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
Dichloropropane							ID	
1,2-Dichloropropane							ID	
Dichloropropane-Dichloropropene mixture	inhalation	43.8	Increased relative kidney and liver weight	3.0	4	12	1000	Parker et al., 1982
1,3-Dichloropropene	inhalation	3.24	Slight cloudy swelling of renal tubular epithelium	4.7	5	24	100	Torkelson and Oyen, 1977
Dichloropropene(s)	inhalation	3.24	Slight cloudy swelling of renal tubular epithelium	4.7	5	24	100	Torkelson and Oyen, 1977
Diethylamine	inhalation	30.2	Pulmonary irritation, multiple punctate corneal erosions and edema, and histological changes in liver	3.3	8	26	100	Drieger and Hodes, 1951
O,O-Dimethyl-O-p-nitrophenyl phosphorothioate (methyl parathion)	oral	10.7	Decreased survival	4.0	10	40	100	NCI, 1979
Dimethylamine	inhalation	37	Necrosis of liver parenchymal cells, hepatic fatty degeneration, tubular degeneration of testes, corneal injury	3.1	6	19	1000	Dow Chemical Co., 1964
Dinitrobenzenes	oral	3.0	Testicular atrophy with indications of possible loss of function	4.8	7	34	100	Cody et al., 1981
4,6-Dinitro-o-cresol	oral	2.45	Cataracts	4.9	8	39	100	U.S. EPA, 1980; NIOSH, 1978; Horner, 1942
Dinitrophenols	oral	14	Cataracts	3.8	8	30	100	U.S. EPA, 1980; Horner, 1942; Tainter et al., 1935
2,4-Dinitrophenol	oral	14	Cataracts	3.8	8	30	100	U.S. EPA, 1980; Horner, 1942; Tainter et al., 1935
Diphenylhydrazine	oral	59.8	Increased mortality, decreased growth	2.8	10	28	100	NCI, 1978

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
Ethane, hexachloro-	inhalation	449	Increased mortality	1.5	10	15	1000	Weeks et al., 1979
Ethane, 1,1,1,2-tetrachloro-							ID	
Ethane, 1,1,2,2-tetrachloro-	inhalation	22	Fatty liver, elevated ACTH in the hypophysis	3.5	5	17	1000	Schmidt et al., 1972
Ethane, 1,1,2-trichloro-							ID	
Ethene, 1,1,2,2-tetrachloro-	inhalation	7266	Increased mortality due to renal disease	1.0	10	10	1000	Rampy et al., 1978
Ethion							ID	
Ethylbenzene	inhalation	724	Slight change in kidney and liver weight	1.2	4	4	5000	Wolf et al., 1956
Fluoranthene							ID	
Formaldehyde	inhalation	12.3	Increased mortality, mucopurulent rhinitis, epithelial dysplasia and squamous metaplasia of nasal cavity	3.9	10	39	100	Swenberg et al., 1980
Hexachlorophene	oral	29.9	Nervousness, paralysis, status spongiosus	3.3	9	30	100	Kimbrough and Gaines, 1971
Hydrogen sulfide							ID	
Indeno(1,2,3-cd)pyrene							ID	
Isoprene	inhalation	550	Decreased O_2? consumption (rat), increased number of leukocytes, slightly decreased number of erythrocytes (rabbits), and increase in some organ weights, bronchial vascular lesions and focal liver dystrophy (all)	1.4	4	5	1000	Gostinskii, 1965
Lead (metallic)							ID	
Lead (and compounds)	oral	22.4 Pb	Decrease in survival of offspring	3.5	10	35	100	Schroeder and Mitchener, 1971

