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Appendix A

AUTHORS

This document is a combined effort of many SRI investigators, internal and external consultants, editors, and management review. The following attributions, therefore, indicate principal responsibilities rather than sole effort:

	Summary	Stephen L. Brown
I.	Introduction	Stephen L. Brown Michael C. McMillan
II.	Project Description	
	A. Proposed Code Change	Stephen L. Brown
	B. Projected Changes in Pipe Use	Therese A. Freeman
	C. Growth of Population Living in Dwellings with Plastic Water Pipe	Stephen L. Brown
	D. Other Major Assumptions	Stephen L. Brown
III.	Environmental Setting: Pipe and Fittings	
	A. Manufacture of Materials	Stephen L. Brown Eleanor M. Connolly H. Ernst Frey
	B. Manufacture of Pipe, Fitting, and Joining Materials	Stephen L. Brown Eleanor M. Connolly H. Ernst Frey
	C. Installation of Plumbing Systems	Douglas P. Fowler
	D. Use of Plumbing Systems	Stephen L. Brown
	E. Water Distribution and Waste Collection	Jack Van Zandt
IV.	Environmental Impacts and Mitigations	
	A. Water Quality	Thomas R. Podoll David Kelly
	B. Public Health	Michael J. Lipsett Ann Winship-Ball J. Wesley Clayton
	C. Worker Safety and Health	Douglas P. Fowler Ann Winship-Ball Samuel D. Kaplan
	D. Fire Safety	Jana Backovsky Raymond S. Alger Stanley B. Martin

IV.	Environmental Impacts and Mitigations (Concluded)	
	E. Smoke and Combustion Product Toxicity	Charles A. Tyson Stanley B. Martin
	F. Fiscal Impacts	Therese A. Freeman Steven R. Pierce
	G. Other Impacts	Sidney J. Everett Richard L. Goen Steven R. Pierce
V.	CEQA Summary	Stephen L. Brown Therese A. Freeman Sidney J. Everett
VI.	Testing Needs and Other Information Gaps	Stephen L. Brown Entire team
VII.	Bibliography	Entire team
Appendices		
	A. Authors	Stephen L. Brown
	B. Organizations and Persons Consulted	Entire team
	C. Glossary of Terms and Abbreviations	Stephen L. Brown
	D. Detailed Toxicology of Substances Associated with Plastic and Metal Pipes	Michael J. Lipsett Ann Winship-Ball J. Wesley Clayton
	E. Details of Worker Safety and Health	Douglas P. Fowler
	F. Smoke Toxicity Details	Stanley B. Martin Charles A. Tyson

Appendix B

ORGANIZATIONS AND PERSONS CONSULTED

The list below, while not exhaustive, shows the principal contacts made by SRI in getting information relevant to the environmental review. The first section shows contacts external to SRI; the second shows SRI personnel who were consulted but are not authors. In each case, we show the name of the person and organization represented, if known, and the general topic(s) of the discussion.

External Contacts	Topic(s)
Adams, Thomas R. Adams, Broadwell & Russell	Extent of Work in Various Activities by Plumbers; Average Hourly Wages
Alarie, Yves University of Pittsburgh	Request for Research Results on Smoke Toxicity
Anand, Vir U.S. Food and Drug Administration	Request for Unpublished Data on Organotins
Anderson, Rosalind Arthur D. Little, Inc.	Smoke Toxicity Testing
Barr, John Air Products and Chemicals, Inc.	Comments on and References for Public Health Draft
Beauchamp, Jr. Robert Chemical Industry Institute of Toxicology	Request for Information on Specific Chemical Leachates
Bellack, Errin Office of Drinking Water U.S. Environmental Protection Agency	Risk Assessment Issues

Brown, Raymond J. Copper Development Association	Manufacture and Sales of Copper Pipe
Caplan, Yale H. Maryland Institute for Emergency Medical Service Systems	Reports of Increased Fire Deaths in Recent Years
Carns, Keith East Bay Municipal Utility District	Field Testing for Water Quality
Chernoff, Gerald University of California, San Diego	Thresholds for Teratogens
Cotruvo, Joseph Office of Drinking Water U.S. Environmental Protection Agency	Request for Information on Risk From Short-Term Exposures
Costello, _____ U.S. National Institute of Occupational Safety and Health	Request for Information on Smoke Toxicity
Craig, Douglas Litton Bionetics	Toxicity of DMF
Doull, John University of Kansas Medical Center	Request for Information on Lead
Dunnigan, Paula B. F. Goodrich Company	Technology and Economics of Plastic Pipe
Dyer, Dr. Robert Health Effects Research Laboratory U.S. Environmental Protection Agency (RTP)	Neurotoxicology of Organotin Compounds
Elmer, Jill Loctite Corporation	Composition of Pipe Joint Compounds
Flint, _____ Ciba-Geigy	Toxicity of Irganox 1010
Gaspar, Robert R & G Sloane Manufacturing Co.	Plastic Pipe Technology
Gorman, Richard U.S. National Institute of Occupational Safety and Health	Information on Exposures for Plumbers and Health Effects
Gralla, E. Toxigenics	Inhalation Toxicology of MEK

