Fourth Annual Report on

Carcinogens

Summary
1985

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U.S DEPARTMENT OF
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Contents

*Agents in italics are new to this Report.

may be in warehouses. Some TRIS-treated children's sleepwear, manufactured prior to 1978 and stored in warehouses, may reappear illegally in the marketplace. Consumers who suspect they may be purchasing pre-1978 TRIS-treated sleepwear are advised to contact the manufacturer or call the CPSC Hotline at (800)638-2772. EPA regulates TRIS under the Resource Conservation and Recovery Act, the Comprehensive Environmental Response Compensation and Liability Act, and under Section 8(a) of the Toxic Substances Control Act, which requires that EPA be notified of intent to resume manufacture or importation.

URETHANE

CARCINOGENICITY

There is sufficient evidence of the carcinogenicity of urethane in experimental animals.[535] Urethane was carcinogenic in mice, rats, and hamsters following inhalation, oral administration (in drinking water or by stomach tube), and subcutaneous or intraperitoneal injection, producing lymph system cancers, liver cancers, melanomas, and vascular, lung, and other tumors. It was an initiator of skin carcinogenesis in mice when given either orally or topically. Urethane also enhanced the leukemogenic effect of x-irradiation in mice. It was carcinogenic in single dose experiments and following prenatal exposure. Neonatal and infant mice were more susceptible to cancer induction by urethane than were adult mice.[536]

PROPERTIES

Urethane, also called ethyl carbamate, is colorless, odorless, and water soluble. Urethane is available in the United States in crystal form or as a fused solid.

USE

Urethane mainly is used as a chemical intermediate in the preparation of amino resins. It also is an intermediate in the production of pharmaceuticals, insecticides, and fungicides, and is used in biochemical research and in human and veterinary medicine. Formerly, urethane was an active ingredient in drugs prescribed for the treatment of neoplastic diseases; it also was a hypnotic, a component of a sclerosing solution for varicose veins, and a topical bactericide. In 1970, approval of new drug applications for products containing urethane as an active ingredient was withdrawn after researchers found that urethane was ineffective. Urethane also has been used as an inactive component or solubilizer in liquid preparations for injections, but FDA withdrew the new drug application approval for all drug products containing urethane as an inactive ingredient.[537] Additionally, urethane can occur as a contaminant in two anticonvulsant drugs (trimethadione and paramethadione), with an allowable limit of 1 ppm; these anticonvulsant drugs may be used only to treat epilepsy that is refractory to other available drugs. No estimate was available [illegible] on the volume of urethane now used in the United States, but it is believed to be small.

PRODUCTION

The 1979 TSCA Inventory identifies five companies producing 6,105,000 million pounds of urethane, with some site limitations.[538] Several companies now produce urethane solely for research. U.S. companies have produced urethane commercially since 1945.

EXPOSURE

Reports of possible human exposure to urethane are not available. In 1974, the National Occupational Hazard Survey made no estimate on the potential worker exposure to urethane. Urethane is volatile at room temperature, and exposure can possibly occur through inhalation and skin absorption during manufacture and processing. Urethane also may possibly be ingested by humans. Investigators have found urethane in diethylpyrocarbonate-treated beverages, and in wine, beer, orange juice, and some soft drinks. Urethane also has been found to occur in foods not treated with diethyl procarbonate but made by a fermentation process, including ale, beer, bread, wine, soy sauce, yogurt, and olives.

REGULATIONS

EPA regulates urethane under the Resource Conservation and Recovery Act and the Comprehensive Environmental Response Compensation and Liability Act. EPA also has designated waste and will determine the appropriateness of additional regulatory or other control actions. The use of urethane in drugs is prohibited; on February 27, 1976, FDA withdrew approval for all drugs containing urethan as either an active or inactive ingredien FDA has prohibited the use of diethy pyrocarbonate as an additive to huma food.

VINYL CHLORIDE

CARCINOGENICITY

There is sufficient evidence that vin chloride is a human carcinogen.[539] target organs are the liver (angiose comas), brain, lung and hemo- and lyr phopoietic systems. Although eviden of a carcinogenic effect of vinyl chlori in humans has come from groups c cupationally exposed to high doses vinyl chloride, there is no evidence th there is an exposure level below whi no increased risk of cancer would cur in humans.[540]

There is sufficient evidence for carcinogenicity of this compound in perimental animals.[540] Vinyl chlor was tested in mice, rats, and hamst by inhalation exposure and in rats oral, subcutaneous, and intraperitor administration. Inhalation exposure duced tumors at different sites in three species, including angiosarcor

[535]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. 292 pp. Lyon, France: IARC, 1982. Ap pordix 1.

[536]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. 326 pp. Lyon, France: IARC, 1974. pp. 111-140.

[537]Federal Register. 41 FR 9523, 4, February 27, 1976.

[538]Toxic Substances Control Act, Chemical Substance Inventory, 1979; public record.

[539]International Agency for Research on Ca IARC Monographs on the Evaluation of the cinogenic Risk of Chemicals to Humans. Su ment 4. 292 pp. Lyon, France: IARC, 1982 260-262.

