METHODOLOGY FOR RANKING THE DEGREE OF HAZARD ASSOCIATED WITH EXPOSURE TO CARCINOGENS AND OTHER TOXIC CHEMICALS[a]

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I. INTRODUCTION

Inadvertent exposures of populations to hazardous chemicals make it necessary for public health officials to have immediate knowledge of the severity of potential effects and the doses that cause the effects observed. A hazard index has been developed in response to the need to establish a rating scheme to characterize hazardous chemicals according to the severity of disease and the associated hazards, and to prescribe quantities of hazardous chemicals which, when spilled, must be reported to the U.S. Environmental Protection Agency. About 200 potential carcinogens and 200 chemicals associated with other diseases have been evaluated. The hazard index for potential carcinogens couples the weight of evidence indicating potential carcinogenicity with the potency of the chemical to rate the relative cancer hazard. Similarly, the hazard index for chemicals that may cause other diseases couples rating factors for the severity of disease with the dose which causes the onset of disease to rate the relative hazards of these chemicals. These hazard indexes and the data for the chemicals thus far evaluated may have more general applications in assessing chemical risks to the public in response to accidental exposures.

Toxicity indexes, such as lethal dose for 50% of animals (LD_{50}) and no-observed-effect-level (NOEL) can be used in the setting of permissible levels of harmful substances in the environment or for setting priorities of concern of harm to human health or the environment. Hazard index can be defined as the overall indicator of potential harm of a hazardous substance to humans and the environment. Hazard indexes can be estimated by taking into consideration all parameters related to the fate, effects, and dose-response characteristics of the hazardous substances. Thus the chemical structure; physicochemical properties; mechanisms of action; chemical, biological and environmental transformation and

transport; and toxicity indexes are important parameters for estimating hazard indexes of chemicals in the environment.

Some of the above parameters can be estimated from experimental data, while others may have to be estimated using statistical techniques. The extent and the form of hazard indexes depends on the purposes for which they are used.

This paper describes the use of a systemic (chronic) toxicity index and a carcinogenicity index in setting reportable quantities (RQ) under Section 101(14) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA or "Superfund") of 1980. Section 103 of CERCLA requires immediate notification from any person in charge of a vessel or an offshore or onshore 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 one pound unless a different RQ has been established pursuant to Section 311(b)(4) of the Federal Water Pollution Control Act. These are statutory RQs for the CERCLA Section 101(14) hazardous substance unless and until the Administrator of EPA promulgates regulations establishing different quantities to be reported when released. CERCLA also permits EPA to establish a single RQ for each hazardous substance, regardless of the environmental medium into which the substance is released.

The Emergency Response Division of the Office of Emergency and Remedial Response proposed to use "Selected Criteria Processing" (SCP) to adjust the statutory RQs. SCP includes ignitability, reactivity, carcinogenicity, aquatic toxicity, acute mammalian toxicity (oral, dermal, inhalation) and chronic toxicity as the six primary criteria for adjusting RQs. The RQ for each hazardous substance is the lowest numerical value of all applicable RQs derived from the primary criteria. The RQ is then readjusted using biodegradability, hydrolysis, and photolysis as secondary criteria.

II. TOXICITY INDEX OF POTENTIALLY CARCINOGENIC SUBSTANCES

Hazardous substances suspected of carcinogenic potential can be ranked using as toxicity index the level of evidence in support of their carcinogenicity and the strength (potency factor) they exhibit in inducing carcinogenic responses. Three types of evidence can be used to evaluate a substance's carcinogenic hazard potential. They are: (1) epidemiologic evidence; (2) experimental evidence derived from long-term animal bioassays; (3) supportive or suggestive evidence from short-term tests, metabolism and pharmacokinetics, and structure-activity correlations.

(1). The Weight-of-Evidence Approach to Evaluating the Evidence for Carcinogenicity

The weight-of-evidence can be defined as the strength of evidence indicating potential carcinogenicity, not relative carcinogenic activity or potency of the agent. Thus, an overall decision as to whether an agent may pose a carcinogenic hazard to humans should be based on a careful evaluation of all relevant scientific data, including the design and conduct of the study and the nature and type of responses. In the most complete form, a weight-of-evidence determination should be made from a consideration of the strengths and weaknesses of each piece of evidence, including epidemiological investigations, long-term animal studies, and supporting information.

A. Primary Sources of Information

1. Epidemiology Studies

Human information can provide direct evidence of the association of increases in tumor incidence or mortality in humans with exposure to chemicals. Well designed and conducted analytical epidemiology studies, especially case-control and cohort investigations, are of prime importance; descriptive studies and case reports provide ancillary information.

Important elements in interpreting the likely causality of epidemiological observations include the magnitude of the risk estimates (strength of the associations); the likelihood of their being due to chance (statistical significance); the rigor of the study design to avoid various kinds of bias, including those related to selection, confounding, classification, and measurement; the dose-response relationships; the temporal relationships between exposure and disease; the specificity of the associations; their biological plausibility; and the reproducibility of the findings.

2. Long-Term Animal Studies

Confidence in the results of animal experiments is gained when carcinogenic effects have been confirmed in repeated experiments, in different animal strains or species, or in different dose groups or sexes within a given study. Other measures include demonstration of a highly significant increase in tumors, the presence of tumors at multiple anatomical sites, the histological types of tumors present, and the shortening of tumor latency in treated groups as compared with controls. Dose-response relationships also support a conclusion of carcinogenicity.

In reaching an overall evaluation of the experimental animal evidence, each long-term study needs to be reviewed with regard to the following factors:

a) tumor incidence

b) tumor development

c) preneoplastic lesions

d) target-organ toxicity

e) other relevant biological and chemical information.

B. Supportive Information

1. Short-Term Testing

Appropriate in vivo and in vitro short-term tests provide ancillary empirical and potentially mechanistic information bearing on the carcinogenicity of an agent.

2. Biological Test Results

Many toxicological, physiological, and biochemical observations, such as comparative metabolism and pharmacokinetic studies and certain mechanistic investigations, can contribute to a determination of carcinogenicity.

3. Structure-Activity Relationships

General information bearing on the biological reactivity of compounds chemically related to the agent under investigation is useful in the evaluation of the carcinogenicity of the agent.

(2). Summarizing the Weight-of-Evidence for Carcinogenicity Using the International Agency for Research on Cancer (IARC) Criteria

After the data have been evaluated, the weight-of-evidence for carcinogenicity may be classified according to the IARC criteria (see Appendix I).

Weight-of-Evidence Statement Using the IARC Criteria

Level of evidence from experimental animal studies

Level of evidence from human studies

IARC grouping

(3). Potency Factor Estimates

After the decision has been made that a compound has the potential for causing cancer in humans, attempts will be made to estimate a potency factor F defined as $1/ED_{10}$. ED_{10} is the estimated dose associated with a lifetime cancer

risk of 10%. The potency factor F will be used together with the qualitative weight-of-evidence for carcinogenicity in the ranking of the carcinogenic hazard potential of the chemicals.