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
Lead arsenate	oral	598	Decreased survival	1.3	10	13	1000	Fairhill and Miller, 1941
Lead chloride	oral	30.8	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead fluoborate	oral	41.2	Decrease in survival of offspring	3.1	10	31	100	By analogy to lead (and compounds)
Lead fluoride	oral	26.5	Decrease in survival of offspring	3.4	10	34	100	By analogy to lead (and compounds)
Lead iodide	oral	49.9	Decrease in survival of offspring	3.0	10	30	100	By analogy to lead (and compounds)
Lead nitrate	oral	37.3	Decrease in survival and longevity	3.1	10	31	100	Schroeder et al., 1965
Lead phosphate	oral	29.3	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead stearate							10	
Lead subacetate	oral	29.1	Decrease in survival of offspring	3.3	10	33	100	By analogy to lead (and compounds)
Lead sulfate	oral	32.8	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Lead sulfide	oral	25.9	Decrease in survival of offspring	3.4	10	34	100	By analogy to lead (and compounds)
Lead thiocyanate	oral	35	Decrease in survival of offspring	3.2	10	32	100	By analogy to lead (and compounds)
Lithium chromate							10	
Mercuric nitrate	inhalation	1.39	Tremor	5.3	8	42	10	Neal et al., 1937, 1941
Mercuric sulfate							10	
Mercuric thiocyanate							10	
Mercurous nitrate							10	

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

Chemical	Route	Dose[a] (mg/day)	Effect	RV^{db}	RV_e	Composite[b] Score	RQ	Reference
Mercury, (acetato-O) phenyl- (phenyl-mercuric acetate)	oral	1.26	Moderate renal damage	5.3	7	37	100	Fitzhugh et al., 1950
Mercury fulminate							10	
Methyl chloride	inhalation	221.3	Neuromuscular damage and death	2.0	10	20	1000	Smith and Von Oettingen, 1947a,b
Methyl methacrylate	inhalation	121.5	Tracheal and suggestive liver histopathologic damage, serum biochemical changes, impaired gastrointestinal motor performance	2.4	7	17	1000	Tansy et al., 1976, 1980a,b
Monochlorobenzene	oral	56	Increased liver and kidney weight	2.9	4	12	1000	Knapp et al., 1971
Monoethylamine							10	
Naphthalene							10	
Nickel (metallic)	inhalation	1.79	Pneumonia	5.1	5	26	100	Johansson et al., 1981
Nickel (and compounds)	inhalation	1.27	Increased mortality, pneumoconiosis	5.3	10	53	10	Ottolenghi et al., 1974
Nickel ammonium sulfate	oral	22.8	Decreased mortality of offspring	3.5	10	35	100	By analogy to nickel (and compounds) (soluble salt)
Nickel carbonyl	inhalation	2.7	Increased mortality	4.9	10	49	10	Sunderman et al., 1957
Nickel chloride	oral	10.3	Increased mortality of offspring	4.0	10	40	100	By analogy to nickel (and compounds) (soluble salt)
Nickel (II) cyanide	inhalation	2.39	Increased mortality, pneumoconiosis	4.9	10	49	10	By analoty to nickel (and compounds) (nickel sulfide)
Nickel hydroxide	inhalation	2.0	Increased mortality, pneumoconiosis	5.0	10	50	10	By analogy to nickel (and compounds) (nickel sulfide)

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
Nickel nitrate	oral	14.5	Increased mortality of offspring	3.8	10	38	100	By analogy to nickel (and compounds) (soluble salt)
Nickel sulfate	oral	12.3	Increased mortality of offspring	3.9	10	39	100	By analogy to nickel (and compounds) (soluble salt)
Nitric acid							ID	
p-Nitrophenol							ID	
2-Nitrophenol							ID	
Nitrophenol (mixed)							ID	
Paraldehyde							ID	
Pentachloroethane							ID	
Phorate							ID	
2-Picoline							ID	
Plumbane, tetraethyl- (tetraethyl lead)	oral	0.0014	Swollen, friable livers, peripancreatic inflammation, cardiac hypertrophy, slight neuronal damage	9.8	5	49	10	Schepers, 1964
Potassium arsenate	oral	372	Decreased survival; enlargement, fibrosis, and lesions of common bile duct	1.6	10	16	1000	By analogy to sodium arsenate
Potassium arsenite	oral	8.36	Decreased survival	4.1	10	41	10	By analogy to sodium arsenite
Potassium bichromate							ID	
Potassium chromate							ID	
Pyridine	oral	177	Mortality	2.1	10	21	100	Pollack et al., 1943
Selenious acid	oral	7.33	Decreased body weight, increased mortality	4.2	10	42	10	By analogy to sodium selenite
Selenium (metallic)							ID	