[540]International Agency for Research on Ca IARC Monographs on the Evaluation of the cinogenic Risk of Chemicals to Humans. Vo 513pp. Lyon, France: IARC, 1979, pp. 377

of the liver, following gastric intubation of a solution in olive oil, vinyl chloride was carcinogenic in rats. Vinyl chloride was carcinogenic in rats following prenatal exposure. A dose response has been demonstrated.[540,541]

PROPERTIES

Vinyl chloride is a colorless gas that is slightly soluble in water.

USE

Vinyl chloride is used mainly in the production of plastics. It also is used to synthesize other chemicals, and it was formerly a component of aerosol propellants. Vinyl chloride-vinyl acetate copolymers are used extensively to produce vinyl asbestos floor tiles.

PRODUCTION

Annual production of vinyl chloride in the United States is about 7 billion pounds. The 1979 TSCA Inventory identifies 17 companies producing 6.9 billion pounds of vinyl chloride, with some site limitations; the CBI Aggregate is more than 1 billion pounds.[542] Earlier, domestic production of the homopolymer of vinyl chloride was reported as 5 billion pounds; imports amounted to 55 million pounds. Estimated domestic production of the acetate copolymer of vinyl chloride is 279 million pounds.

EXPOSURE

Potential human exposure to vinyl chloride occurs mainly through inhalation and, less frequently, through skin absorption. More than 3.5 million workers possibly are exposed to the chemical. Others potentially exposed include 4.6 million people who live within 5 miles of industrial sites at which environmental emissions occur. Air emissions measured near several production facilities contained 3.1 to 12.5 ppb of vinyl chloride. Very low exposure may occur if unreacted vinyl chloride remaining in packaging materials made from polyvinyl chloride leaches into food and beverages (0.05 to 25 ng/kg) or medical products. Also, cigarette smoke is reported to contain 5 ng to 16 ng/cigarette of vinyl chloride.[543]

REGULATIONS

CPSC, EPA, and FDA each banned the use of vinyl chloride as an aerosol propellant, eliminating exposure of 1 million to 5 million people annually. Under the Clean Water Act, EPA published a water quality criteria document for the protection of human health, addressing vinyl chloride. The Clean Air Act, National Emission Standards for Hazardous Air Pollutants, addresses vinyl chloride emissions from production and manufacturing facilities. The Resource Conservation and Recovery Act subjects the chemical's waste products, off-specification batches, and spill residues to handling and report/recordkeeping requirements; it also designates vinyl chloride as a hazardous constituent of waste and subjects wastes known to

[541] International Agency for Research on Cancer.

ing requirements under the Comprehensive Environmental Response Compensation and Liability Act.

FDA eliminated the use of vinyl chloride in drug products and has alerted food manufacturers to the need for monitoring packaging materials that may contain it. FDA's Center for Food Safety and Applied Nutrition presently is reevaluating its position on the

September 3, 1975, proposal and t
withdraw it. In October, 1974, OS
adopted a standard of 1 ppm for v
chloride, as an 8-hour time weigh
average, with a 5-ppm ceiling for
15-minute period; OSHA requ
medical surveillance, training
workers, use of protective clothing
respirators, warning signs, proc
labeling, and periodic monitoring

Occupational Exposures Associated Wi A Technological Process

HEMATITE UNDERGROUND MINING

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity in humans of underground hematite mining (with exposure to radon).[544] Underground hematite miners have a high incidence of lung cancer, whereas surface hematite miners do not. It is not known whether this excess risk may be due to hematite; to radon (a known lung carcinogen); to inhalation of ferric oxide or silica; or to a combination of these or other factors. Some studies of metal workers exposed to ferric oxide dusts have shown an creased incidence of lung cancer, w other studies have not.[544,545] The fluence of factors in the workplace, o than ferric oxide, cannot eliminated.[545]

No carcinogenic effects were served in mice, hamsters, or gui pigs given ferric oxide intratrac ally.[545]

PROPERTIES

Hematite is iron ore, and ferric oxid its major constituent. Most iron ore contains between 10 and 20 perc silica. Iron and ferric oxide are solu in acids, but not in water. In damp sally air, iron oxidizes to ferric oxi

[544] International Agency for Research on Cancer

Occupational Epidemiology

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ial mortality ratios. SMRs for all causes

auses, usually by 10 to 20%. Therefore, even if there is no absolute excess among a group of deceased persons, for methodologic reasons an excess of might be expected. Note that in the realm of rate ratios, this is a very weak n.

PMRs tend to be more interpretable for uncommon causes of death than for causes. If the rate of some uncommon disease such as lung cancer is increased 00%, the SMR and the SPMR will each reflect this increase. However, if a illness such as circulatory disease is increased by 200%, the SMR will still s increase, while the SPMR will be increased considerably less. Also, whereas two or more causes are essentially independent of each other, SPMRs for ore causes are interdependent, since the sum of the expected numbers must sum of the observed numbers.

e of these limitations to SPMR analyses, they are most useful and provide ion that usually differs little from that obtained in an SMR analysis. It is instructive to do SPMR and SMR analyses on the same data, so as to evalpretation of the results of these two methods of analysis.