Dose-Response Data That Can Be Used For Potency Factor Estimates

Animal Data

Human Data

The potency factor F is used in place of the potency factor $q_1^{*\dagger}$, which the Carcinogen Assessment Group (CAG) normally uses in the estimation of risk, because the objective here is to rank chemicals for their potential to cause carcinogenic harm and not to estimate risk associated with a particular level of exposure. Furthermore, it is advantageous to use the potency factor F because it can be estimated without the use of the many assumptions that are required for calculating and/or using q_1^*. This is possible because the dose associated with a lifetime cancer risk of 10% is usually within or close to the experimentally observable range.

Other advantages of the potency factor F are:

a. It is relatively insensitive to the choice of the dose-response extrapolation model.

b. The point estimation of ED_{10}, which has some optimal statistical properties, can be used to calculate F. Therefore, it is not necessary to use the upper-bound estimate, which is more stable for estimating risk at very low doses.

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† q_1^* is the upper confidence limit for the linear coefficient in the multistage model. See Appendix II, Description of the Quantitative Risk Extrapolation Models Used by the U.S. Environmental Protection Agency.

(4). Potency Factor Grouping

The potency factor estimates are indicators of relative magnitude (potency) to cause carcinogenic harm. These numerical values are useful tools for setting toxicity indexes.

When the relative potency factors are estimated by the procedure outlined in (3) above, they can be aggregated into four groups. Those chemicals with the highest potency factor can be placed in group 1, intermediate potency factor chemicals can be placed in group 2, low potency factor chemicals can be placed in group 3, and the lowest potency factor chemicals can be placed in group 4. The method used for grouping 192 chemicals for the RQ project is to place chemicals with potency factors (F) above 100 into group 1; chemicals with potency factors from 10-100 into group 2; chemicals with potency factors from 1-10 into group 3; and chemicals with potency factors below 1 into group 4. The major disadvantage of this method is that the grouping of chemicals with borderline potencies between groups is arbitrary. While toxicologic information could be used to aid in placement, the process would still be somewhat subjective. Another method of grouping is analysis for clustering in addition to potency numerical value cut-off points.

(5). Cancer Hazard Ranking Based on Combined Qualitative and Quantitative Assessment

The culmination of the hazard ranking process described in this study is accomplished by combining the qualitative weight-of-evidence for carcinogenicity with the potency group placement to arrive at a final carcinogenicity index for each chemical. Substances are ranked as posing a high, medium, or low cancer hazard according to the following scheme:

Carcinogenicity Indexing for Reportable Quantities under CERCLA

IARC Group	Potency Group 1 F>100	2 F = 10-100	3 F = 1-10	4 F<1
1	HIGH	HIGH	MEDIUM	LOW
2A	HIGH	MEDIUM	MEDIUM	LOW
2B	HIGH	MEDIUM	LOW	LOW
3	Cannot Be Ranked in General*			

The hazard rankings for about 200 suspected carcinogens are presented in Table I (page 12).

III. TOXICITY INDEX FOR SUBSTANCES WITH SYSTEMIC (CHRONIC) TOXICITY POTENTIAL

The toxicity indexes on chronic toxicity reflect two primary attributes of each chemical:

1. The minimum effective dose (MED) levels for chronic exposures (mg/day for a 70-kg man) via alternative environmental media (air, water, etc.).
2. Type of effect (liver necrosis, teratogenicity, etc.).

(1) The Minimum Effective Dose (MED)

The dose rating for a given chemical is based upon the MED transformed to values ranging from 1-10 using the graph in Figure 1 (page 27). Substances having an effect at a low dose (i.e., those that are more highly toxic) will be given a high rating on this graph, while those requiring a high dose (less toxic) will

* The group 3 category includes chemicals for which the evidence from animal studies is limited or inadequate, and for which there is no human evidence. For those studies with reliable dose-related data, a potency estimate is determined and a hazard ranking is performed.

be given a low rating. The rating values range from 1 to 10.

(2) Rating Potentially Hazardous Chemicals According to the Severity of Disease

The effect rating for an individual chemical will range from 1 to 10 depending on severity (Table II, page 28), with 10 being the most severe. These values must be assigned on a chemical-by-chemical basis.

(3) Toxicity Hazard Ranking Based on the MED and the Severity of Disease

A final Composite Score (CS) which is the chronic toxicity index is determined by multiplying the dose rating by the effect rating. The possible range of CSs is thus 1 to 100. Using this scheme, only those compounds inducing what are judged to be the most severe effects at low levels of exposure would fall into the high toxicity index category.

The following step-by-step text gives additional details for this procedure:

1. Identify subchronic or chronic no observed adverse effect levels (NOAELs), lowest observable effect level (LOAELs) or frank effect level (FELs) based on animal or human data from the available literature. Note the dose/exposure and the effect.
2. Convert all NOAELs, LOAELs and FELs to units of mg/kg/day. Inhalation, dietary or drinking water exposure data will be converted to units of mg/kg/day doses based on the methods outlined previously (U.S. EPA, 1980).
3. If the NOAEL, LOAEL or FEL is based on subchronic exposure, a corresponding chronic value will be estimated by dividing the subchronic value by 10 or less.
4. The MEDs based on animal data will be converted to human MEDs using the cubed root of the body weight ratio approximation,

and the subsequent value will be multiplied by 70 kg to put the MED in units of mg/day for a 70 kg man.**

5. Assign a dose rating value (RV_d) to the dose associated with the MED as described in Figure 1.

6. Assign an effect rating value (RV_e) to the effect associated with the MED as described in Table II.

7. Calculate the SC as:

$$CS = RV_d \times RV_e$$

8. If more than one MED can be used to calculate a CS for a route of exposure (oral or inhalation), the MED for the route of exposure which will be considered in setting the RQ will be selected by the following criteria:

   - o If adequate chronic data are available, disregard MEDs based on subchronic data.
   - o If more than one MED remains, select the MED which is based on the "best" data.
   - o If considerations of data quality do not lead to the selection of a single MED, the MED resulting in the highest CS for a given route will be used.

9. Having selected a single MED and derived a CS for each route of exposure, the MED used to determine the RQ will be the MED from the route of exposure with the highest CS.

**This is based on the assumption that metabolic rate is a function of body weight to the two-thirds power. Thus, the human dose, assuming a body weight of 70 kg, is equal to:

$$\text{animal dose} \times \left(\frac{70\ \text{kg}}{\text{animal weight}}\right)^{2/3}.$$

This equation can be rearranged so that the human dose in mg/day equals:

$$\text{animal dose} \times \frac{\text{animal weight}}{70\ \text{kg}}^{1/3} \times 70\ \text{kg}.$$

10. The reportable quantities (RQs) are then assigned based on the following relationship to CS:

Composite Score (or chronic toxicity index)	RQ (lbs)
81-100	1
41-80	10
21-40	100
6-20	1000
1-5	5000

The composite scores for about 200 potentially hazardous chemicals are presented in Table III (page 29).

