidine hydrochloride	00636215	Inadequate	Sufficient	B2	0.069	3	LOW
185	Toxaphene	08001352	No Data	Sufficient	B2	9.79	2	MED
186	1,1,2-Trichloroethane	00079005	No Data	Limited	C	0.36	3	LOW
187	Trichloroethylene	00079016	Inadequate	Sufficient	B2	0.10	3	LOW
188	Trichlorophenol (mixed)	25167822	No Data	Sufficient	B2[z4]	0.08[z4]	3	LOW
189	2,4,5-Trichlorophenol	00095954	Inadequate	Inadequate	D	None	None	None[b]
190	2,4,6-Trichlorophenol	00088062	No Data	Sufficient	B2	0.08	3	LOW
191	Tris(2,3-dibromopropyl) phosphate	00126727	No Data	Sufficient	B2	9.76	2	MED
192	Trypan blue	00072571	No Data	Sufficient	B2	a	2	MED
193	Uracil mustard	00066751	No Data	Sufficient	B2	a	2	MED
194	Vinyl chloride	00075014	Sufficient	Sufficient	A	18.1	2	HIGH

FOOTNOTES

GENERAL FOOTNOTES

a Data available are inadequate for calculating a potency factor and no quantitative inferences can be made. Hence, the substance is assigned to Potency Group 2, the mid-range potency group.

ab The bioassay used to calculate the potency factor suggests that the substance may be highly carcinogenic (i.e., all treated animals developed tumors, and therefore there is no basis for calculating a specific ED_{10} dose). Hence, the substance is assigned to Potency Group 1.

abc The bioassay used to calculate the potency factor suggests that the substance is a possible weak carcinogen, but due to uncertainties associated with the pharmacokinetics of the substance, there is no basis for calculating a specific ED_{10} dose. Hence, the substance is assigned the lowest potency group, Potency Group 3.

b No RQ can be assigned based on potential carcinogenicity. Other primary criteria must be used for assigning RQs.

f Potency factor estimate is derived from human epidemiology data.

m When the weight of evidence is expressed as a range, for example, B2/C, the hazard ranking is based on the higher weight-of-evidence group.

s This particular compound is not classified due to the inadequate nature or nonexistence of data. However, there is a potential of its being converted into a carcinogenic form when released into the environment. For reportable quantity ranking purposes it should be considered as having a weight of evidence similar to that of the known carcinogenic form.

The basis for the Agency's determination that lead and lead compounds are potential carcinogens is undergoing review by EPA's Science Advisory Board. No hazard ranking will be assigned to these compounds at this time.

CHEMICAL-SPECIFIC FOOTNOTES

d Arsenic--The weight of evidence for the carcinogenicity of inorganic arsenic compounds is based on positive human studies in which exposure was by either water or air. The weight of evidence is group A. The exact species of inorganic arsenic that is directly carcinogenic to humans is not known, but it is assumed that since arsenic is chemically convertible among the chemical species both in vitro and in vivo, that all inorganic species of arsenic are of equal concern. The potency factor is the same as that given for "arsenic" (potency factor = 142.31). Arsenic trioxide and potassium arsenite are classified as having sufficient human evidence because human studies that specifically identify those compounds have been conducted and show sufficient evidence of causal association.

g Chromium metal--The latest Health Assessment Document on Chromium (EPA-600/8-83-014F, August 1984) states that chromium metal is biologically inert and has not been reported to produce toxic effects or other harmful effects in man (p. 7-1).

h Chromium compounds (hexavalent)--Grouping is based on weight of evidence for chromate production workers and animal data which indicate that the inhalation of hexavalent chromium is carcinogenic. The potency estimate is based on epidemiological data for the inhalation of hexavalent chromium by chromate workers (potency factor = 388.99, weight-of-evidence group A).

i Benzo(b)fluoranthene--Calculated, using the potency factor estimate for benzo(a)pyrene as a reference.

k Cadmium weight of evidence and potency are based on epidemiology data for cadmium workers exposed to cadmium oxide and/or cadmium fume. Although human data for cadmium salts are lacking, due to the responsiveness of animals to soluble cadmium compounds, especially cadmium chloride, the weight of evidence for cadmium acetate, bromide and chloride are considered to be the same as those cadmium compounds to which workers are exposed.

n Chloromethyl methyl ether [CMME]--Technical grade chloromethyl methyl ether is contaminated with 1% - 8% bis(chloromethyl)ether which is a known human carcinogen. Hence the human evidence for this compound and the hazard ranking is based on the evidence for bis(chloromethyl)ether.

p Asbestos--A potency factor estimate for asbestos is inappropriate here because the carcinogenic potential of asbestos is related to specific fiber shapes, sizes, and atmospheric concentrations. Air concentrations are usually measured either as a number of fibers or mass. However, no direct relationship exists between air, fiber/ml (75 microns) concentrations (by the phase contrast light microscope method) and mass concentrations in mg/m^3 (determined by electron microscopy). The relationship depends on the type of environmental sample, the type of asbestos in the air, and the size of the fibers. As a delibrate policy choice, asbestos is assigned a "HIGH" hazard ranking, as are most group "A" substances.