ple — Rubber Workers

ler again the data in Table 6.1. In assessing whether a specific cause of death ess, *one might* look only at causes for which the SMR is greater than 100. If rion is used, only leukemia and cancers of the stomach, large intestine, and are in excess among the entire group of rubber workers. However, it might be hat because of the HWE (or because of some other bias), SMRs greater than -causes" SMR should be considered to be in excess. Intuitively, one assesses cess by dividing each cause-specific SMR by the all-causes SMR to obtain a ted" SMR (CSMR).[20]

esults of such a division are illustrated in Table 6.17. In Column I are the same s in Table 6.1 (note that the SMRs differ slightly because the analyses were out at different times). In Column II are the CSMRs. CSMRs less than 100 only for diseases other than cancer or cardiovascular disease. *In Column III* SPMRs from a proportional mortality analysis. By definition the all-cause and the SPMR are 1.00.

n be seen that the CSMR and the SPMR for the several causes illustrated are Part of the similarity no doubt is due to the relatively weak associations beisease and working in the rubber industry. However, under any of the three ls used to compute expected numbers, one would wish to investigate further rom bladder cancer and the lymphatic and hematopoietic cancers.

e is one tendency in Table 6.17 that may be of interest. For diseases of old s, e.g., bladder cancer and stroke, the CSMR is higher than the SPMR. For s of young persons, e.g., brain cancer and external causes of death, the SPMR er than the CSMR. Whether this tendency is a general property of the CSMR e SPMR is unknown. If it is a general property, it no doubt results from the ie weights differ between a SMR computation and SPMR computation, i.e., -years vs. numbers of deaths.

mple — Vinyl Chloride Workers

974, three cases of angiosarcoma of the liver among vinyl chloride workers were

Division	All causes: Ever	All causes: Usual	All cancers: Ever	All cancers: Usual
"Laid Off"	—	81 (319)	—	69
Chemical	74 (161)	74 (68)	85 (32)	80
Aerospace	74 (711)	81 (282)	92 (155)	89
Tires	79 (1968)	81 (1345)	92 (397)	93
Industrial products	76 (1600)	81 (796)	84 (309)	94
Services	83 (2238)	84 (1638)	90 (405)	94
Rubber reclaim	75 (313)	72 (93)	94 (68)	100
Processing	79 (833)	87 (538)	98 (177)	111
Total	—	82 (5079)	—	94

* Data differ slightly from those presented in Table 6.1.

Table 6.17
NUMBER OF DEATHS OBSERVED AMONG RUBBER WORKERS AND RATIOS OF OBSERVED TO EXPECTED ACCORDING TO THREE METHODS

Cause of death	Observed deaths	Observed/expected* I	II	III
All causes	4982*	0.82	1.00	1.00
All cancer	980	0.94	1.17	1.17
Digestive	364	0.98	1.22	1.21
Bladder	48	1.22	1.52	1.45
Brain	20	0.80	1.00	1.10
Lymphatic and hematopoietic	106	1.13	1.42	1.44
CNS vascular	493	0.91	1.13	1.09
Circulatory	2445	0.83	1.03	1.03
External	278	0.62	0.77	0.80
All other causes	786	0.65	0.74	0.73

* Excludes 97 deaths of unknown cause.

* I Expected numbers based on 5-year age-time specific mortality rates for U.S. white males (SMR/100).

II Expected ratios in I have been divided by 0.82 (all causes SMR/100) and by 0.98 to correct for 97 deaths of unknown cause (CSMR/100).

III Expected numbers based on 5-year age-time specific proportional mortality ratios for U.S. white males (SPMR/100).

reported.[21] Later in the same year, the results of two epidemiol
ported. In one, a standardized proportional mortality analysis
causes of death among 161 deceased persons, most of whom had
plant as the three with angiosarcoma.[22] In the second, a standard

Table 6.18
OBSERVED AND EXPECTED DEATHS AMONG VINYL CHLORIDE WORKERS IN A PROPORTIONAL MORTALITY STUDY*

Cause of death	Observed	Expected	SPMR†
All causes	161	161.0	100
All cancer	41	27.9	150
Digestive	13	8.3	160
Liver and biliary	8	0.7	1100
Lung	13	7.9	160
Brain	5	1.2	420
Other	10	10.5	95
CNS vascular	8	9.5	80
Circulatory	66	68.6	96
External	22	24.5	90
All other causes	24	30.5	79

* Expected numbers based on proportional mortality ratios for United States white males.
† SPMR = Standardized proportional mortality ratio = 100 × observed/expected.

s was conducted on the mortality among 8384 men who had worked with vinyl e, including those at the same plant as above.[23] Among these 8384 workers were o had died, including most of the 161 included in the above report.
able 6.18 are presented the results of the SPMR study. A 50% excess of cancer n, which was due entirely to cancers of the liver, the lung, and the brain. In 6.19 are presented the results of the SMR study. As compared to the general tion, there was essentially no excess of cancer. However, the CSMR was (102/ 00 or 136. There were large excesses of cancers of the liver and of the brain, piratory cancer, while the SMR was close to 100, the CSMR was 140.
the two studies reported similar results, even though one was smaller and based on a SPMR analysis. In this study an analysis according to age and year of of persons with cancer was also done (Table 6.20). As can be seen, while there end with age at death, there is a steady increase in the SPMR with year of This suggests that many more persons will die from cancer because of exposure l chloride.
judgment as to whether the excesses of specific causes of death are likely to be is based on reason rather than any statistical significance. There can be little that vinyl chloride (or some closely related compound) is responsible for the rcoma. This disease was extremely rare before it was discovered among vinyl e workers. The rate ratio among vinyl chloride workers must be in the 1000s. sease occurred mainly in the men who worked for many years (10+) cleaning ctors; these men accumulated a high dosage of exposure to vinyl chloride. While rcoma association is at the top of the highly likely to be causal group. This g in epidemiology (or any science) is ever absolutely certain, the vinyl-chloride-rcoma association is at the top of the highly likely to be casual group. This after the first three cases of angiosarcoma were identified.
respect to cancers of the brain and of the lung, a causal interpretation of the