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Acenaphthene	(83-32-9)	Inadequate	Inadequate	3	NA	NA	b
Acenaphthylene	(208-96-8)	Inadequate	Inadequate	3	NA	NA	b
2-Acetylaminofluorene	(53-96-3)	Inadequate	Sufficient	2B	32.00	2	Medium
Acrylonitrile	(107-13-1)	Limited	Sufficient	2A	0.06	4	Low
Aflatoxin B_1	(1162-65-8)	Limited	Sufficient	2A	10,000.00	1	High
Aldrin	(309-00-2)	Inadequate	Limited	2B	63.00	2	Medium
4-Aminobiphenyl	(92-67-1)	Sufficient	Sufficient	1	87.00	2	High
Amitrole	(61-82-5)	Inadequate	Sufficient	2B	9.20	3	Low
Ammonium bichromate	(7789-09-5)	Inadequate	Inadequate	1[g]	g	NA	Medium
Ammonium chromate	(7788-98-9)	Inadequate	Inadequate	1g	g	NA	Medium
Anthracene	(120-12-7)	Inadequate	Inadequate	3	NA	NA	b
Arsenic and Compounds	(7440-38-2)	Sufficient	Inadequate	1	130.00	NA	High
Arsenic acid	(7778-39-4)	Limited	Inadequate	2A[d]	d	NA	High
Arsenic disulfide	(1303-32-8)	Limited	Inadequate	2Ad	d	NA	High
Arsenic trichloride	(7784-34-1)	Limited	Inadequate	2A[d]	d	NA	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Arsenic pentoxide	(1303-28-2)	Limited	Inadequate	2A[d]	d	NA	High
Arsenic trioxide	(1327-53-3)	Sufficient	Inadequate	1	130.00	1	High
Arsenic trisulfide	(1303-33-9)	Limited	Inadequate	2A[d]	d	NA	High
Asbestos	(1332-21-4)	Sufficient	Sufficient	1	p	p	p
Auramine	(2465-27-2)	Inadequate	Sufficient	2B	1 20	3	Low
Azaserine	(115-02-6)	Inadequate	Sufficient	2B	e	NA	e
Aziridine	(151-56-4)	Inadequate	Limited	2B	310.00	1	High
Benzene	(71-43-2)	Sufficient	Limited	1	0.26	4	Low
Benzidine and its salts	(92-87-5)	Sufficient	Sufficient	1	1.90	3	Medium
Benzo[a]pyrene	(50-32-8)	Inadequate	Sufficient	2B	500.00	1	High
Benzo[b]fluoranthene	(205-99-2)	Inadequate	Sufficient	2B	150.00[1]	1	High
Benzo[ghi]perylene	(191-24-2)	Inadequate	Inadequate	3	NA	NA	b
Benzo[k]fluoranthene	(207-08-9)	Inadequate	Limited	3[r]	NA	NA	c
Benzyl Chloride	(100-44-7)	Inadequate	Limited	3[r]	NA	NA	c
Benz[a]anthracene	(56-55-3)	Inadequate	Sufficient	2B	21.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Benz[c]acridine	(225-51-4)	Inadequate	Limited	3[r]	1500.00	1	Medium
Beryllium and Compounds	(7440-41-7)	Limited	Sufficient	2A[e]	17.00[j]	2	Medium
Bis(2-chloroethyl)ether	(111-44-4)	Inadequate	Sufficient	2B	13.00	2	Medium
Bis(chloromethyl)ether	(542-88-1)	Sufficient	Sufficient	1	1900.00	1	High
Cacodylic acid	(75-60-5)	Inadequate	Inadequate	3	NA	NA	b
Cadmium and Compounds	(7440-43-9)	Limited	Sufficient	2A[f]	60.00[k]	2	Medium
Cadmium acetate	(543-90-8)	Limited	Sufficient	2A[f]	k	NA	Medium
Cadmium bromide	(7789-42-6)	Limited	Sufficient	2A[f]	k	NA	Medium
Cadmium chloride	(10108-64-2)	Limited	Sufficient	2A[f]	k	NA	Medium
Cadmium sulfate	(10124-36-4)	Limited	Sufficient	2A[f]	k	NA	Medium
Calcium arsenate	(7778-44-1)	Limited	Inadequate	2A[d]	d	NA	High
Calcium arsenite	(52740-16-6)	Limited	Inadequate	2A[d]	d	NA	High
Calcium chromate	(13765-19-0)	Sufficient	Sufficient	1[g]	g	NA	Medium
Carbon tetrachloride	(56-23-5)	Inadequate	Sufficient	2B	39.00	2	Medium
Chlorambucil	(305-03-3)	Sufficient	Sufficient	1	a	NA	c

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Chlordane	(57-74-9)	Inadequate	Limited	3[r]	83.00	2	Low
Chlornaphazine	(494-03-1)	Sufficient	Limited	1	[a]	NA	c
Chlorobenzilate	(510-15-6)	Inadequate	Sufficient	2B	1.60	3	Low
Chloroform	(67-66-3)	Inadequate	Sufficient	2B	2.00	3	Low
Chloromethyl methyl ether (technical grade)[n]	(107-30-2)	Sufficient[n]	Sufficient[n]	1	[n]	n	High[n]
Chloromethyl methyl ether	(107-30-2)	Inadequate	Inadequate	3	NA	NA	b
4-Chloro-o-toluidine hydrochloride	(3165-93-3)	Inadequate	Sufficient	2B	0.07	4	Low
Chromium and Compounds	(7440-47-3)	Sufficient	Sufficient	1[g]	1.90[g]	3	Medium
Chromic acetate	(1066-30-4)	Inadequate	Inadequate	1[g]	[g]	NA	b
Chromic acid	(7738-94-5)	Limited	Inadequate	1[g]	[g]	NA	Medium
Chromic sulfate	(10101-53-8)	Inadequate	Inadequate	1[g]	[g]	NA	b
Chromous acid	(10049-05-5)	Inadequate	Inadequate	1[g]	[g]	NA	b
Chrysene	(218-01-9)	Inadequate	Sufficient	2B	5.00[l]	3	Low
Creosote	(8001-58-9)	Limited	Sufficient	2A	58.00	2	Medium
Cupric acetoarsenite	(12002-03-8)	Inadequate	Inadequate	2A[d]	[d]	NA	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Cyclophosphamide	(50-18-0)	Sufficient	Sufficient	1	18.00	2	High
Daunomycin	(20830-81-3)	Inadequate	Sufficient	2B	[a]	NA	[c]
DDD	(72-54-8)	Inadequate	Sufficient	2B	0.10	4	Low
DDE	(72-55-9)	Inadequate	Sufficient	2B	3.80	3	Low
DDT	(50-29-3)	Inadequate	Sufficient	2B	5.60	3	Low
Diallate	(2303-16-4)	Inadequate	Sufficient	2B	2.40	3	Low
2,4-Diaminotoluene	(95-80-7)	Inadequate	Sufficient	2B	3.00	3	Low
1,2,7,8-Dibenzopyrene	(189-55-9)	Inadequate	Sufficient	2B	[a]	NA	[c]
Dibenz[a,h]anthracene	(53-70-3)	Inadequate	Sufficient	2B	1000.00	1	High
1,2-Dibromo-3-chloropropane	(96-12-8)	Inadequate	Sufficient	2B	170.00	1	High
Dibutylnitrosamine	(924-16-3)	Inadequate	Sufficient	2B	34.00	2	Medium
3,3'-Dichlorobenzidine	(91-94-1)	Inadequate	Sufficient	2B	7.10	3	Low
1,2-Dichloroethane	(107-06-2)	Inadequate	Sufficient	2B	0.23	4	Low
1,1-Dichloroethylene	(75-35-4)	Inadequate	Limited	3[f]	4.60	3	Low
Dichlorophenylarsine	(696-28-6)	Inadequate	Inadequate	3	NA	NA	[b]