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

Chemical	Route	Dose[a] (mg/day)	Effect	RV_b[d]	RV_e	Composite[b] Score	RQ	Reference
Selenium (and compounds)	oral	2.69 (selenium)	Increased mortality among neonates	4.9	10	49	10	Schroeder and Mitchener, 1971b
Selenium dioxide (selenium oxide)	oral	6.28	Decreased body weight, increased mortality	4.3	10	43	10	By analogy to sodim selenite
Selenium disulfide							ID	
Silver (and compounds)	oral	0.10	Argyria (development of blue/gray skin pigmentation)	7.0	1	7	1000	U.S. DHEW, 1962
Sodium arsenate	oral	385	Decreased survival, enlargement and lesions of bile duct	1.6	10	16	1000	Byron et al., 1967
Sodium arsenite	oral	8.54	Decreased survival	4.1	10	41	10	Schroeder and Balassa, 1967
Sodium bichromate							ID	
Sodium bifluoride	oral	13	Mottled teeth resulting from fluoride moiety	3.8	5	19	1000	U.S. EPA, 1980
Sodium chromate							ID	
Sodium nitrite	oral	1,409	Marked hepatic atrophy and hemosiderosis	1.0	7	7	1000	Inai et al., 1979
Sodium selenite	oral	9.8	Decreased body weight, increased mortality	4.0	10	40	100	Schrauzer et al., 1976
Sulfuric acid, thallium (I) salt (thallium sulfate)	oral	0.86	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallim I acetate
1,2,4,5-Tetrachlorobenzene	oral	20.5	Elevated alkaline phosphatase and bilirubin levels	3.5	1	3	5000	Braun et al., 1978
2,3,4,6-Tetrachlorophenol	oral	10.7	Fetotoxicity	4.0	8	32	100	Schwetz et al., 1974a
Tetraethyl pyrophosphate							ID	
Thallic oxide [thallium (III) oxide]	oral	1.2	Alopecia, increased kidney weight	5.4	4	22	100	Downs et al., 1960