Halperin, William U.S. National Institute of Occupational Safety and Health	Information on Exposures for Plumbers and Health Effects
Harwich, Nancy Security Pacific Bank	Amount and Value of Construction in California
Hilado, Carlos Product Safety Corporation	Smoke Toxicity Testing
Jackson, Richard California Department of Health Services	Existence of Thresholds for Teratogens
Jaeger, R. J. New York University	PVC Smoke Toxicity
Juodecka, Lois U.S. National Toxicology Program	Bioassay Status of Leachates
King, M. E. California Department of Housing and Community Development	Building Codes and Standards
Lappé, Marc University of California Berkeley	Comments on and References for Public Health Draft and Other Relevant Information
Lassiter, Donald V. Consultant	Work Injuries and Illnesses among Plumbers
Lassouszky, Peter Office of Drinking Water U.S. Environmental Protection Agency	Lead Solder
Levine, Robert S. U.S. National Bureau of Standards	Fire Safety and Smoke Toxicity
Lyman, Stuart Copper Development Association	Manufacture and Sales of Copper Pipe
McAllister, Scott California Division of Occupational Safety and Health	Plumbing Trades Practices and Hazards
McCarthy, Ann Chemical Industry Institute of Toxicology	Inhalation Toxicology of MEK

McClelland, Nina, et al. National Sanitation Foundation	Acceptance, Listing and Monitoring of Plastic Pipes and Related Materials
Marbach, Dr. Howard U.C. San Francisco School of Medicine	Skin Absorption of Organic Compounds
Melius, James U.S. National Institute of Occupational Safety and Health	Request for Information on Exposures of Plumbers
Moskowitz, Susan Office of Drinking Water U.S. Environmental Protection Agency	References for Drinking Water Contaminants
Needleman, Herbert University of Pittsburgh	Safe Levels for Lead
Nelson, Steven Menlo Park Building Department	Building Inspection Practices
Ogara, Kevin California Department of Industrial Relations	Records of Occupational Injury among Plumbers
Parker, William U.S. National Bureau of Standards	Fire Safety Testing of Plastic Pipe
Pfaff, Marie Cancer Assessment Group U.S. Environmental Protection Agency	Methodology of Cancer Assessment
Reid, Thomas Thomas Reid and Associates	Public Health Hazards of Leachates from Plastic Pipe
Richmond, Brad California State Compensation Insurance Fund	Changes in Risk of Plumbers over Time
Rondet, _____ California Division of Occupational Safety and Health	Request for Information on Exposures of Plumbers
Schuler, R. U.S. National Institute of Occupational Safety and Health	Mutagenicity of DMF, Cyclohexanone
Schwemmer, Bruce Ciba Geigy	Toxicity of Irganox 1010

Shedroff, T. Lake Chemical Company	Composition of Soldering Flux
Skory, Lyman Consultant	References on Toxicology
Spath, David California Department of Health Services	Background Levels of Water Quality in California
Stein, Ilene Science Advisory Board U.S. Environmental Protection Agency	Review of Health Assessment Documents
Stevens, Richard National Fire Protection Association	Various Aspects of Smoke Toxicity and Test Development
Szamborski, Eugene Society of the Plastics Industry	Comments on Public Health Draft
Thorslund, Todd Carcinogen Assessment Group U.S. Environmental Protection Agency	Cancer Risk Assessment Methodology
Torey, Henry U.S. Federal Emergency Management Agency	National Fire Information Retrieval System
Vraun, Tre California Department of Finance	Employment in California Industries
Wagner, W. E. U.S. National Institute of Occupational Safety and Health	Inhalation Study of DMF
Wong, Joel California Division of Occupational Safety and Health	Request for Information on Exposures of Plumbers
Zumwalde, Ralph U.S. National Institute of Occupational Safety and Health	Request for Information on Exposures of Plumbers
_____, _____ F n' F Plumbing Supply	Plumbing Materials Prices
_____, _____ Ward Supply Company	Plumbing Materials Prices
_____, _____ Familiar Pipe and Supply	Plumbing Materials Prices

_____, A-1 Turf	Plumbing Materials Prices
_____, P. E. O'Hair	Plumbing Materials Prices
_____, Penn Plumbing Supply	Plumbing Materials Prices
_____, Reeve's Plastic Pipe Company	Plumbing Materials Prices
_____, Surplus Plumbing Supply Company	Plumbing Materials Prices
_____, Torrance Tube Company	Manufacture of Steel Pipe in California
_____, International Association of Plumbing and Mechanical Officials	Uniform Plumbing Code and Uniform Building Code

SRI Contacts

Fishman, Norman Chemical Industries Division	Polymer Technology and Applications
Helmes, C. Tucker Life Sciences Division	Structural Analogies to Known Carcinogens
Parkinson, Dean Physical Sciences Division	Polymer Composition and Combustion Characteristics
Sigman, Caroline Life Sciences Division	Structural Analogies to Known Carcinogens
Stone, Gene Project and Facility Support Services	Pipe and Fitting Use in Dwellings
Thiers, Eugene Industry Consulting Division	Metal Pipe Technology and Prices
Von Axelson, Carl-Fredrik Industry Consulting Division	Copper Pipe Technology