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TABLE 1. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Dieldrin	(60-57-1)	Inadequate	Sufficient	2B	130.00	1	High
Diepoxybutane	(1464-53-5)	Inadequate	Sufficient	2B	8.50	3	Low
Diethanolnitrosamine	(1116-54-7)	Inadequate	Sufficient	2B	17.00	2	Medium
Diethyl Arsine	(692-42-2)	Inadequate	Inadequate	3	NA	NA	b
1,2-Diethylhydrazine	(1615-80-1)	Inadequate	Sufficient	2B	a	NA	c
Diethylnitrosamine	(55-18-5)	Inadequate	Sufficient	2B	1000.00	1	High
Diethylstilbestrol	(56-53-1)	Sufficient	Sufficient	1	7900.00	1	High
Dihydrosafrole	(94-58-6)	Inadequate	Sufficient	2B	1.10	3	Low
3,3'-Dimethoxybenzidine	(119-90-4)	Inadequate	Sufficient	2B	0.01	4	Low
Dimethyl sulfate	(77-78-1)	Inadequate	Sufficient	2B	a	NA	c
Dimethylaminoazobenzene	(60-11-7)	Inadequate	Sufficient	2B	280.00	1	High
7,12-Dimethylbenz[a] anthracene	(57-97-6)	Inadequate	Sufficient	2B	200,000.00	1	High
Dimethylcarbamoyl chloride	(79-44-7)	Inadequate	Sufficient	2B	510.00	1	High
1,1-Dimethylhydrazine	(57-14-4)	Inadequate	Sufficient	2B	13.00	2	Medium
1,2-Dimethylhydrazine	(540-73-8)	Inadequate	Sufficient	2B	870.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Dimethylnitrosamine	(62-75-9)	Inadequate	Sufficient	2B	29.00	2	Medium
2,3-Dinitrotoluene	(602-01-7)	Inadequate	Inadequate	3	NA	NA	b
2,4-Dinitrotoluene	(121-14-2)	Inadequate	Sufficient	2B	3.80	3	Low
2,5-Dinitrotoluene	(619-15-8)	Inadequate	Inadequate	3	NA	NA	b
2,6-Dinitrotoluene	(606-20-2)	Inadequate	Limited	3[r]	NA	NA	a
3,4-Dinitrotoluene	(610-39-9)	Inadequate	Inadequate	3	NA	NA	b
1,4-Dioxane	(123-91-1)	Inadequate	Sufficient	2B	0.03	4	Low
N,N-Diphenylamine	(122-39-4)	Inadequate	Inadequate	3	NA	NA	b
1,2-Diphenylhydrazine	(122-66-7)	Inadequate	Sufficient	2B	4.60	3	Medium
Dipropylnitrosamine	(621-64-7)	Inadequate	Sufficient	2B	a	NA	a
Epichlorohydrin	(106-89-8)	Inadequate	Sufficient	2B	0.16	4	Low
Ethyl Methanesulfonate	(62-50-0)	Inadequate	Sufficient	2B	140.00	1	High
Ethylene dibromide	(106-93-4)	Inadequate	Sufficient	2B	13.00	2	Medium
Ethylene Oxide	(75-21-8)	Limited	Limited	2A	6.00	3	Medium
Ethylenethiourea	(96-45-7)	Inadequate	Sufficient	2B	0.97	4	Low

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
1-Ethyl-1-nitrosourea	(759-73-9)	Inadequate	Sufficient	2B	8.70	3	Low
Ferric dextran	(9004-66-4)	Inadequate	Sufficient	2B	o	NA	b
Fluoranthene	(206-44-0)	Inadequate	Inadequate	3	NA	NA	b
Fluorene	(86-73-7)	Inadequate	Inadequate	3	NA	NA	b
Glycidaldehyde	(765-34-4)	Inadequate	Sufficient	2B	1.20	3	Medium
Heptachlor	(76-44-8)	Inadequate	Sufficient	2B	36.00	2	Medium
Heptachlor Epoxide	(1024-57-3)	Inadequate	Sufficient	2B	36.00[q]	2	Medium
Hexachlorobenzene	(118-74-1)	Inadequate	Sufficient	2B	12.00	2	Medium
Hexachlorobutadiene	(87-68-3)	Inadequate	Limited	3[r]	0.50	4	Low
α-Hexachlorocyclohexane	(319-84-6)	Inadequate	Sufficient	2B	211.00	1	High
β-Hexachlorocyclohexane	(319-85-7)	Inadequate	Limited	3[r]	1.70	3	Low
γ-Hexachlorocyclohexane	(58-89-9)	Inadequate	Limited	2B	1.70	3	Low
δ-Hexachlorocyclohexane	(319-86-8)	Inadequate	Inadequate	3	NA	NA	b
Hexachloroethane	(67-72-1)	Inadequate	Limited	3[r]	0.27	4	Low
Hydrazine	(302-01-1)	Inadequate	Sufficient	2B	100.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Indeno(1,2,3-cd)pyrene	(193-39-5)	Inadequate	Limited	2B	a	NA	c
Iodomethane	(77-88-4)	Inadequate	Limited	3[r]	NA	NA	c
Isosafrole	(120-58-1)	Inadequate	Limited	3[r]	0.54	4	Low
Kepone	(143-50-0)	Inadequate	Sufficient	2B	44.00	2	Medium
Lasiocarpine	(303-34-4)	Inadequate	Sufficient	2B	38.00	2	Medium
Lead acetate	(301-04-2)	Inadequate	Sufficient	2B	7.30	3	Low
Lead arsenate	(3687-31-8)	Limited	Inadequate	2A[d]	d	NA	High
Lead phosphate	(7446-27-7)	Inadequate	Limited	2B	a	NA	c
Lead subacetate	(1335-32-6)	Inadequate	Sufficient	2B	0.17	4	Low
Lithium chromate	(14307-35-8)	Inadequate	Inadequate	1[g]	g	NA	Medium
3-Methylcholanthrene	(56-49-3)	Inadequate	Sufficient	2B	12.00	3	Medium
4,4'-Methylene-bis-(2-chloroaniline)	(101-14-4)	Inadequate	Sufficient	2B	1.70	3	Low
Methylnitrosourea	(684-93-5)	Inadequate	Sufficient	2B	12,000.00	1	High
Methylthiouracil	(56-04-2)	Inadequate	Sufficient	2B	30.00	2	Medium
Methylvinylnitrosamine	(4549-40-0)	Inadequate	Sufficient	2D	a	NA	c