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
Thallium (metallic)							ID	
Thallium (and compounds)	oral	0.70 (thallium)	Alopecia, increased kidney weight	5.7	4	23	100	Downs et al., 1960
Thallium (I) chloride	oral	0.82	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallium I acetate
Thallium (I) nitrate	oral	0.91	Alopecia, increased kidney weight	5.6	4	22	100	By analogy to thallium I acetate
Thallium (I) selenide							ID	
Toluene	inhalation	4,036	CNS dysfunction	1.0	7	7	1000	SRC, 1981
Tribromomethane (bromoform)	oral	6.6	Suppression of hepatic phagocytosis	4.3	6	26	100	Munson et al., 1978
Trichlorfon (trichlorofon)	oral	45	Decreased survival	3.0	10	30	100	Teichmann and Hauschild, 1978
1,2,4-Trichlorobenzene	oral	37.3	Increased adrenal weight	3.1	4	13	1000	Robinson et al., 1981
1,1,1-Trichloroethane	inhalation	54,592	Histologic changes in hepatocytes	1.0	6	6	1000	McNatt et al., 1975
Trichloroethene	oral	9.5	Decreased immune response	4.0	5	20	1000	Tucker et al., 1980; Sanders et al., 1980
2,4,5-Trichlorophenol	oral	179.6	Mild diuresis; slight degenerative changes in the liver and kidneys	2.1	6	13	1000	McCollister et al., 1961
2,4,6-Trichlorophenol							ID	
Triethylamine							ID	
Trimethylamine							ID	
1,3,5-Trinitrobenzene							ID	
Arsenic D004	oral	4.94	Decreased survival	4.5	10	45	10	Schroeder and Balassa, 1967
Cadmium D006	oral	4.49 as Cd	Decreased survival	4.5	10	45	10	Schroeder et al., 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	Reference
Chromium (VI) D007	inhalation	6.4	Epithelial necrosis, atrophy, hyperplasia of the bronchial tree; emphysema-like changes and focal scarring in alveoli of some mice	4.3	8	34	100	Nettesheim et al., 1971
Lead D008	oral	22.4 Pb	Decrease in survival of offspring	3.5	10	35	100	Schroeder and Mitchener, 1971
Selenium D010	oral	3.69 selenium	Increased mortality among neonates	4.9	10	49	10	Schroeder and Mitchener, 1971a
Uranyl acetate	oral	1.68	Kidney injury	5.2	6	31	100	By analogy to uranyl nitrate
Uranyl nitrate	oral	2.1	Degeneration of renal tubular epithelium	5.0	6	30	100	Anghelova, 1966
Vanadium (V) oxide (vanadium pentoxide)	oral	4,277	Mortality	1.0	10	10	1000	Stokinger et al., 1953
Vanadyl sulfate	oral	14	Reduced serum cholesterol and elevated serum fasting glucose levels	3.8	1	3	5000	Schroeder et al., 1970
Vinyl chloride	inhalation	228	Slight increase in mortality and moribundity	2.0	10	20	1000	Hong et al., 1981
Zinc (metallic)	oral	150	Hypochromic, microcytic anemia	2.2	8	18	1000	By analogy to zinc (and compounds)
Zinc (and compounds)	oral	150 (zinc)	Hypochromic, microcytic anemia	2.2	8	18	1000	Porter et al., 1977; Prasad et al., 1978
Zinc acetate	oral	421	Hypochromic, microcytic anemia	1.6	8	13	1000	By analogy to zinc (and compounds)
Zinc ammonium chloride	oral	558	Hypochromic, microcytic anemia	1.4	8	11	1000	By analogy to zinc (and compounds)
Zinc borate	oral	285	Hypochromic, microcytic anemia	1.8	8	14	1000	By analogy to zinc (and compounds)
Zinc bromide	oral	517	Hypochromic, microcytic anemia	1.4	8	11	1000	By analogy to zinc (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
Zinc carbonate	oral	2,869	Cessation of reproduction, anemia	1.0	9	9	1000	Sutton and Nelson, 1937
Zinc chloride	oral	313	Hypochromic, microcytic anemia	1.8	8	14	1000	By analogy to zinc (and compounds)
Zinc cyanide							ID	
Zinc fluoride	oral	12.6	Mottled teeth resulting from fluoride moiety	3.8	5	19	1000	U.S. EPA, 1980a
Zinc formate	oral	357	Hypochromic, microcytic anemia	1.7	8	14	1000	By analogy to zinc (and compounds)
Zinc hydrosulfite							ID	
Zinc nitrate	oral	435	Hypochromic, microcytic anemia	1.5	8	12	1000	By analogy to zinc (and compounds)
Zinc phenolsulfonate							ID	
Zinc phosphide							ID	
Zinc silicofluoride							ID	
Zinc sulfate	oral	370	Hypochromic, microcytic anemia	1.6	8	13	1000	Porter et al., 1977; Prasad et al., 1978
Zirconium potassium fluoride							ID	

[a]Equivalent human dose

[b]All values have been rounded to two significant digits.

ID = Insufficient data

IV. REFERENCES

Andersen, E.L., and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency. 1983. Quantitative approaches in use to assess cancer risk. Risk Analysis 3:4.

Court-Brown, W.M., and R. Doll. 1957. Leukemia and aplastic anemia in patients irradiated for ankylosing spondylitis. Special Report Series No. 295. Medical Research Council, Her Majesty's Stationery Office, London, p. 1).

Cox, C.R. 1972. Regression model and life tables, J. Roy. Stat. Soc. B, 34:187-220.

Crump, K.S. 1980. An improved procedure for low-dose carcinogenic risk assessment from animal data. J. Environ. Pathol. Toxicol. 5:675-684.

Crump, K.S., H.A. Guess, and L.L. Deal. 1977. Confidence intervals and test of hypotheses concerning dose-response relations inferred from animal carcinogenicity data. Biometrics 33:437-451.

Crump, K.S., and W. W. Watson. 1979. GLOBAL79: A FORTRAN program to extrapolate dichotomous animal carcinogenicity data to low doses. National Institute of Environmental Health Sciences, Contract No. 1-ES-2123.

Doll, R. 1971. Weibull distribution of cancer: Implications for models of carcinogenesis. J. Roy. Stat. Soc. A. 13:133-166.

Dourson, M.L., and J.F. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Reg. Toxicol. Pharmacol. (In press).