Appendix C

GLOSSARY OF TERMS AND ABBREVIATIONS

ABS	Acrylonitrile-butadiene-styrene plastic.
Additive effects	The combined biological effects of two or more substances are additive when equal to the sum of the effects of the substances acting alone.
Adverse reproductive outcome	Any of a variety of deleterious effects on reproduction, including impaired fertility, sterility, spontaneous abortion, stillbirth, birth defects, developmental retardation in offspring.
AN or ACN	Acrylonitrile.
Antagonistic effects	Two or more substances are antagonistic when the combined biological effects are less than the sum of the effects of the substances acting alone.
Btu	British thermal unit (a measure of heat energy).
CPVC	Chlorinated polyvinyl chloride.
Carcinogen	A chemical or physical agent that can cause cancer.
Central nervous system	The brain and spinal cord.
Chase	An enclosed space in walls or columns or between floor and ceiling in which piping is concealed.
Clastogen	A chemical or other agent that injures chromosomes or causes damage to chromosomal structure.
Cyclo	Cyclohexanone.
Dermal	Via the skin.
DHCD	California's Department of Housing and Community Development.
DMF	Dimethyl formamide.
DWV	Drain, waste, and vent.

Dose	The quantity of a physical or chemical agent administered to a living system (typically an animal or human). The term may also refer to the amount of the agent that reaches the target organ, tissue, or cells; in this case it is usually referred to as the "target" dose or "effective" dose.
Dose-response curve	A diagrammatic representation of the intensity of biological response to different dose levels. A typical curve is S-shaped, showing responses of an individual organism or system or of a percentage of a population.
Dwell time	The time water stands in a pipe system between withdrawals.
Fittings	Plumbing items that join two or more pieces of pipe and enable changes in direction or branching.
Fixtures	The hardware (sinks, tubs, toilets, and so on) to which plumbing is attached.
Flashover	A phenomenon in which an entire room bursts into flame as a critical temperature is exceeded.
Flushing	Running numerous void volumes of water through a pipe to discharge any leached materials.
GI	Gastrointestinal.
HCl	Hydrochloric acid.
HCN	Hydrogen cyanide.
IAPMO	Internation Association of Plumbing and Mechanical Officials.
IARC	International Agency for Research on Cancer.
Idiosyncratic reaction	An unusual individual sensitivity or susceptibility to the effects of one or more substances.
Initiator	In theoretical carcinogenesis, an agent capable of directly affecting cellular DNA, "initiating" a cell, tissue, or organ for the evolution of a tumor.
LC_{50}	Median lethal concentration (i.e., the concentration level of an agent that is fatal for 50% of the population exposed to it).
LD_{50}	Median lethal dose.

Leachates	Chemicals that move (leach) into water from plastic or metal pipes, fittings, and joining materials.
MCL	Maximum contaminant level.
MEK	Methyl ethyl ketone.
Monomer	The single molecules that are joined together to make a polymer.
Mutagen	A physical or chemical agent causing mutations in genetic material.
Mutation	A change in genetic material, typically involving a single gene. Mutations can be spontaneous or caused by a chemical or physical agent. Mutations affecting reproductive cells are called germ cell mutations; all others (in animals) are called somatic mutations. If a mutation is repaired or is fatal to a cell, it is not passed on to the cell's or organism's progeny: otherwise the change may become hereditary.
NSF	National Sanitation Foundation.
NTP	National Toxicology Program.
Neurotoxin	An agent that is capable of injuring nerve tissue.
PB	Polybutylene.
PE	Polyethylene.
PEL	Permissible exposure level.
Permeation	Movement of chemicals from outside a pipe through the pipe or its joints into water.
Peripheral nervous system	The nerves connecting the brain and spinal cord with the rest of the body. Sensory nerves transmit signals from receptors such as the eyes, nose, ears, mouth and skin, while in the other direction, motor nerves conduct impulses to the muscles, and autonomic nerves to the heart, glands, and other internal organs.
Polymer	A high-molecular-weight organic chemical consisting of a straight or branched chain of monomer units.
Potentiation	An agent can potentiate or augment the toxic effects of another agent even though the former does not cause such effects by itself.

Primer	A material used to clean and presoften plastic pipe prior to solvent cementing.
Promoter	In theoretical carcinogenesis, an agent that promotes the appearance of a tumor in a tissue or organ whose DNA has been changed or "initiated." This represents a particular case of potentiation, in that a promoter cannot cause cancer by itself. However, some carcinogens have capabilities of both initiation and promotion.
PVC	Polyvinyl chloride.
Pyrolysis	Decomposition of a material under heat. Often used to refer to thermal breakdown without flame, especially in a low-oxygen environment.
SNARL	Suggested no adverse response level.
Solvent cement	A material consisting of one or more solvents and other materials that softens plastic pipe and allows it to be permanently joined.
Stabilizer	A chemical added to plastic formulations to prevent the polymer from breaking down under heat, ultraviolet radiation, or other attack.
STEL	Short-term exposure limit.
Synergistic effects	The combined biological effects of two or more agents are synergistic if they are greater than the sum of the effects of the agents acting alone.
Teratogen	A physical or chemical agent capable of causing physical defects in an embryo (birth
Thermoplastic	A plastic material that softens when hea d hardens when cooled.
Thermoset plastic	A plastic material that hardens permanently after heating.
THF	Tetrahydrofuran.
Threshold	A dose or exposure level below which a particular toxic effect is not observed.
TLV	Threshold limit value.
TWA	Time-weighted average.