Table 6.19
OBSERVED AND EXPECTED DEATHS AMONG VINYL CHLORIDE WORKERS IN A MORTALITY STUDY*

Cause of death	Observed	Expected	SMR
All causes	352	467.3	75
All cancer	79	77.2	102
Digestive	19	21.7	88
Liver	7	1.7	412
Respiratory	25	23.9	105
Brain	7	2.5	280
Other	10	9.3	108
CNS vascular	13	24.5	57
Circulatory	142	178.8	79
External	52	91.7	57
All other causes	66	95.1	69

* Expected numbers based on mortality rates for United States white males.

Table 6.20
OBSERVED AND EXPECTED DEATHS FROM ALL CANCERS AMONG VINYL CHLORIDE WORKERS IN A PROPORTIONAL MORTALITY STUDY ACCORDING TO AGE AND YEAR OF DEATH

Characteristic	Category	Observed	Expected	SPMR
Age of death	<50	11	7.6	140
	50—59	17	8.1	210
	≥60	13	12.2	110
Year of death	<1965	12	11.4	110
	1965—69	10	7.3	140
	≥1970	19	9.2	210

lung cancer. Exposure must be reduced because of its highly likely role i angiosarcoma. If some lung and brain cancer are also prevented, so much t

IV. CASE-CONTROL STUDIES WITHIN A COHORT

On occasion, personnel records may be available for a cohort of employe but it may be too expensive to review all of the records to determine the wo of each person. Some sample of the records is selected to be reviewed. Since interest in such review is to determine association between work and diseas is given to reviewing the work histories of persons with one or more diseases o For purposes of comparison, the work histories of "controls" are also deter

A. Procedure

...erican Medical Association, *Standard Nomenclature of Diseases and Operations*, 5th ed., Thomp-..., S. T., and Hayden, A. C., Eds., McGraw-Hill, New York, 1961.
...ne, D., Shapiro, S., and Miettinen, O. S., Case-control surveillance of serious illnesses attributable ...ambulatory drug use, in *Epidemiological Evaluation of Drugs*, Columbo, F., Shapiro, S., Slone, ... and Tognoni, G., Eds., Elsevier, Amsterdam, 1977, 59.
...ne, D., Shapiro, S., Rosenberg, L., Kaufman, D. W., Hartz, S. C. Rossi, A. C., Stolley, P. D., ...d Miettinen, O. S., Relation of cigarette smoking to myocardial infarction in young women, *N. ...gl. J. Med.*, 298, 1273, 1978.

Chapter 9

CURRENT PROBLEMS IN OCCUPATIONAL EPIDEMIOLOGY

I. INTRODUCTION

The purpose of occupational epidemiology is to provide information on ... health that can be used to prevent human illness. As time goes by data accumul... the relationship between occupational exposures and human diseases. Some ... data can be interpreted unequivocally and can provide a firm basis for a cha... behavior. Other data are subject to more than one interpretation or may be cha... as to veracity. As indicated throughout these pages, data by themselves pro... indication as to whether or not they reflect true processes in human populations.

In this chapter a variety of problems related to occupational exposures are ... ered. These problems are illustrated by referring to recent literature in occupa... epidemiology. The intent is to provide an overview of general problems rather ... provide a detailed review of specific issues. Excellent reviews of the known an... pected effects of exposure to substances used in industry can be found in the C... Documents published by the National Institute for Occupational Safety and ... (NIOSH) and in the reports of the International Agency for Research on ... (IARC).[1,2]

For each of the studies reviewed in this chapter, the collection, analysis, and ... pretation of the data are presented and the meaning of the results is discussed. ... of the studies are models on how to conduct research; some of the studies illu... problems in methodology that should be avoided. All of the studies illustrate th... ities encountered in conducting research in occupational epidemiology and in ... preting the results of that research.

II. OCCUPATION AND REPRODUCTIVE EFFECTS

Exposure to substances used in industry may lead to effects on the reprod... system in men or in women or may lead to an effect on the unborn fetus. Few ... have been published on the general relationship between occupation and proble... reproduction. Until recently few pregnant women have been exposed to industr... vironments. Any effects on male workers are difficult to detect. Any effects on ... have not been studied to any extent.

A. Vinyl Chloride and Fetal Deaths

In October 1974, interviews were conducted with male workers exposed to ... chloride monomer (VCM), polyvinyl-chloride (PVC) or rubber.[3] Questions were ... about the interviewee's health as well as about the outcomes of pregnancy of the ... ers' wives. The fetal death rate subsequent to exposure for VCM was higher ... the families of exposed men than among the families of controls (Table 9.1).