Dripps, R.D., J.E. Eckenhoff, and L.D. Vandam. 1977. In: Introduction to anesthesia, the principles of safe practice, 5th ed. W. B. Saunders Co., Philadelphia, pp. 121-123.

Federation of American Societies for Experimental Biology (FASEB). 1974. Biological data books, 2nd ed., Vol. III. Philip L. Altman and Dorothy S. Dittmen, eds. Library of Congress No. 72-87738.

Hansch, C., and A.J. Leo. 1981. Pomona College Medicinal Chemistry Project. Seaver Chemistry Laboratory, Claremont, CA.

Hempelmann, L.H., W.J. Hall, M. Phillips, R.A. Cooper, and W.R Ames. 1975. Neoplasms in persons treated with X-rays in infancy: Fourth survey in 20 years. J. Natl. Cancer Inst. 55:519.

IARC (International Agency for Research on Cancer). 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to Humans: Chemicals and industrial processes associated with cancer in humans. IARC Monograph Supplement 1. Lyon, France.

ICRP (International Commission on Radiologic Protection). 1977. Recommendations of the International Commission on Radiologic Protection. ICRP Publication 26. Pergamon Press, Elmsford, NY, p. 50.

ICRP (International Commission on Radiologic Protection). 1979. Radionuclide release into the environment: Assessment of doses to man. ICRP Publication 29. Pergamon press, Elmsford, NY, p. 76.

Kushner, L.M., R.C. Wards, and V. Fong. 1983. The potential use of the ADI in Superfund implementation. Mitre Corporation, McLean, VA. p. 68.

Lewis, E.B. 1957. Leukemia and ionizing radiation. Science 125:965.

Linsell, C.A. and F.G. Peers. 1977. Field studies on liver cancer, pp. 549-556 in H.H. Hiatt, J.D. Watson, and J.A Winsten, eds., Origins of human cancer (Cold Spring Harbor Laboratory, Cold Spring Harbor, New York).

Mantel, N., and M.A. Schneiderman. 1975. Estimating "safe" levels, a hazardous undertaking. Cancer Research 35:1379-1386.

McNamara, B.P. 1976. Concepts in health evaluation of commercial and industrial chemicals. In: New concepts in safety evaluation: Advances in modern toxicology 1(1): 61-115.

Myrden, J.A., and J.J. Quinlan. 1974. Breast carcinoma following multiple fluoroscopies with pneumothorax treatment of pulmonary tuberculosis, Ann. R. Coll. Physicians Surg. Can. 7:45.

NIOSH (National Institute for Occupational Safety and Health), 1982. Registry of toxic effects of chemical substances. U.S. Department of Health, Education, and Welfare, Cincinnati, OH.

Stara, J.F., D. Kello, and P.R. Durkin. 1980. Human health hazards associated with chemical contamination of aquatic environment. Environ. Health Perspect. 34:145-188.

Stara, J.F., M.L. Dourson, and C.T. DeRosa. 1981. Water quality criteria: methodology and applications. In: Conference Proceedings: Environmental risk assessment: How new regulations will affect the utility industry. Electric Power Research Institute, Palo Alto, CA.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin, and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan, J. Natl. Cancer Inst. 40:453-463.

U.S. EPA. 1976 (May 25). Interim procedures and guidelines for health risk and economic impact assessments of suspected carcinogens. Federal Register 41:21402.

U.S. EPA. 1980 (Nov 25). Guidelines and methodology for the preparation of health effects assessment chapters of the ambient water quality criteria documents. Federal Register 45:79347.

U.S. EPA. 1980. Guidelines and methodology used in the preparation of health effects assessment chapters of the consent decree water quality criteria. Federal Register 45:79318-79379.

Weil, C.S., and D.D. McCollister. 1963. Safety evaluation of chemcials. Relationship between short-and long-term feeding studies in designing an effective toxicity test. Agric. Food Chem. 11:486-491.

APPENDIX I

IARC CRITERIA AND SCHEME FOR EVALUATION OF CARCINOGENS

METHODS

The data on each chemical were reviewed in detail before the meeting by selected members of the group: the animal studies and short-term test results were evaluated by experimentalists and the human studies by an epidemiologist. During the meeting of the Working Group these assessments were debated and adopted, and overall evaluations of carcinogenicity for humans were made on the basis of the combined evidence from humans and experimental systems (Table 1). Brief descriptions of the data on which the assessments and evaluations were based are given in the section on Results, together with references to the Monographs volumes in which they were evaluated previously and, when applicable, to papers published subsequently.