UPC	Uniform Plumbing Code, published by IAPMO.
Void volume	The volume of water standing in a pipe during static conditions.

Appendix D
DETAILED TOXICOLOGY OF SUBSTANCES
ASSOCIATED WITH PLASTIC AND METAL PIPES

Substances Associated with PVC Plastic Pipes

Dimethylformamide

Dimethylformamide (DMF), a common constituent of adhesives used for PVC piping, is a colorless liquid that is highly soluble in water and miscible with other organic solvents. It is used as a solvent in a wide variety of industrial processes, particularly in the production of acrylic fibers, vinyl-based polymers used in coatings and adhesives, and polyurethanes.

NIOSH (1980) estimates that in 1980, 69,000 workers in 25 major industries were exposed to DMF. Occupational exposure to DMF occurs primarily through inhalation or skin contact (Proctor and Hughes, 1978). The compound is effectively absorbed by the skin. Workplace airborne concentrations ranging from less than 10 ppm to more than 200 ppm have been reported (Lyle et al., 1979). Because levels are equal to or may exceed 10 ppm the OSHA Permissible Exposure Limit (OSHA, 1981) and ACGIH Threshold Limit Value (ACGIH, 1982), some workers are at risk of exposure to potentially harmful concentrations.

Consumers may also be exposed to dimethylformamide through inhalation and skin contact. The NIOSH Tradename Data Base lists 25 products containing 1 to 99 percent DMF, including coatings, adhesives, degreasers, paint strippers, deicing agents, and other compounds that may be used in the home in addition to the workplace (NIOSH, 1981). In a 1979 study of organic solvent use, DMF was ranked twelfth out of 34 solvents on the exposure index for consumers (Lee et al., 1979).

Because DMF is stable in water at neutral pH (Eberling, 1980), the public may be exposed by drinking water containing the compound. DMF has been detected in the effluent from several industries and domestic sewage treatment plants (Shackelford and Keith, 1976) and is a leachate from plastic piping systems (Montgomery, 1980).

Absorption and Metabolism

DMF is absorbed through the skin and lungs as well as the gastrointestinal tract; free DMF appears in the blood and urine regardless of the route of administration. DMF is metabolized by humans, dogs, and rats to N-methylformamide (NMF) and formamide, two suspected teratogenic agents (Maham, 1977; Kimmerle and Eben, 1975a, 1975b). Maham (1977) has proposed a sequence for the metabolism of DMF that includes N-methyl-N-hydroxy-methyl formamide, formaldehyde, N-methyl formamide, formamide, ammonia, and formic acid. Not all steps have been empirically verified in animal species.

In humans exposed to approximately 8 ppm for 6 hours on 5 consecutive days, the majority of the absorbed dose was eliminated within 24 hours. The main urinary metabolite is N-methyl formamide (NMF); its presence in the urine is a sensitive indicator of exposure to DMF, even at levels lower than the current OSHA permissible inhalation exposure limit, 10 ppm (Krivanek et al., 1978; Maxfield et al., 1975). Unmetabolized DMF is also found in the urine after exposure. Toxic doses result in a higher concentration of DMF relative to NMF; essentially nontoxic doses produce the opposite result (Sanotskii et al., 1978). NMF is considered to be a more toxic compound than DMF.

Ethanol alters the rate of DMF metabolism in humans and animals; DMF may, in turn, alter ethanol metabolism, most likely by inhibition of acetaldehyde metabolism. Daily alcohol consumption retarded DMF metabolism in workers handling surface-treating agents containing the compound (Yonemoto and Suzuki, 1980). Prior administration of ethanol retarded DMF metabolism in four human volunteers exposed by inhalation and in beagle dogs

exposed by inhalation before or after treatment with ethanol (Eben and Kimmerle, 1976). Mice pretreated with DMF and then given alcohol had significantly higher blood alcohol levels than ethanol-only controls (Sharkawi, 1980).

Acute Toxicity

DMF is moderately irritating to the skin, eyes and respiratory tract. Prolonged or repeated contact with the liquid may defat the skin and cause dermatitis (Proctor and Hughes, 1978). DMF also appears to lower the resistance of the skin to other compounds and to enhance absorption in a manner and degree similar to DMSO (Munro and Stoughton, 1965; Schulze, 1971). Although there is no experimental evidence that it is a skin sensitizer, exposed workers have reportedly experienced eczema, vitiligo, and delayed skin sensitivity (Bainova, 1975).