This study is difficult to classify. It is not a retrospective cohort study, ... workers were not followed either in retrospect or in prospect for the occurr... fetal deaths. It is not a case-control study, because subject selection was not b... presence or absence of fetal deaths. It is best thought of as a cross-sectiona... where exposure is presence or absence of a history of VCM exposure and di...

Table 9.1
FETAL DEATH RATES AMONG FAMILIES OF MEN EXPOSED TO VINYL CHLORIDE MONOMER AND AMONG FAMILIES OF CONTROLS

	Fetal death rate*			
	Prior to exposure		Subsequent to exposure	
Group	Crude	Standardized	Crude	Standardized
Exposed	10.1	6.1	16.5	15.8
Controls	6.9	6.9	8.8	8.8

* Number of fetal deaths per 100 pregnancies.

to increased fetal death, but if controls with fetal deaths terminated at a higher han exposed workers with fetal deaths. This can be thought of as selection bias. ction bias also was possible because not all workers eligible for the study were iewed. The data in Table 9.1 could have resulted if exposed workers with a his- f fetal deaths selectively agreed to participate in the study.

ause the interviews were not conducted blindly, observation bias was possible. ata in Table 9.1 could result if workers with exposure to VCM over-reported, or trols under-reported, the occurrence of fetal deaths.

information on smoking of mothers is presented. Smoking is known to be asso- l with an increased fetal death rate.[4] The data in Table 9.1 could have resulted confounding by smoking if the wives of VCM workers smoked more than the of controls.

: primary procedure used in the analysis was direct standardization of rates, be- the age distribution differed between exposed and control groups. Because the ard used was the age-distribution of the controls, the crude and standardized for controls in Table 9.1 were identical. For the exposed, there was a substantial tion in the standardized rate prior to exposure. This occurred because the exposed was older than the control group, and because the rate of fetal deaths increased ge (Table 9.2).[5]

this example the standardization behaved well, since the age-standardized rates ll as the age-specific rates showed essentially no differences in fetal death rates en the exposed and the control groups. However, the potential difficulties of standardization with respect to small numbers can be seen. If there had been controls in the <20 category, and if there had been two or three fetal deaths g the seven exposed persons in the <20 category, that stratum would have con- d heavily to a high standardized rate among the exposed group. In such a situ- it is best to limit the analysis to overlapping age-strata in which there are suffi- numbers, e.g., ages 20 to 29. In any standardization procedure attention must en to the elements being standardized.

meaning of this single study is unclear. Some of the criticisms raised above must wed as far-fetched. The likelihood of selection bias seems remote. The possibility servation bias is more real, inasmuch as the interviews were conducted shortly the carcinogenic properties of vinyl chloride were announced. If anything, the

Table 9.2
FETAL DEATH RATES PRIOR TO EXPOSURE AMONG FAMILII OF MEN EXPOSED TO VINYL CHLORIDE MONOMER AND AMONG CONTROLS ACCORDING TO AGE OF FATHER

		Age of father					
	Group	<20	20—24	25—29	30—34	≥35	
Number of pregnancies	Exposed	7	44	56	27	14	1
	Control	31	80	38	6	4	1
Fetal death rate*	Exposed	0.0	4.5	12.5	18.5	7.1	
	Control	6.5	5.0	10.5	16.7	0.0	

* Number of fetal deaths per 100 pregnancies.

if wives of exposed men smoked more, the association between smoking deaths is weaker than the association seen in this study.

As suggested by the above paragraph, the meaning of the results of this matter of opinion, not of science. Different persons will raise different cri different defenses. Certainly the results of this one study are not definitive.

With respect to future public health policy, it is not a major concern whe chloride exposure to men tends to increased fetal deaths among their offsp association between VCM and angiosarcoma is many times stronger and VCM exposure must be reduced. Such reduction would be expected to min adverse effects of VCM on the reproductive system.

However, it is of public health concern that VCM might affect pregnat directly. In order to address this concern, studies must be made of pregnat exposed to VCM and of their children.

B. Paternal Occupation and Childhood Cancer

1. Children in Quebec

"In reviewing, for other purposes, a small sample of birth and death certi Quebec children, the impression emerged of a large number of fathers in petr occupations when the cause of death was cancer."[6] To quantify this impre occupation of the father was obtained from the birth certificate of 386 child the age of 5 who died from cancer. For comparison purposes, two matchec per case were selected — the preceding and succeeding child in the birth registry. As seen in Table 9.3, approximately twice as many cases had fat potential exposure to petrol and other hydrocarbons. The odds ratio is (71 (75 × 315) = 2.1. The 95% confidence interval of the odds ratio is 1.5 to 3.0.

Selection bias is an unlikely explanation since paternal occupation was tained until after cases were defined. Observation bias could have led to the The authors admit to a prior notion that petro-related occupations were childhood cancer. In classifying a father's occupation, it is possible that oc difficult to classify were coded as petrol-related for cases but not for contr ever, the authors state that occupation was coded by a person who was blin case-control status. Thus, for this reason, observation bias was not possible.