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN HUMANS

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

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

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

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. 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 are concordant in showing 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.

The degrees of evidence for carcinogenicity from studies in humans were categorized as:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.
2. 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.
3. Inadequate evidence, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias or confounding; (c) studies were available which do not show evidence of carcinogenicity.

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN EXPERIMENTAL ANIMALS

These assessments were classified into four groups:

1. Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or 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.

2. 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; or (b) the experiments are restricted by inadequate dosage levels inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice).

3. 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; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

4. No data indicates that data are not available to the Working Group.

The categories sufficient evidence and limited evidence refer only to the strength of the experimental evidence that these chemicals are carcinogenic

and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

ASSESSMENT OF DATA FROM SHORT-TERM TESTS

Because of the large number and wide variety of short-term tests that may be relevant for the prediction of potential carcinogens, the data relative to each compound have been summarized in the form of tables. These indicate both the type of test used and the biological complexity of the test system. "DNA damage" includes evidence for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria and a positive response in tests of comparative survival in DNA repair-proficient and DNA repair-deficient bacteria. "Mutagenicity" refers to induction of mutations in cultured cells or in organisms (e.g., heritable alterations in phenotype, including forward or reverse point mutations, recombination, gene conversion, and specific-locus mutation). "Chromosomal anomalies" refers to the induction of chromosomal aberrations, including breaks, gaps, rearrangements and micronuclei, sister chromatid exchange and aneuploidy. "Other" refers to various additional endpoints, including cell transformation (T), i.e., morphological transformation and colony formation in agar; dominant lethal (DL) tests; morphological abnormalities in sperm (SA); and mitochondrial mutation (Mt). The biological systems include: "Prokaryotes," i.e., bacteria, in the presence of absence of an exogenous metabolic activation system, and cellular systems; "Fungi and green plants;" "Insects," usually Drosophila melanogaster; "Mammalian cells (in vitro)," studies in which the test compound was administered to intact experimental animals; and "Humans (in vivo),"

studies of cells from groups of individuals drawn from a population exposed to the substance in question.

METHODS

In these tables, a "+" indicates that the result was judged by the Working Group to be significantly in one or more assays; "-" indicates that it was judged to be negative from an evaluation of one or more assays; and "?" indicates that contradictory results were obtained in assays from different laboratories or in different biological systems, or that the result was judged to be equivocal. The individual tables for each compound are summarized, for purposes of comparison, in Appendix 3.

The overall evidence summarized in the table was adjudged to fall into one of three categories, sufficient, limited and inadequate:

1. Sufficient evidence, when there were at least three positive results in at least two of three test systems measuring DNA damage, mutagenicity or chromosomal effects. When two of the positive results were for the same genetic effect, they had to be derived from systems of different biological complexity.

2. Limited evidence, when there were at least two positive results, either for different endpoints or in systems representing two levels of biological complexity.

3. Inadequate evidence, when there were generally negative or only one positive test results. Up to two positive test results were considered inadequate if they accompanied by two or more negative test results.

The Working Group was unable to define criteria for "negative" evidence.

In establishing these categories, the Working Group gave greater weight to the three primary endpoints - DNA damage, mutagenicity and chromosomal effects - and judgments were made on the quality as well as on the quantity of the evidence. In a minority of cases, strict interpretation of these criteria was tempered by consideration of a variety of other factors (such as the purity of the test compound, problems of metabolic activation, appropriateness of the test system) which, in the judgment of the Working Group, would place a compound in a category above or below that indicated by the summary table.

EVALUATION OF CARCINOGENIC RISK TO HUMANS

At present, no objective exist to interpret data from studies in experimental animals or from short-term tests directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiological and experimental evidence. The breadth of the categories of evidence defined above allows substantial variation within each. The decisions reached by the Group regarding overall risk incorporated these differences, even though the could not always be reflected adequately in the placement of an exposure into a particular category, as listed in Table 1.