According to Gosselin et al. (1976), the probable lethal oral dose in humans ranges from 500 mg to 5,000 mg/kg. DMF is toxic to the liver and highly irritating to the gastrointestinal tract. In one incident workers exposed to concentrations ranging from < 20 ppm to 35 ppm for 32 weeks complained of nausea, vomiting and abdominal pain; liver enlargement was detected in some cases (Proctor and Hughes, 1978). In a second report, complaints of stomach disorders, headache, nausea and loss of appetite occurred among 24 workers exposed to an unknown concentration of DMF; several of these individuals, however, had reported stomach problems before exposure (Massman, 1956). Several other reports of gastrointestinal disorders resulting from exposure to DMF were reviewed, all describing similar symptoms. Employees exposed to DMF in a synthetic rubber plant reported frequent headaches and dizziness (Wink, 1972).

A Soviet investigator reported an increase in spontaneous abortions in women occupationally exposed to DMF (Schottek, 1972). The abstract reviewed contained insufficient information to permit a critical evaluation and interpretation of the findings, but Eastern European scientists often report

such events without addressing the questions of background incidence and documented exposure.

One of the potentially important aspects of DMF biological activity is its interaction with ethanol. Although some workers have noticed facial flushing after inhaling DMF vapors alone, the effect was especially pronounced when alcoholic beverages were taken coincidentally (a single glass of beer was sufficient to induce the reaction (Lyle et al., 1979). Alcohol intolerance (a reaction similar to that produced by Antabuse) has also been reported (Chivers, 1978).

A 10 mg dose applied to rabbit skin produced irritation 24 hours after treatment (NIOSH, 1981); 20 mg instilled in the rabbit eye was moderately irritating (E. I. DuPont, 1980).

Numerous studies of the acute toxicity of DMF have been performed. In range-finding experiments using cats, rabbits, and mice, the most prominent features of toxicity were liver and kidney damage. The cat and dog are the most sensitive laboratory species tested, with a median lethal oral dose (the dose estimated to kill half the animals tested) of approximately 500 mg/kg (Massman, 1956; NIOSH, 1981). Cats showed severe effects at inhalation exposures of 100 ppm (Massman, 1956). The compound is much less toxic to the rat, mouse, rabbit and guinea pig by all routes tested.

The major target organ of DMF is the liver. Single intraperitoneal injections of 0.5 ml/kg to 1.2 ml/kg have produced degenerative changes in the liver in hamsters (Ungar et al., 1976) and rats (Mathew et al., 1980). Neurological effects have also been reported. A single DMF dose of 2 ml/kg (intraperitoneal) or 5 ml/kg (oral) administered to rats caused cholinesterase depression; carbaryl-induced cholinesterase inhibition was also enhanced (Weiss and Orzel, 1967). White rats exposed by inhalation continously for 2 months to 0.5 or 10 mg/m^3 DMF in air exhibited significantly reduced cholinesterase levels and decreased coproporphyrin elimination in the liver (Odoshashvili, 1963). DMF had no direct effect on the central nervous system when administered intraperitoneally to mice in

sublethal doses (0.75 to 3.2 g/kg). However, it lengthened the narcosis induced by hexobarbital, chloral, or urethane, and increased the duration of penetrazole-induced convulsions (Chanh et al., 1973).

Chronic Toxicity

DMF has produced liver damage in several species when applied to the skin, given orally, or administered in inhalation chambers. Kidney damage and changes in blood pressure and cardiac function have also been seen. Dogs, rabbits, guinea pigs, rats, and mice were exposed to air concentrations of 23 ppm DMF for 5-1/2 hours followed by a 1/2-hour exposure to 426 ppm for 58 weekdays. Functional effects on the liver, pancreas, spleen, kidneys, adrenals, and thymus of all animals were seen. Degenerative changes in the heart and cardiovascular effects, including decreased systolic blood pressure, were seen in dogs (Clayton et al., 1963).

Rats exposed to unspecified concentrations of DMF for 1/2 hour per day for 30 days exhibited hemorrhage and edema of the lung, hemorrhage and degeneration of the liver, and less severe changes in the kidney and heart. The degree of pathologic change was positively correlated with the concentration and duration of exposure (Cruz and Corpino, 1978; Cruz and Maccioni, 1978). Details of testing were not available in the English language summaries.

Effects on Genes and Chromosomes

The mutagenic potential of DMF has been studied in several test systems and the majority of results have been negative. Results in 6 of 7 Salmonella reversion assays have been negative (see section on carcinogenicity). The compound was also negative in an E. coli reversion assay (Vasil'eva, 1975), a transplacental host-mediated hamster cell culture system (Quarles et al., 1979), and an hepatocyte primary culture/DNA repair system (Williams and Laspia, 1979). Recently DMF was tested under the National Toxicology Program in the following assays: Drosophila sex-linked recessive lethal, rat dominant lethal, mouse sperm head morphology, rat bone

marrow cytology, and *in vitro* unscheduled DNA synthesis in human fibroblasts. Results have been requested but have not been received.

Carcinogenicity

No results of standard bioassays or long term studies designed to determine the carcinogenic potential of DMF have been conducted, although an inhalation bioassay is now in progress at Litton Bionetics. The only report of induced carcinogenesis found in the literature is the work done in rats by Kommineni (1972). This study suffered from several design deficiencies, and results were not statistically significant. It is difficult to evaluate the biological significance of these results.