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
N-Methyl-N'-nitro-N-nitrosoguanidine	(70-25-7)	Inadequate	Sufficient	2B	58.00	2	Medium
Mitomycin C	(50-07-7)	Inadequate	Sufficient	2B	[a]	NA	c
Mustard gas	(505-60-2)	Sufficient	Limited	1	[a]	NA	c
1-Naphthylamine	(134-32-7)	Inadequate	Limited	3[r]	NA	NA	c
2-Naphthylamine	(91-59-8)	Sufficient	Sufficient	1	5.20	3	Medium
Nickel and Compounds	(7440-02-0)	Limited	Sufficient	2A[h]	1.10[1]	3	Medium
Nickel Ammonium Sulfate	(15699-18-0)	Limited	Limited	2A[h]	1	NA	Medium
Nickel carbonyl	(13463-39-3)	Limited	Sufficient	2A[h]	1	NA	Medium
Nickel chloride	(7718-54-9)	Limited	Limited	2A[h]	1	NA	Medium
Nickel cyanide	(557-19-7)	Limited	Limited	2A[h]	1	NA	Medium
Nickel hydroxide	(12054-48-7)	Limited	Limited	2A[h]	1	NA	Medium
Nickel nitrate	(13478-00-7)	Limited	Limited	2A[h]	1	NA	Medium
Nickel subsulfide	(12035-72-2)	Limited	Sufficient	2A[h]	1.10[1]	1	Medium
Nickel sulfate	(7786-81-4)	Limited	Limited	2A[h]	1	NA	Medium
Nitrosomethylurethane	(615-53-2)	Inadequate	Sufficient	2B	2400.00	1	High

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
N-Nitrosopiperidine	(100-75-4)	Inadequate	Sufficient	2B	170.00	1	High
N-Nitrosopyrrolidine	(930-55-2)	Inadequate	Sufficient	2B	290.00	1	High
5-Nitro-o-toluidine	(99-55-8)	Inadequate	Limited	3[r]	0.53	4	Low
Pentachloronitrobenzene	(82-68-8)	Inadequate	Limited	3[r]	1.50	3	Low
Phenacetin	(62-44-2)	Inadequate	Sufficient	2B	0.02	4	Low
Phenanthrene	(85-01-8)	Inadequate	Inadequate	3	NA	NA	[b]
Phenobarbital	(50-06-6)	Inadequate	Limited	3[r]	0.75	4	Low
Phenylalanine Mustard	(148-82-3)	Sufficient	Sufficient	1	1100.00	1	High
Polychlorinated biphenyls	(1336-36-3)	Inadequate	Sufficient	2B	37.00[m]	2	Medium
Potassium arsenate	(7784-41-0)	Limited	Inadequate	2A[d]	[d]	NA	High
Potassium arsenite	(10124-50-2)	Limited	Inadequate	2A[d]	[d]	NA	High
Potassium bichromate	(7778-50-9)	Limited	Inadequate	1[g]	[g]	NA	Medium
Potassium chromate	(7789-00-6)	Limited	Inadequate	1[g]	[g]	NA	Medium
Propane sultone	(1120-71-4)	Inadequate	Sufficient	2B	37.00	2	Medium
Propyleneimine	(75-55-8)	Inadequate	Sufficient	2B	15.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
Pyrene	(129-00-0)	Inadequate	Inadequate	3	NA	NA	[b]
Saccharin	(81-07-2)	Inadequate	Limited	3[c]	0.01	4	Low
Safrole	(94-59-7)	Inadequate	Sufficient	2B	0.20	4	Low
Sodium arsenate	(7631-89-2)	Limited	Inadequate	2A[d]	[d]	NA	High
Sodium arsenite	(7784-46-5)	Limited	Inadequate	2A[d]	[d]	NA	High
Sodium bichromate	(10588-01-9)	Limited	Inadequate	1[g]	[g]	NA	Medium[e]
Sodium chromate	(7775-11-3)	Limited	Inadequate	1[g]	[g]	NA	Medium
Streptozotocin	(18883-66-4)	Inadequate	Sufficient	2B	110.00	1	High
Strontium chromate	(7789-06-2)	Inadequate	Inadequate	1[g]	[g]	NA	Medium
2,3,7,8-Tetrachloro-dibenzo-p-dioxin	(1746-01-6)	Inadequate	Sufficient	2B	120,000.00	1	High
1,1,1,2-Tetrachloroethane	(630-20-6)	Inadequate	Limited	3	0.13	4	Low
1,1,2,2-Tetrachloroethane	(79-34-5)	Inadequate	Limited	3[c]	1.70	4	Low
Tetrachloroethylene	(127-18-4)	Inadequate	Limited	3[c]	0.18	4	Low
Thioacetamide	(62-55-5)	Inadequate	Sufficient	2B	27.00	2	Medium
Thiourea	(62-56-6)	Inadequate	Sufficient	2B	80.00	2	Medium

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking
O-Tolidine	(119-93-7)	Inadequate	Sufficient	2B	27.00	2	Medium
O-Toluidine and its hydrochloride	(636-21-5)	Limited	Sufficient	2A	0.22	4	Low
Toxaphene	(8001-35-2)	Inadequate	Sufficient	2B	9.70	3	Low
1,1,2-Trichloroethane	(79-00-5)	Inadequate	Limited	3[r]	0.30	4	Low
Trichloroethylene	(79-01-6)	Inadequate	Limited	3[r]	0.18	4	Low
2,4,6-Trichlorophenol	(88-06-2)	Inadequate	Sufficient	2B	0.08	4	Low
Tris(2,3-dibromopropyl) phosphate	(126-72-7)	Inadequate	Sufficient	2B	9.80	3	Low
Trypan blue	(72-57-1)	Inadequate	Sufficient	2B	0.01	4	Low
Uracil Mustard	(66-75-1)	Inadequate	Sufficient	2B	a	NA	a
Urethane	(51-79-6)	Inadequate	Sufficient	2B	0.64	4	Low
Vinyl chloride	(75-01-4)	Sufficient	Sufficient	1	0.16	4	Low

Note: The data herein without additional analysis should not be used for risk assessment purposes.

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

Chemical Name	Chemical (CAS)	Degree of Evidence Humans	Degree of Evidence Animals	Grouping Based on IARC Criteria	Potency Factor Estimate	Potency Group	Hazard Ranking

[a]Data available are inadequate for calculation of potency factor using current methodology. An appropriate method of estimating a potency factor for these types of data is currently under development by CAG.

[b]Other toxicity endpoints must be used as a basis for hazard ranking.

[c]Carcinogen hazard ranking will be possible when methodology to calculate a reasonable potency factor is developed or new data becomes available.

[d]Grouping and potency factor estimate is based on weight of evidence for arsenic and arsenic compounds in the drinking water of humans (assumed to be predominantly the trioxide).

[e]Grouping is based on weight of evidence for beryllium sulfate.

[f]Grouping is based on weight of evidence for cadmium compounds as a class.

[g]Grouping is based on weight of evidence for chromate production and animal data which indicates that hexavalent chromium is carcinogenic. The potency estimate is based on epidemeology data for total chromium exposure of chromate workers..

[h]Grouping is based on weight of evidence for nickel compounds as a class.