The chemicals, groups of chemicals, industrial processes or occupational exposures were thus put into one of three groups:

Group 1

The chemical, group of chemicals, industrial process or occupational exposure is carcinogenic to humans. This category was used only when there

was sufficient evidence from epidemiological studies to support a causal association between the exposure and cancer.

Group 2

The chemical, group of chemicals, industrial process or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost "sufficient," as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of sufficient evidence in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process or occupational exposure cannot be classified as to its carcinogenicity to humans.

APPENDIX II

DESCRIPTION OF THE QUANTITATIVE RISK EXTRAPOLATION MODELS USED BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY*

1.0 INTRODUCTION/CHOICE OF MODEL

There is no really solid scientific basis for any mathematical extrapolation model relating carcinogen exposure to cancer risks at the extremely low levels of concentration that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly using either animal experiments or epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time, the dominant view of the carcinogenic process involves the concept that most agents that cause cancer also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response characteristic of mutagenesis is associated with a linear nonthreshold dose-response relationship. Indeed, there is substantial evidence (from mutagenesis studies with both ionizing radiation and a wide variety of chemicals) that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear nonthreshold dose-response relationship

*Adapted from "Water Quality Criteria Documents; Availability," Federal Register, Vol. 45, No. 231, Friday, November 28, 1980, pp. 79350-79353.

is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible [e.g., radiation-induced leukemia, breast and thyroid cancer (Lewis 1957, Court-Brown et al., 1957, Hempelman, et al., 1975 and Myrden et al., 1974); skin cancer induced by arsenic in drinking water (Tseng,1968) and liver cancer induced by aflatoxin in the diet (Linsell et al., 1977)]. There is also some evidence from animal experiments that is consistent with the linear nonthreshold hypothesis (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the linear nonthreshold model has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk assessments made with this model should be regarded as conservative, representing the most plausible upper limit for the risk; i.e., the true risk is not likely to be higher than the estimate, but it could be smaller.

2.0 THE MULTISTAGE MODEL

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the modified multistage model developed by Crump (1980). This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95 percent confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment. For this reason, it may be called a "linearized" multistage model.

2.1 Procedure for Low-Dose Extrapolation Based on Animal Carcinogenicity Data

2.1.1 Description of the Extrapolation Model

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i > 0, \text{ and } i = 0, 1, 2, \ldots, k$$

Equivalently,

$$A(d) = 1 - \exp\left[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$A(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d.

The point estimate of the coefficients q_i; i = 0, 1, 2, ..., k; and consequently the extra risk function A(d); at any given dose, d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95 percent upper confidence limit of the extra risk A(d) are calculated by using the computer program GLOBAL79 developed by Crump and Watson (1979). Upper 95 percent confidence limits on the extra risk and lower 95 percent confidence limits on the dose producing a given risk are determined from a 95 percent upper confidence limit, q_1^*, on a parameter q_1. Whenever $q_1 \neq 0$, at low doses the extra risk A(d) has approximately the form $A(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95 percent upper confidence limit on the extra risk and R/q_1^* is an approximate 95 percent lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper limit, q_1^*, is calculated by increasing q_1 to a value q_1^*, such that when the log-likelihood is remaximized subject to

this fixed value, q*, for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2(L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90 percent point of the chi-square distribution with one degree of freedom, which corresponds to a 95 percent upper limit (one-sided). This approach of computing the upper confidence limit for the extra risk A(d) is a modification of the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken an an upper bound of the potency of the chemical in inducing cancer at low doses.

In fitting the dose-response model, the number of terms in the polynomial, g(d), is chosen equal to (h-1), where h is the number of dose groups in the experiment including the control group.

Whenever the multistage model does not fit the data sufficiently, data at the highest dose are deleted and the model is refitted to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square

$$x^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1 - P_i)}$$

is calculated, where N_i is the number of animals in the i^{th} dose group, x_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probility of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever chi-square (X^2) is larger than the cumulative 99 percent point of the chi-square distribution

with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

2.1.2 Selection and Form of Data used to Estimate Parameters in the Extrapolation Model

For some chemicals, several studies in different animal species, strains, and sexes, each conducted at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies are to be used in the model. It is also necessary to correct for metabolism differences between species and for differences in absorption via different routes of administration. The procedures listed below, used in evaluating these data, are consistent with the estimate of a maximum likely risk.

a. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals; that is, if two sets of data show a similar dose-response relationship and one has a very small sample size, the set of data which has the larger sample size is selected for calculating the carcinogenic potency.

b. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk

assessment. The geometric mean of numbers A_1, A_2, ..., A_m is defined as $(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$.

c. If sufficient data exist for two or more significant tumor sites in the same study, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

d. Following the suggestion of Mantel and Schneiderman (1975), we assume that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the 2/3 power of the weight, as would be the case for a perfect sphere, the exposure in mg/2/3 power of the body weight/day is similarly considered to be an equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner. Let:

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e)

W = average weight of the experimental animal.

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. For example, in most feeding studies, exposure is expressed as ppm in the diet. In this case the exposure (mg/day) is derived by

$$m = ppm \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet, F is the

weight of the food consumed per day in kg, and r is the absorption fraction.

In the absence of any data to the contrary, r is assumed to be one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area of the 2/3 power of the weight, so that

$$m \propto ppm \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto ppm$$

As a result, ppm in the diet is often assumed to be an equivalent exposure between species. However, we feel that this is not justified, since the calories/kg of food are significantly different in the diet of man as contrasted with that of laboratory animals, primarily due to differences in the moisture content of the foods eaten. Instead, we use an empirically derived food factor, f = F/W, which is the fraction of a species body weight that is consumed per day as food. We use the rates given as follows:

Species	W	f
Man	70	0.028
Rat	0.35	0.05
Mouse	0.03	0.13

Thus, when the exposure is given as a certain dietary concentration in ppm, the exposure in $mg/W^{2/3}$ is

$$\frac{m}{r \times W^{2/3}} = \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = m/Wr = s, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}$$

When exposure is via inhalation, the calculation of dose can be considered for two cases where (1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and (2) where the carcinogen is a poorly water-soluble gas which 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 metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

Case 1

Agents that are in the form of particulate matter or virtually completely absorbed gases, such as SO_2, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I is inhalation rate per day in m^3, v is mg/m^3 of the agent in air, and r is the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observation that 25 g mice breathe 34.5 liters/day and 113 g rats breathe 105 liters/day (Federation of American Societies for Experimental Biology, 1974)

For mice and rats of other weights W (expressed in kg), the surface area proportionality can be used to determine breathing rates (in m^3/day) as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977).

The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are as follows.

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

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$\frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}\ vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

Case 2

The dose in mg/day of partially soluble vapors is proportional to O_2 consumption, which in turn is proportional to $W^{2/3}$ and to the solubility of gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, when expressing O_2 consumption as $O_2 = k\ W^{2/3}$, where k is a constant independent of species, it follows that

$$m = k\ W^{2/3} \times v \times r$$

$$d = \frac{m}{W^{2/3}} = kvr$$

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 ug/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 were 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.

e. If the duration of the experiment, L_e, is less than the natural life-span of the test animal, L, the slope, q_1^*, or more generally the exponent, g(d), is increased by multiplying a factor $(L/L_e)^3$. 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 2nd 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 3rd power of age. Using this fact, we assume that the slope, q_1^*, or more generally the exponent, g(d), would also increase by at least the 3rd power of age. As a result, if the slope, q_1^* [or g(d)], is calculated at age L_e, we would expect that if the experiment had been continued for the full life span, L, at the given average exposure, the slope, q_1^* [or g(d)], would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Crump and Watson (1979), in which the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp[-f(t) \times g(d)]$$

3.0 CALCULATION OF CARCINOGENIC POTENCY BASED ON HUMAN DATA

If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor q_1^*. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist but it is smaller than could have been observed in the epidemiologic study, and an upper limit of cancer incidence is calculated assuming hypothetically that the true incidence is just below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals compared to the control group. In the analysis of this data, it is assumed that the excess risk, or relative risk minus one, $R(X) - 1$, is proportional to the lifetime average exposure, X, and that it is the same for all ages. It follows that the carcinogenic potency is equal to $[R(X) - 1]/X$ multiplied by the lifetime risk at that site in the general population. Except for an unusually well-documented human study, the confidence limit for the excess risk is not calculated, due to the difficulty in accounting for the uncertainty inherent in the data (exposure and cancer response).