The short-term screen used most often to predict carcinogenicity is the Ames Salmonella assay in which positive "carcinogens" induce mutations in the bacteria; survival rates reflect mutation rates. DMF was negative (not mutagenic) in five of six batteries of Ames assays reported (Amlacher and Ziebarth, 1979; Commoner, 1976; Ong et al., 1980; Purchase et al., 1976; NTP, 1980; ICI Ltd, undated). Concentrations were not consistently reported, but included 100 µl/plate and $\leq$ 400 µl/plate. A test with four unspecified strains produced positive results at 200 µl/plate.

A large number of studies of DMF have concerned antitumorigenic effects, particularly differentiation of tumor cells (Avdalovec and Aden, 1978; Bendich et al., 1974; Borenfreund et al., 1975; Calabresi et al., 1979; Collins et al., 1978; Dexter et al., 1979; Dexter and Hager, 1980; Dexter et al., 1978; Fontana et al., 1980; Hager et al., 1980; Madhavan, 1972; Novogrodsky et al., 1980; Preisler, 1976; Santoro et al., 1978; Spilker, 1970). In one study, DMF treatment of cell cultures from a murine rhabdomyosarcoma induced morphologic differentiation and a marked reduction in the tumorigenicity of the sarcoma cells. Of 17 CE/J mice receiving injections of DMF-treated cells, 14 did not develop tumors after 6 months. All 21 mice receiving untreated sarcoma cells died of disease between 11 and 32 days after inoculation (Dexter, 1977).

DMF may protect rats and mice from the tumorigenic action of dimethylinitrosamine through inhibition of its metabolism. This inhibition has been demonstrated in vitro using rat liver microsomes (Arcos et al., 1976) and in vivo using a radioactively labelled chemical to demonstrate reduced binding to liver protein in rats pretreated with DMF (Mirvish and Sidransky, 1971). In another study partially hepatectomized female rats were given an intraperitoneal injection of 6 to 9 mg/kg dimethylnitrosamine alone or in combination with DMF. One to two years later, animals treated with dimethylnitrosamine alone showed a high incidence of liver nodules and carcinomas. None of the rats receiving the combination treatment developed nodules or liver tumors (Craddock, 1971).

DMF has also exhibited effects associated with tumor induction or promotion (Argus et al., 1966; Blau and Epstein, 1979; Porter, 1979; Sato et al., 1975). The ability of DMF to induce cell transformation was tested in several systems. Positive results (transformations) were obtained with DMF in human peripheral lymphocytes (Koudela and Spazier, 1979); negative results were obtained with Syrian hamster embryo cells (Pienta, 1980) and Syrian hamster kidney fibroblasts (Purchase et al., 1976).

Effects on Reproduction

DMF is metabolized to formamide and N-methyl formamide, both of which have been identified by NIOSH as experimental teratogens (NIOSH, 1981). It is known to cross the placenta to the fetal blood circulation in the rat (Sheveleva et al., 1977). Many results of teratogenicity screens cannot be fully evaluated because dose levels were not reported (Scheufler, 1976; Schmidt, 1976) or because the administered dose produced maternal toxicity (Merkle and Zeller, 1980). In several studies, no teratogenic effects were reported (Gleich, 1974; Kimmerle and Machemer, 1975; Sheveleva et al., 1979; Thiersch, 1971).

DMF administered by gavage to groups of 10 pregnant rabbits on Days 6 through 18 of gestation caused a small decrease in fertility and growth retardation and malformations in fetuses, but the overall number of

experimental animals was too small to produce statistically significant results (Merkle and Zeller, 1980). Inhalation exposure of rats to concentrations as great as 17 times the OSHA PEL (10 ppm) resulted in no biologically significant effect on reproductive outcome (Kimmerle and Machemer, 1975). At higher exposure levels however, the compound was embryotoxic and abortifacient (Sheveleva et al., 1979). Exposure to DMF in several fractions was more embryotoxic to rats than the same dose given in a single application (Stula and Krauss, 1977). Pregnant Sprague-Dawley rats (N = 19/group) were exposed for 6 hours per day on Days 6-15 of gestation to 0, 32, or 301 ppm DMF. Exposure to 32 ppm did not affect survival, fetal weight, or development. Exposure to 301 ppm caused slight depression of fetal weights and slight increases in normal ossification variations. No excess of soft tissue or skeletal abnormalities was observed, and therefore, the compound was not teratogenic under the conditions of the test (Keller and Lewis, 1981).

The studies reviewed suggest that DMF is embryotoxic and may also decrease fertilty. The available data do not indicate that it is teratogenic. Many data gaps exist, however, and most investigations have not been conducted with sufficient numbers of animals to ensure statistically significant results.

Tetrahydrofuran

Tetrahydrofuran (THF) is a solvent used in plastics and resins manufacture as well as in adhesives made for use with PVC and CPVC piping. It is miscible with water and other organic solvents. It has a vapor pressure of 143 mm Hg at 20°C and is quite volatile. The chief hazard associated with the use of THF is not its toxicity, but its flammability (duPont, 1977).