[i]Calculated, using the potency factor estimate for benzo[a]pyrene as a reference.

[j]Potency estimate is based on data from beryllium sulfate exposure in rats.

[k]Potency estimate is based on epidemeology data for cadmium smelters. Please note that potency estimate based on animal data would be at least 100 times higher. Please refer to OHEA document "Addendum to the Health Assessment Document for Cadmium, 1983" for details.

[l]Potency estimate is based on data for nickel subsulfide.

[m]Potency estimate is based on data for Aroclor 1260.

[n]Technical grade chloromethyl methyl ether is contaminated with bis(chloromethyl)ether, and the hazard ranking is therefore based on the evidence for bis(chloromethyl)ether.

[o]Inappropriate to group or rank for environmental considerations because available evidence is based on subcutaneous and intramuscular injection experiments.

[p]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 number of fibers or mass. However, no direct relationship exists between air fiber/ml (>5 microns) concentrations (by the phase contrast light microscope method) and mass concentrations in $\mu g/m^3$ (determined by electron microscopy). The relationship depends on the type of environment sampled, the type of asbestos in the air, and the size of the fibers.

[q]Potency factor estimate is based on data for heptachlor since heptachlor epoxide is a metabolite of heptachlor.

[r]The Group 3 category includes chemicals for which the evidence from animal studies is limited or inadequate and there is no human evidence. These are group 3 chemicals with limited animal evidence. For those with good dose-related data, a potency estimate is determined and a hazard ranking is performed.

Compounds with group 1 potency factor estimates (>100) are given "medium" hazard ranking. Compounds in potency group 2,3 or 4 are given "low" hazard rankings.

NA = Not applicable

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS (Continued)

The substances identified for re-evaluation and profile revision are:

hexachlorocyclohexane
sodium arsenite
N-nitrosodiethanolamine
DDE
dibutylnitrosamine
dipropylnitrosamine
N,N-diphenylamine
cadmium choride
amitrole
thioacetamide
N-nitrosodiethanolamine
mustard gas
phenacetin
benzene

Note: The data herein without additional analysis should not be used for risk assessment purposes.

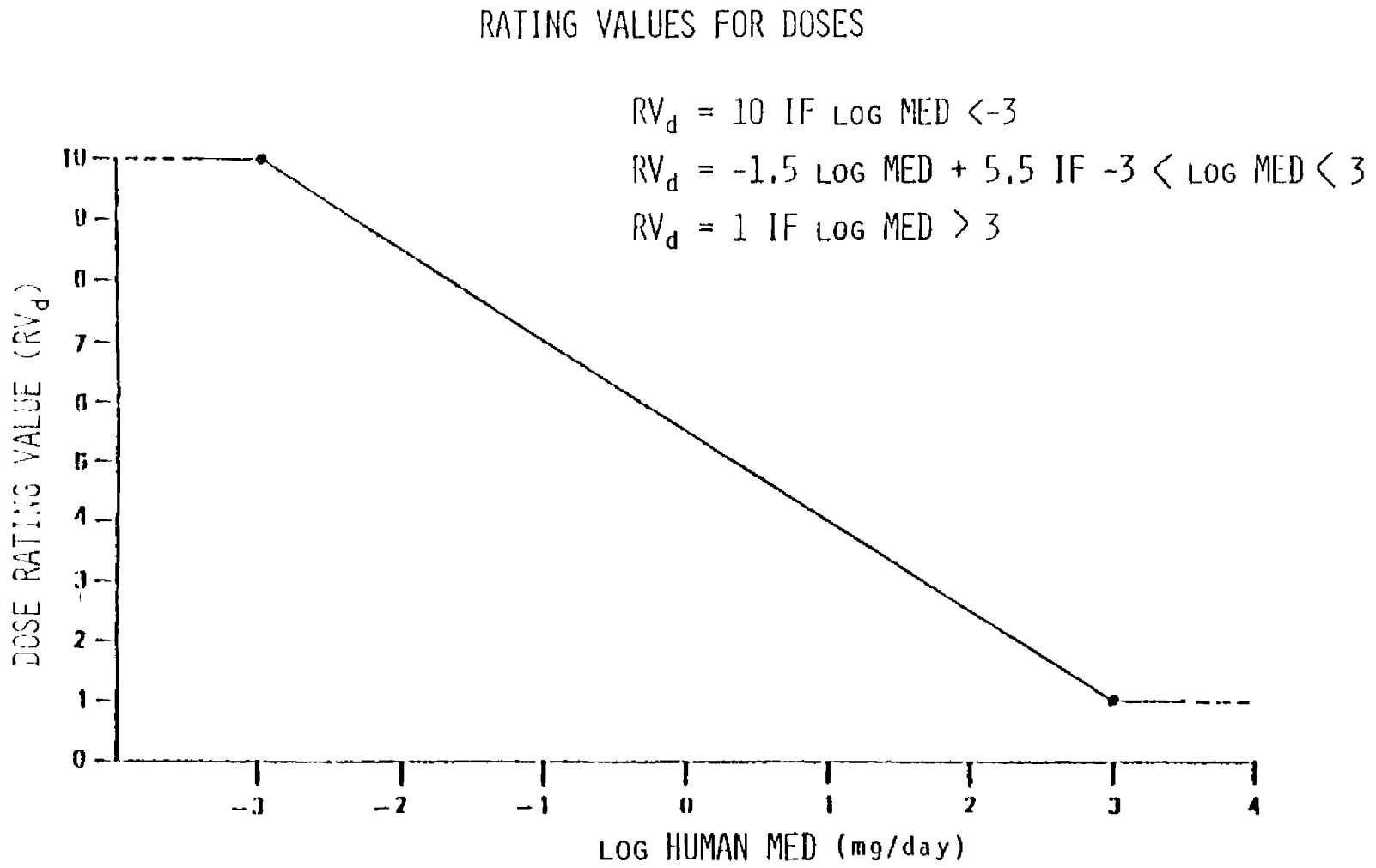

FIGURE 1. RATING VALUES FOR DOSES USED TO DERIVE REPORTABLE QUANTITIES BASED ON CHRONIC TOXICITY.

TABLE II.