Confounding by some factor related to occupation and childhood cancer ways be an explanation. However, no data on potential confounding fact

PB85-167006

Methodology for Ranking the Degree of Hazard Associated with Exposure to Carcinogens and Other Toxic Chemicals

(U.S.) Environmental Protection Agency
Washington, DC

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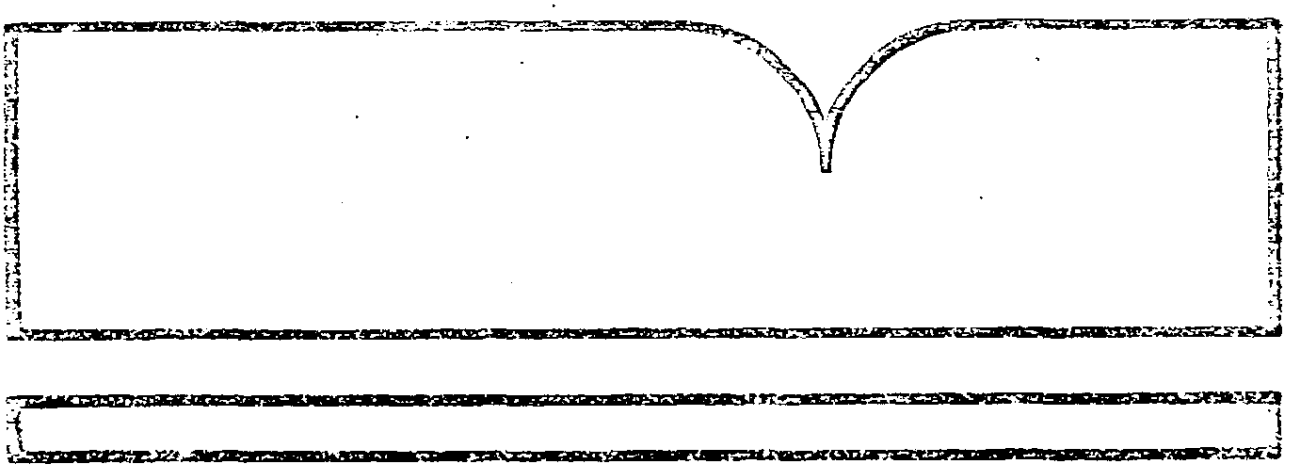

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METHODOLOGY FOR RANKING THE DEGREE OF HAZARD ASSOCIATED WITH EXPOSURE TO CARCINOGENS AND OTHER TOXIC CHEMICALS

by

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

Elizabeth L. Anderson[b], Margaret Chu[c], Michael Dourson[d], and Christopher DeRosa[e]

[a]This paper is adapted from two documents prepared by the Office of Health and Environmental Assessment, Office of Research and Development, U. S. Environmental Protection Agency: Technical Support Document and Summary Table for the Ranking of Hazardous Chemicals Based on Carcinogenicity (Carcinogen Assessment Group, External Review Draft, OHEA-C-073, July 1983); and Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data (External Review Draft, Environmental Criteria and Assessment Office, ECAO-CIN-R245, August 1983).

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16. ABSTRACT A hazard index is an overall indicator of the potential harm of a hazardous substance to humans and the environment. This paper describes the use of a carcinogenicity index and a systemic (chronic) toxicity index in setting reportable quantities under Section 101(14) of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980.

The three types of evidence used to evaluate a substance's carcinogenic hazard are 1) epidemiological, 2) experimental and 3) supportive evidence from short-term tests, metabolism and pharmacokinetics and structure-activity correlations. Hazardous substances suspected of carcinogenic potential are ranked by the level of this evidence and the potency factor. The potency factor is $1/ED_{10}$, where ED_{10} is the estimated dose associated with a lifetime cancer risk of 10^{-5}.

The toxicity index for substances with systemic (chronic) toxicity potential is based on the minimum effective dose levels for chronic exposures via environmental media and the type of effect. About 200 potential carcinogens and 200 chemicals associated with other diseases have been evaluated and assigned a hazard ranking.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

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I. INTRODUCTION

Inadvertant 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 deperds 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 are 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 are 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.

THE WEIGHT-OF-EVIDENCE APPROACH TO EVALUATING THE EVIDENCE FOR CARCINOGENICITY

The weight-of-evidence is 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 is 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.

Primary Sources of Information

Epidemiology Studies--

Human information provides 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.

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 is 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.

Supportive Information

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.

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.

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.

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 is classified according to the IARC criteria (see Appendix). In this approach the strength of the evidence for human and animal studies is evaluated separately, and all relevant factors are combined into an overall qualitative evaluation of the likelihood that the agent is a human carcinogen.

POTENCY FACTOR ESTIMATES

After the decision has been made that a compound has the potential for causing cancer in humans, a potency factor F, defined as $1/ED_{10}$, is estimated. ED_{10} is the estimated dose associated with a lifetime cancer risk of 10%. The

potency factor F is used together with the qualitative weight-of-evidence for carcinogenicity in the ranking of the carcinogenic hazard potential of the chemicals.

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 upper bounds 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, using the potency factor F has the advantage of avoiding 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 a statistical upper-bound estimate.