NIOSH (1980) estimates that approximately 95,000 workers are exposed annually to THF. Both the current OSHA Permissible Exposure Limit (OSHA,

1981) and ACGIH Thresnold Limit Value (ACGIH, 1982) are an 8-hour time-weighted average of 200 ppm.

Absorption and Metabolism

No information on the metabolism of THF was found. Because the compound is so volatile, most of an inhaled dose is likely to be eliminated unchanged in the expired air.

Acute Toxicity

No fatal human exposures were reported in the literature reviewed. THF is a mild irritant of the eyes and mucous memberanes. Exposure may defat the skin and cause dermatitis (duPont, 1977). Exposure to concentrations above the PEL may result in nausea, dizziness and headache, but these symptoms are readily reversible in fresh air (AIHA, 1959). THF has good warning properties; its odor is detectable at 25-50 ppm, levels well below the permissible exposure limit (duPont, 1977). Gosselin et al. give THF a toxicity rating of 4; the probably lethal human dose is estimated to be 50-500 mg/kg (Gosselin et al., 1976).

Two reports of injury potentially attributable to THF exposure were reviewed. In the first, a worker exposed to a mixture of THF and MEK experienced symptoms of peripheral neuropathy (Viader et al., 1975). In the second, a pipefitter exposed to THF, cyclohexanone, and acetone reported disturbed olfactory function (Emmet, 1976). In both cases exposures were mixed, and the cause of the disorders cannot be determined. No other systemic effects of exposure to THF were reported.

The lowest oral dose of THF lethal to the rat is 3,000 mg/kg; the lowest lethal concentration is 2,800 mg/m^3 for 2 hours (NIOSH, 1981). In cats, rabbits, rats and mice, concentrations of approximately 60,000 ppm were required to produce narcosis. Concentrations above 3,000 ppm produced upper respiratory tract irritation in animals exposed for 8 hours/day for 20 days. Cats and rabbits subjected to 30 6-hour exposures to 3,400 ppm THF in

air exhibited no liver or kidney damage. Dogs exposed to concentrations of 336 ppm and 2,100 ppm for 6 hours per day, 5 days per week over a 12-week period exhibited decreased blood pressure, but no demonstrable pathology was present in the lungs, heart, liver, pancreas, kidneys or spleen (duPont, 1977).

Chronic Toxicity

No chronic effects attributed to THF have been reported. One study reported liver and kidney injury in animals exposed to 3,000 ppm, but these effects are believed to have been caused by the presence of contaminants in the test compound (Proctor and Hughes, 1978). THF supplied by Du Pont, the major producer in the U.S., is reported to be more than 99.9 percent pure. A prechronic test of THF has been completed under the NCI/NTP carcinogenesis bioassay program; it has not been scheduled for chronic testing (Juodeika, 1983). Results of the prechronic test have been requested but not received.

Cyclohexanone

Cyclohexanone, a cyclic 6-carbon ketone, is a colorless liquid with a peppermint-like odor. It is used widely in organic synthesis and as a solvent for various materials, including natural and synthetic resins. it is a common component of cements used with PVC and CPVC piping (Department of Housing and Community Development, 1983).

NIOSH (1980) estimates that approximately 10,000 workers are exposed annually to cyclohexanone. Cyclohexanone is considered to be moderately toxic by dermal, oral, and inhalation routes. It has mild narcotic properties (Sax, 1979). A pipefitter experienced olfactory disturbances after exposure to cyclohexanone, THF, and acetone (Emmet, 1976). The relationship between the disturbance and exposure to any one of the solvents could not be determined from the evidence presented. At an atmospheric concentration of 75 ppm, cyclohexanone is mildly irritating to the eyes and respiratory tract (NIOSH, 1981). Repeated skin contact may cause defatting of the skin and dermatitis, but absorption through the skin is insignificant

(Proctor and Hughes, 1978). The current ACGIH TLV is set at 25 ppm (ACGIH, 1982); the OSHA PEL is 50 ppm (OSHA, 1981).

Absorption and Metabolism

Cyclohexanone is reduced to cyclohexanol, which is then glucuronidated in the liver (Elliot et al., 1959). Approximately 74-100 percent of administered cyclohexanone was converted to cyclohexanol and excreted in the urine as a glucuronide conjugate in less than 24 hours (Martis et al., 1980). In rats dosed intraperitoneally with cyclohexanone, urinary excretion constituted a minor pathway, with only 15-24 percent of the administered dose being excreted as the glucuronide and 1 percent excreted as cyclohexanone or cyclohexanol; no sulfate conjugates were detected. The authors suggest that the majority of the compound was excreted in the breath as the ketone or alcohol, or in the feces as a conjugate of cyclohexanol (Greener et al., 1982). Gupta et al. (1979) administered cyclohexanone and pentobarbital concurrently to mice. Because cyclohexanone did not increase pentobarbital-induced sleeping time, the authors concluded that the compound did not significantly affect the hepatic microsomal oxidation function responsible for pentobarbital metabolism.