t PCBs--The Aroclors are mixtures of polychlorinated biphenyls (PCBs). The manufacturing process for commercial PCB products, such as the Aroclors, yields products composed of a mixture of 20-60 different PCB compounds. Individual lots of Aroclors of the same average chlorine content may differ greatly in both their components and amount of each component. Only Aroclors 1254 and 1260 have been tested for carcinogenic potential and both produce a positive response. Therefore, for the purpose of RQ hazard ranking, all Aroclors are considered to have carcinogenic potential similar to Aroclor 1254, and Arocolor 1260.

u Beryllium--Every soluble beryllium compound that has been tested, including beryllium sulfate, fluoride, oxide, phosphate, as well as beryl ore, zinc beryllium silicate, and beryllium metal have been shown to be carcinogenic. It is therefore considered highly likely that all soluble forms of beryllium are carcinogenic in animals. The potency factor for all soluble forms of beryllium is based on beryllium sulfate exposure in rats. It is believed that these forms of beryllium would pose a similar hazard to humans. The potency factor for beryllium metal is based on human occupational exposure to much less soluble forms of beryllium, mostly beryllium oxides.

v Benzo(a)pyrene--This compound is generally found in the environment as part of a complex mixture of polycyclic aromatic hydrocarbons. Benzo(a)pyrene has been found to be carcinogenic in animals and thus its presence in the mixtures usually indicates the presence of a known animal carcinogen. Many mixtures containing benzo(a)pyrene have also been causally related to human cancer, e.g., soots, tars, coke oven emissions, cigarette smoke. Therefore, benzo(a)pyrene should be treated as a human carcinogen.

x Creosote--There are no adequate studies of workers exposed to creosote wood preservatives. It has been demonstrated that chimney sweeps exposed to the creosote from the burning of wood or coal have an elevated risk of cancer. In addition, creosote, including creosote wood preservative, contains many of the compounds in other polycyclic aromatic hydrocarbon mixtures such as roofing tar pitch and coke oven emissions that have been found to be carcinogenic.

y Lead phosphate--The animal evidence is based in part on consistent findings for other inorganic lead salts.

z N-Nitrosomethylvinylamine--No control data for animal studies exist. However, based on more than one study and structure-activity relationship with other nitrosamines, the weight of evidence is considered to be sufficient.

z2 Melphalan--The "limited" designation given to the human evidence for carcinogenicity is based only upon three independent series of cases of multiple myelomas that were treated with melphalan. The case studies represent meager evidence of the carcinogenicity of melphalan and hence the evidence is less than "limited" but greater than "inadequate."

z3 Dinitrotoluene--In the absence of analytical data, it should be considered that the mixture contains 2,4-dinitrotoluene which is a potential human carcinogen. Therefore, for hazard ranking purposes, the mixture should be considered as hazardous as 2,4-dinitrotoluene.

z4 Trichlorophenol--In the absence of analytical data, it should be considered that the mixture contains 2,4,6-trichlorophenol which is a potential human carcinogen. Therefore, for hazard ranking purposes, the mixture should be considered as hazardous as 2,4,6-trichlorophenol.

z7 Nickel--The latest Health Assessment Document on Nickel states that the nickel ion (Ni+2) could be the ultimate carcinogenic form of nickel. Although this is unproven, it is considered prudent to make this assumption for covalent nickel (forms that generate Ni+2) and nickel salts. Proven carcinogenic forms of nickel are nickel refinery dust and nickel subsulfide (both in man) and nickel carbonyl (demonstrated in test animals). The former two substances are in weight-of-evidence group A, while the latter substance is in weight-of-evidence group B2. The salts of nickel show some carcinogenic activity. The testing of these nickel salts is inc nclusive for

assessment of cancer at this time due to limitations of the data base on these nickel salts, but since there is some cancer activity it is recommended by the HHAG that the hazard ranking under CERCLA be reported as "LOW." This "LOW" hazard ranking reflects the current data base on the nickel salts.

z9 Organic arsenic compounds are considered to be chemically different from the inorganic arsenic compounds such that they are assessed for carcinogenicity separately from the inorganic arsenic compounds. There are no data (weight-of-evidence group D) implicating organic arsenic compounds so that the carcinogenicity is indeterminate at this time.

z-10 Pentachloronitrobenzene - The potency estimate is for technical grade pentachloronitrobenzene, which contains the probable human carcinogen hexachlorobenzene.

NOTE: The gaps in the letters assigned to the footnotes in this table exist so that consistency with the numbers assigned to the footnotes in the summary table in OHEA-C-073 (Appendix A in "Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, (Proposed Rulemaking)," Volume 3, March 1985), is maintained.