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 above, they are aggregated into four groups. Those chemicals with the highest potency factor are placed in group 1, intermediate potency factor chemicals are

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† q_1^* is the upper confidence limit for the linear coefficient in the multistage model.

placed in group 2, low potency factor chemicals are placed in group 3, and the lowest potency factor chemicals are 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.

CANCER HAZARD RANKING BASED ON COMBINED QUALITATIVE AND QUANTITATIVE ASSESSMENTS

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.).

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

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.

TOXICITY HAZARD RANKING BASED ON THE MED AND THE SEVERITY OF DISEASE

A final Composite Score (CS) which is the chronic toxicity index is deter-

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* 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.

mined 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 observed adverse effect levels (LOAELs) or frank effect levels (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.**

**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:

$$\text{animal dose} \times \left(\frac{\text{animal weight}}{70\ \text{kg}}\right)^{1/3} \times 70\ \text{kg}$$

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 CS 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 used in setting the RQ will be selected by the following criteria:

   - If adequate chronic data are available, disregard MEDs based on subchronic data.
   - If more than one MED remains, select the MED which is based on the "best" data.
   - 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.

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 1. 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[e]	e	NA	Medium
Ammonium chromate	(7788-98-9)	Inadequate	Inadequate	1[e]	e	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	2A[d]	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

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	o
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[f]	1	High
Benzo[ghi]perylene	(191-24-2)	Inadequate	Inadequate	3	NA	NA	b
Benzo[k]fluoranthene	(207-08-9)	Inadequate	Limited	3[f]	NA	NA	c
Benzyl Chloride	(100-44-7)	Inadequate	Limited	3[f]	NA	NA	o
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 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
Benz[a]acridine	(225-51-4)	Inadequate	Limited	3[c]	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[d]	[g]	NA	Medium
Carbon tetrachloride	(56-23-5)	Inadequate	Sufficient	2B	39.00	2	Medium
Chloramphenicol	(305-03-3)	Sufficient	Sufficient	1	[a]	NA	[a]

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

TABLE I. SUMMARY OF HAZARD RANKING FOR CHEMICALS REGULATED

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[f]	0.35	2	Low
Chlornaphazine	(494-03-1)	Sufficient	Limited	1	[e]	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	3[g]	[g]	NA	[b]
Chromic acid	(7738-94-5)	Limited	Inadequate	3[g]	[g]	NA	Medium
Chromic sulfate	(10101-53-8)	Inadequate	Inadequate	3[g]	[g]	NA	[b]
Chromous acid	(10049-05-5)	Inadequate	Inadequate	3[g]	[g]	NA	[b]
Chrysene	(218-01-9)	Inadequate	Sufficient	2B	5.00[i]	3	Low
Creosote	(8001-58-9)	Limited	Sufficient	2A	50.00	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 [illegible] (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	a
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	a
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[c]	4.60	3	Low
Dichlorophenylarsine	(696-28-6)	Inadequate	Inadequate	3	NA	NA	b

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

TABLE I. SUMMARY OF HAZARD RANKING FOR POTENTIAL CARCINOGENS [illegible]

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	(57-14-7)	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	3.00	3	Low
2,5-Dinitrotoluene	(619-15-8)	Inadequate	Inadequate	3	NA	NA	b
2,6-Dinitrotoluene	(606-20-2)	Inadequate	Limited	3[c]	NA	NA	c
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	•	NA	c
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	0.47	4	Low

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
1-Ethyl-1-nitrosourea	(759-73-9)	Inadequate	Sufficient	2B	8.70	3	Low
Ferric dextran	(9004-66-4)	Inadequate	Sufficient	2B	0	NA	c
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[a]	2	Medium
Hexachlorobenzene	(118-74-1)	Inadequate	Sufficient	2B	12.00	2	Medium
Hexachlorobutadiene	(87-68-3)	Inadequate	Limited	3[c]	0.50	4	Low
α-Hexachlorocyclohexane	(319-84-6)	Inadequate	Sufficient	2B	211.00	1	High
β-Hexachlorocyclohexane	(319-85-7)	Inadequate	Limited	3[c]	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[c]	0.27	4	Low
Hydrazine	(302-01-2)	Inadequate	Sufficient	2B	100.00	1	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
Indeno(1,2,3-cd)pyrene	(193-39-5)	Inadequate	Limited	2B	a	NA	a
Iodoethane	(75-03-6)	Inadequate	Limited	3[f]	NA	NA	a
Isosafrole	(120-58-1)	Inadequate	Limited	3[f]	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]	a	NA	High
Lead phosphate	(7446-27-7)	Inadequate	Limited	2B	a	NA	a
Lead subacetate	(1335-32-6)	Inadequate	Sufficient	2B	0.17	4	Low
Lithium chromate	(14307-35-8)	Inadequate	Inadequate	3[f]	a	NA	Medium
3-Methylcholanthrene	(56-49-5)	Inadequate	Sufficient	2B	12.00	3	Medium
4,4'-Methylene-bis-(2-chloroaniline)	(101-14-4)	Inadequate	Sufficient[e]	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	2B	a	NA	a