Rating Values for NOAELs, LOAELs, and FELs used to Derive Reportable Quantities Based on Chronic Toxicity

RATING	EFFECT
1	ENZYME INDUCTION OR OTHER BIOCHEMICAL CHANGE WITH NO PATHOLOGIC CHANGES AND NO CHANGE IN ORGAN WEIGHTS
2	ENZYME INDUCTION AND SUBCELLULAR PROLIFERATION OR OTHER CHANGES IN ORGANELLES BUT NO OTHER APPARENT EFFECTS.
3	HYPERPLASIA, HYPERTROPHY, OR ATROPHY BUT NO CHANGE IN ORGAN WEIGHTS.
4	HYPERPLASIA, HYPERTROPHY, OR ATROPHY WITH CHANGES IN ORGAN WEIGHTS.
5	REVERSIBLE CELLULAR CHANGES: CLOUDY SWELLING, HYDROPIC CHANGE, OR FATTY CHANGES.
6	NECROSIS OR METAPLASIA WITH NO APPARENT DECREMENT OF ORGAN FUNCTION. ANY NEUROPATHY WITHOUT APPARENT BEHAVIORAL, SENSORY, OR PHYSIOLOGIC CHANGES.
7	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH A DETECTABLE DECREMENT OF ORGAN FUNCTIONS. ANY NEUROPATHY WITH A MEASURABLE CHANGE IN BEHAVIORAL, SENSORY, OR PHYSIOLOGIC ACTIVITY.
8	NECROSIS, ATROPHY, HYPERTROPHY, OR METAPLASIA WITH DEFINITIVE ORGAN DYSFUNCTION. ANY NEUROPATHY WITH GROSS CHANGES IN BEHAVIOR, SENSORY, OR MOTOR PERFORMANCE. ANY DECREASE IN REPRODUCTIVE CAPACITY. ANY EVIDENCE OF FETOTOXICITY.
9	PRONOUNCED PATHOLOGIC CHANGES WITH SEVERE ORGAN DYSFUNCTION. ANY NEUROPATHY WITH LOSS OF BEHAVIORAL OR MOTOR CONTROL OR LOSS OF SENSORY ABILITY. REPRODUCTIVE DYSFUNCTION. ANY TERATOGENIC EFFECT WITH MATERNAL TOXICITY.
10	DEATH OR PRONOUNCED LIFE SHORTENING. ANY TERATOGENIC EFFECT WITHOUT SIGNS OF MATERNAL TOXICITY.

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	Reference
Acenaphthene							ID	
Acetic acid, lead salt (lead acetate)	oral	35.2	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Acetic acid, thallium (I) salt [thallium (I) acetate]	oral	0.90	Alopecia, increased kidney weight	5.6	4	22	100	Downs et al., 1960
Acetonitrile	inhalation	115	Neurological disorders and hemorrhages in the brain	2.4	8	19	1000	Pozzani et al., 1959
Acrylonitrile	oral	29.9	Teratogenicity with maternal toxicity	3.3	9	30	100	Murray et al., 1976
Allyl alcohol	inhalation	3.54	Focal necrosis of liver and kidney	4.7	6	28	100	Torkelson et al., 1959
Ammonia	inhalation	42.5	Hydropic changes in adrenal glands, cloudy swelling in kidney tubules, increased splenic hemosiderin	3.1	5	15	1000	Weatherby, 1952
Ammonium bichromate							ID	
Ammonium bifluoride	oral	12	Mottled teeth resulting from fluoride moiety	3.9	5	19	1000	U.S. EPA, 1980
Ammonium silicofluoride							ID	
Antimony (metallic)							ID	
Antimony (and compounds)	inhalation (antimony trisulfide)	0.7 of Sb	Altered ECG patterns possibly indicating greater susceptibility to heart failure	5.7	8	46	10	Brieger et al., 1954
Antimony potassium tartrate	oral	12.8	Shortening of life span	3.8	10	38	100	Schroeder et al., 1970
Antimony pentachloride							ID	
Antimony tribromide							ID	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	References
Antimony trichloride							ID	
Antimony trifluoride							ID	
Antimony trioxide	inhalation	132	Histologic alterations of the lung producing greater susceptibility to pneumonia	2.3	8	18	1000	Gross et al., 1955
Arsenic (metallic)							ID	
Arsenic (and compounds)	oral	1.0	Hyperpigmentation and hyperkeratosis of skin, arteriosclerotic gangrene of extremities	5.5	9	50	10	Tseng et al., 1968; Tseng, 1977
Arsenic acid	oral	297	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.8	10	18	1000	By analogy to sodium arsenate
Arsenic disulfide							ID	
Arsenic (III) oxide	oral	0.114	Hepatic cloudy swelling and spotty necrosis, bile duct proliferation with angitis and fibrosis, sloughing of renal tubular epithelium	6.9	6	41	10	Ishinishi et al., 1980
Arsenic (V) oxide	oral	238	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.9	10	19	1000	By analogy to sodium arsenate
Arsenic trichloride	oral	0.216	Hepatic cloudy swelling and spotty necrosis, bile duct proliferation with angitis and fibrosis, sloughing of renal tubular epithelium	6.5	6	39	100	By analogy to arsenic (III) oxide
Arsenic trisulfide	oral	5.15	Polyneuropathy, hyperpigmentation and hyperkeratosis of skin	4.4	8	35	100	Tay and Seah, 1975
Arsine, diethyl-							ID	
Asbestos	inhalation	0.027	Asbestosis	7.9	10	79	10	Gillam et al., 1976
1,2-Benzanthracene							ID	

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite Score[b]	RQ	References
Benzene	inhalation	345	Decrease in survival, marked effects on hematopoietic system	1.7	10	17	1000	Green et al., 1981
Benzene, 1,3-dichloro-	inhalation	277	Increased liver and kidney weight, hepatocellular cloudy swelling	1.8	5	9	1000	By analogy to dichlorobenzene (a,4-)
Benzene, hexachloro-	oral	50	Increased mortality	3.0	10	30	100	Cam and Nigogosyan, 1963
Benzene, hydroxy- (phenol)	inhalation	20.8	Death	3.5	10	35	100	Deichmann et al., 1944
Benzene, 1-methyl-2,4-dinitro- (2,4-dinitrotoluene)	oral	46.7	Shortening of lifespan, anemia, aspermatogenesis	3.0	10	30	100	Lee et al., 1978
Benzene, 1-methyl-2,6-dinitro- (2,6-dinitrotoluene)	oral	29.9	Methemoglobinemia, anemia, incoordination, CNS demyleination, gliosis, testicular atrophy with aspermatogenesis	3.3	9	30	100	Ellis et al., 1976
Benzene, nitro-							10	
Benzene, pentachloro-	oral	215	Tremors in pups	2.0	7	14	1000	Linder et al., 1980
Benzene, pentachloronitro-	oral	479	Kidney lesions	1.5	7	10	1000	Fytizas-Danielidou, 1975
1,2-Benzenedicarboxylic acid, dibutyl ester (dibutyl phthalate)	oral	420	Fetotoxicity (evidence of delayed ossification)	1.6	8	13	1000	Shiota et al., 1980
1,2-Benzenedicarboxylic acid, diethyl ester (diethyl phthalate)	oral	29,925	Weight loss	1.0	4	4	5000	Food Research Labs, Inc., 1955
Benzidine	oral	22.4	Hepatic foci of cellular alteration	3.5	8	28	100	Frith et al., 1980
Benzo(b)fluoranthene							10	
3,4-Benzopyrene	oral	0.6	Fetotoxicity without maternal toxicity	5.8	8	46	10	Rigdon and Rennels, 1964

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	References
p-Benzoquinone							ID	
1,2-Benzphenanthrene							ID	
Beryllium (metallic)							ID	
Beryllium (and compounds)	inhalation	0.011	Chronic pneumonitis, epithelial hyperplasia	8.5	8	68	10	Vorwald and Reeves, 1959
Beryllium chloride	inhalation	0.594	Increased lung weight, pneumonitis, epithelial hyperplasia	5.8	8	47	10	By analogy to beryllium and compounds
Beryllium fluoride	inhalation	0.350	Increased lung weight, pneumonitis, epithelial hyperplasia	6.2	8	50	10	By analogy to beryllium and compounds
Beryllium nitrate	inhalation	0.983	Increased lung weight, pneumonitis, epithelial hyperplasia	5.5	8	44	10	By analogy to beryllium and compounds
(1,1'-Biphenyl)-4,4'-diamine, 3,3'-dichloro- (dichlorobenzidine)							ID	
Bis(2-chloro-isopropyl)ether	oral	743	Decreased survival	1.2	10	12	1000	NCI, 1979
Bis(chloromethyl)ether							ID	
1,3-Butadiene, 1,1,2,3,4,4-hexachloro-	diet	23.9	Increased urinary coproporphyrin and renal hyperplasia	3.4	3	10	1000	Kociba et al., 1977
2-Butanone (methyl ethyl ketone)	inhalation	860	Fetotoxicity	1.1	8	8	1000	Schwetz et al. 1974
Cadmium (metallic)							ID	
Cadmium (and compounds)	inhalation	0.075 as Cd	Pulmonary and renal dysfunction	7.2	8	58	10	Lauwerys et al., 1974
Cadmium acetate	oral	9.18	Decreased survival	4.1	10	41	10	Schroeder et al., 1964
Cadmium bromide	oral	0.65	Necrosis of renal tubular epithelium	5.8	7	41	10	By analogy to cadmium chloride

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	Reference
Cadmium chloride	oral	0.44	Necrosis of renal tubular epithelium, decreased immunologic response	6.0	7	42	10	Koller et al., 1975
Calcium arsenate	oral	3.3	Polyneuropathy	4.7	7	33	100	Tay and Seah, 1975
Calcium arsenite	oral	10.8	Decreased survival	3.9	10	39	100	By analogy to sodium arsenite
Calcium chromate	inhalation	19.3	Epithelial necrosis, atrophy, and hyperplasia of the bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	3.6	8	29	100	Nettesheim et al., 1971
Captan	oral	251.3	Teratogenicity with maternal toxicity	1.9	9	17	1000	Robens, 1970
Carbamimidoselenoic acid (selenourea)							ID	
Carbon disulfide (carbon bisulfide)	inhalation	33	Decreased immunological reactivity, altered menstrual cycle	3.2	7	23	100	Kashin, 1965; Vasilyeva, 1973
Carbon tetrachloride	inhalation	17.9	Reduced corneal sensitivity	3.6	7	25	100	Mueller, 1973
Carbonic acid, dithallium (I) salt [thallium (I) carbonate]	oral	0.80	Alopecia, increased kidney weight	5.6	4	23	100	By analogy to thallium I acetate
Chloral (hydrate)							ID	
1-Chloro-2,3-epoxypropane	inhalation	16.9	Squamous metaplasia of nasal turbinates	3.7	7	26	100	Quast et al., 1979a,b
Chlorodibromomethane (dibromochloromethane)	oral	6.6	Suppression of hepatic and splenic phagocytosis	4.3	6	26	100	Munson et al., 1978
Chloroethane							ID	
Chloromethyl methyl ether	inhalation	5.9	Bronchial hyperplasia and squamous metaplasia	4.3	7	30	100	Laksin et al., 1975

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	Reference
2-Chlorophenol (2-monochlorophenol)							ID	
Chromic acetate							ID	
Chromic acid	inhalation	1.6	Perforation of the nasal septum	5.2	6	31	100	NIOSH, 1973
Chromic sulfate							ID	
Chromium (metallic)							ID	
Chromium (and compounds)	inhalation	6.4	Epithelial necrosis, atrophy, hyperplasia in bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	4.3	8	34	100	Nettesheim et al., 1971
Chromous chloride							ID	
Cobaltous bromide							ID	
Cobaltous formate							ID	
Cobaltous sulfamate							ID	
Copper (metallic)							ID	
Copper (and compounds)	oral	14	Elevated serum aspartate transaminase levels, jaundice	3.8	5	19	1000	Suttle and Mills, 1966b
Copper sulfate, ammoniated	oral	54	Elevated serum aspartate transaminase levels, jaundice	2.9	5	15	1000	By analogy to copper (and compounds)
Creosote	oral	1,496	Decreased food consumption	1.0	1	1	5000	Miyazato et al., 1981
Cresol	inhalation	1.34	Bone marrow depression of erythroid series	5.3	4	21	100	Uzhdavini et al., 1972
Cupric acetate	oral	44	Elevated serum aspartate transaminase levels, jaundice	3.0	5	15	1000	By analogy to copper (and compounds)
Cupric acetoarsenite							ID	
Cupric chloride	oral	30	Elevated serum aspartate transaminase levels, jaundice	3.3	5	16	1000	By analogy to copper (and compounds)

TABLE III. SUMMARY OF HAZARD RANKING BASED ON CHRONIC TOXICITY (Continued)

Chemical	Route	Dose[a] (mg/day)	Effect	RV_d[b]	RV_e	Composite[b] Score	RQ	Reference
Cupric nitrate	oral	65.2	Elevated serum aspartate transaminase levels, jaundice	2.8	5	14	1000	By analogy to copper (and compounds)
Cupric oxalate							ID	
Cupric sulfate	oral	35.6 $CuSO_4$?	Elevated serum aspartate transaminase levels, jaundice	3.2	5	16	1000	Suttle and Mills, 1966
Curpic tartrate	oral	47	Elevated serum aspartate transaminase levels, jaundice	3.0	5	15	1000	By analogy to copper (and compounds)
2,4-Dichlorophenoxyacetic acid and (2,4-D esters)	oral	129 (as 2,4-D)	Fetotoxicity	2.3	8	18	1000	Schwetz et al., 1971
Dibenz(a,h)anthracene							ID	
Dichlorobenzene (1,2-)	oral	154	Increased liver and kidney weight	2.2	4	8	1000	Hollingsworth et al., 1958
Dichlorobenzene (1,4-)	inhalation	277	Increased liver and kidney weight, hepatocellular cloudy swelling	1.8	5	9	1000	Hollingsworth et al., 1956
1,2-Dichloroethane	inhalation	145	Liver and gall bladder diseases	2.3	8	18	1000	Kozik, 1957
1,1-Dichloroethane	inhalation	542	Kidney injury evidenced by histological changes and increased blood urea	1.4	7	9	1000	Hofmann et al., 1971
1,1-Dichloroethylene (vinylidene chloride)	oral	37.7	Increased incidence of liver necrosis	3.1	6	19	1000	NTP, 1982
1,2-Dichloroethylene	inhalation	189	Fat accumulation in the liver and histologic changes in the lung	2.1	5	10	1000	Freundt et al., 1977
Dichloromethane	inhalation	21,750	Increased mortality	1.0	10	10	1000	Burek et al., 1980
2,4-Dichlorophenol	oral	121	Non-specific hepatic changes!--swelling of hepatocytes with some differences in cell size and infiltration of round cells	2.4	5	12	1000	Kobayashi et al., 1972
2,6-Dichlorophenol							ID	
Dichlorophenylarsine							ID	