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

TABLE I. SUMMARY OF HAZARD RANKING INFORMATION FOR 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	[e]	NA	c
Mustard gas	(505-60-2)	Sufficient	Limited	1	[e]	NA	a
1-Naphthylamine	(134-32-7)	Inadequate	Limited	3[c]	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[i]	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[i]	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[c]	0.53	4	Low
Pentachloronitrobenzene	(82-68-8)	Inadequate	Limited	3[c]	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[c]	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[e]	[e]	NA	Medium
Potassium chromate	(7789-00-6)	Limited	Inadequate	1[e]	[e]	NA	Medium
Propane sultone	(1120-71-4)	Inadequate	Sufficient	2B	37.00	2	Medium
Propylenimine	(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 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
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[e]	[e]	NA	Medium[e]
Sodium chromate	(7775-11-3)	Limited	Inadequate	1[e]	[e]	NA	Medium
Streptozotocin	(18883-66-4)	Inadequate	Sufficient	2B	110.00	1	High
Strontium chromate	(7789-06-2)	Inadequate	Inadequate	1[e]	[e]	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	0.11	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 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
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[c]	0.30	4	Low
Trichloroethylene	(79-01-6)	Inadequate	Limited	3[c]	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	*	NA	*
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]Ot...r 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 epidemiology 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 epidemiology 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, 1981" 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

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HUMAN HEALTH AND THE ENVIRONMENT

SOME RESEARCH NEEDS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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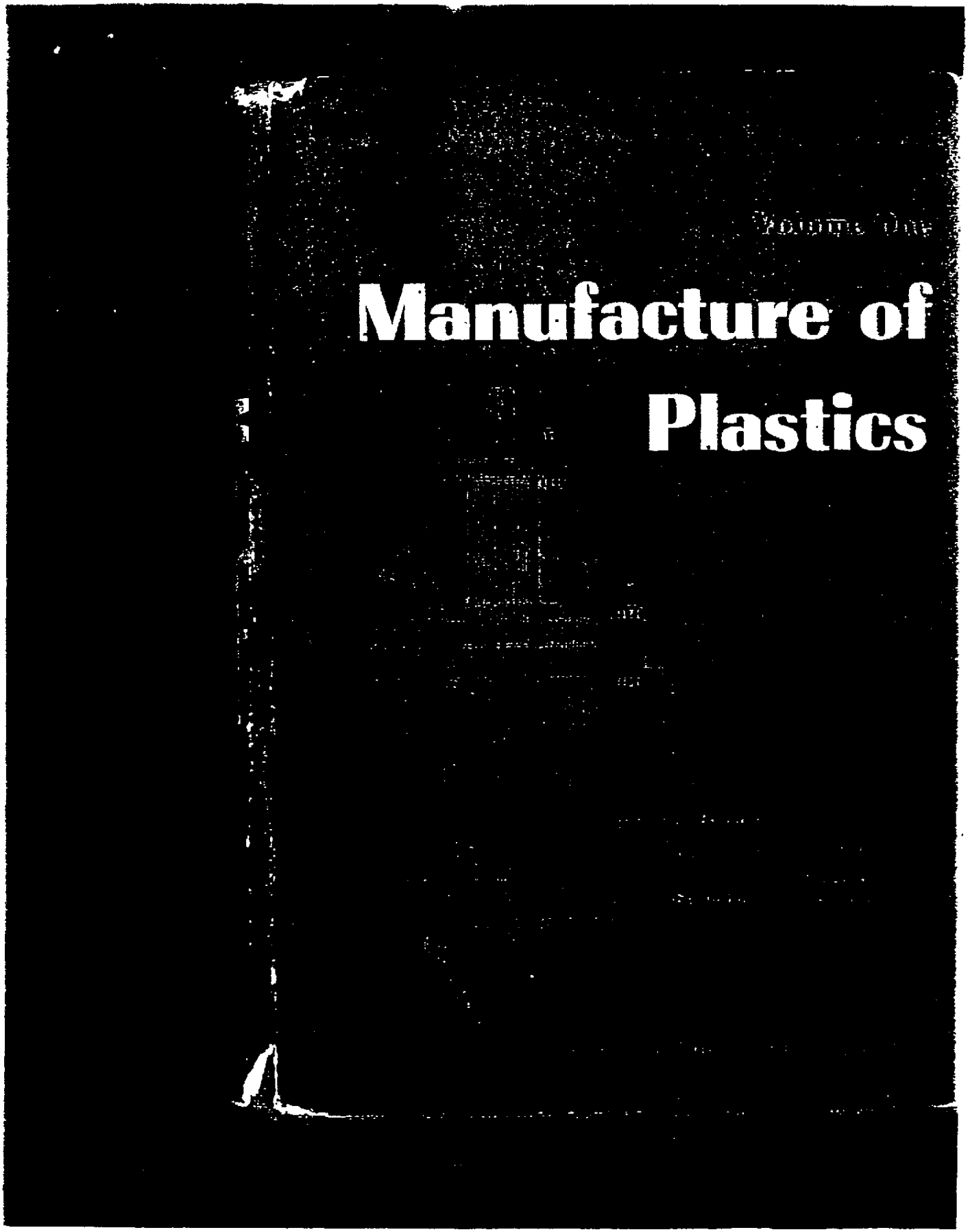

MANUFACTURE OF PLASTICS

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