Acute Toxicity

The lowest median lethal oral dose (LD_{50}) of cyclohexanone reported for rats is 1620 mg/kg; the lowest concentration lethal to rats exposed by inhalation is 2,000 ppm for 4 hours. The rabbit dermal LD_{50} is 1,000 mg/kg (NIOSH, 1981). Gupta et al. (1979) performed a series of acute toxicity tests with mice, rats, and guinea pigs using intraperitoneal or intragastric administration. Dying animals exhibited peritoneal and intestinal congestion, and signs of irritation. Repeated doses produced cumulative effects in mice as indicated by a significant reduction (approximately 90 percent) in the median lethal dose as the period of administration increased from one day to ten weeks.

Cyclohexanone is irritating to the eyes and skin, the degree of irritation being a function of the applied concentration. In rabbits, a 12.4 percent cyclohexanone/cottonseed oil solution applied to the shaven back was only slightly irritating; a 99 percent solution was very irritating. Similar concentration-dependent results were obtained when various concentrations were instilled in the rabbit eye; a 2.5 percent solution was not irritating, whereas a 99 percent solution was very irritating (Gupta et al., 1979).

Greener et al. (1982) administered cyclohexanone intravenously to rats for 28 days at 0, 50, or 100 mg/kg. No toxic effcts were observed, but the number of animals per group (N = 10) was small. Rengstorff treated guinea pigs by dermal application or subcutaneous injection with 500 mg cyclohexanone three times weekly for 3 weeks. He observed cataract development in four of the twelve animals exposed. The details of the experiment were not available and therefore the significance of the result is difficult to evaluate (Rengstorff et al., 1972). The formation of corneal opacities is a response that is frequently seen in laboratory animals exposed to organic solvents. The effect is usually reversible, and no correlation between the development of opacities in laboratory animals and the formation of cataracts in humans has been established.

Chronic Effects

No long-term studies of the effects of cyclohexanone were reported in the literature.

Effects on Genes and Chromosomes

Cyclohexanone has been tested in a NIOSH-sponsored Tier II mutagenicity screening program (McGregor, 1980). No effects on genes or chromosomes were observed in any of the tests, which included the following:

(1) Unscheduled DNA synthesis (UDS) assay in human diploid fibroblasts with exposures of 3 hours duration and concentrations of up to 9.48 mg/ml of culture medium.

(2) Dominant lethal test in male rats with exposure to atmospheres containing 50 ppm or 400 ppm cyclohexanone for 7 hours per day for 5 consecutive days.

(3) Sperm abnormality test in male mice using the same exposure conditions as in (2).

(4) Cytogenetic test in male and female rat bone marrow cells using the same exposure conditions as in (2) or a single exposure of 7 hours duration followed by sampling after 6 hours, 24 hours, and 48 hours.

(5) Sex-linked recessive lethal (SLRL) test in Drosophila melanogaster with exposure to atmospheres of 50 ppm for 7 hours or 400 ppm for 40 minutes.

Cyclohexanone was reported to be mutagenic in assays using B. subtilis and S. typhimurium; no details of the test protocol and methods were supplied (Massoud et al., 1980). No other data on mutagenic potential were located. The cytotoxicity of cyclohexanone was determined by Gupta et al. (1979); a medium containing 1.95×10^{-2} moles/liter inhibited the growth of mouse fibroblast cells by 50 percent. The composition of the medium was not reported.

Carcinogenicity

Cyclohexanone is currently being tested in an NTP/NCI bioassay (Juodeika, 1983). No results were available at the time of this writing. Only one report related to carcinogenicity was available for review. Massoud et al. (1980) reported that cyclohexanone was positive in both a forward mutation test using Bacillus subtilis and an Ames Salmonella assay.

Details of the tests, including applied concentrations, incubation times, metabolic activation employed (if any), and number of forward mutants or revertants obtained were not supplied. In the Ames test, TA98 produced the greatest number of revertants, indicating a possible frame-shift mutation.

Effects on Reproduction

No data on teratogenicity or reproductive effects were available.

Methyl Ethyl Ketone

Methyl ethyl ketone (MEK) is a colorless liquid with an acetone-like odor. It is used extensively in industry in organic synthesis and as a solvent for plastics, inks, and coatings. It is found in variable concentrations in cements for plastic piping (Department of Housing and Community Development, 1983).

The National Institute for Occupational Safety and Health (1980) estimates that approximately 2.5 million U.S. workers are exposed annually to MEK. The current ACGIH TLV and OSHA PEL are set at 200 ppm to prevent irritation (ACGIH, 1982; OSHA, 1981). Because the odor of the compound can be recognized at 25 ppm, it may serve as a warning of potentially dangerous concentrations.

Absorption and Metabolism

MEK is effectively absorbed by any route of administration and is readily eliminated unchanged in the breath, and in the urine in unchanged or metabolized form (Tado et al., 1972). The dermal absorption of MEK was tested using absorption cells strapped to the arms of human volunteers. Fifteen minutes after the beginning of exposure, MEK was detected in the expired breath (Munies and Wurster, 1965).

Di Vincenzo et al. (1976) administered a single intraperitoneal dose of 450 mg/kg MEK to guinea pigs and examined the serum and urine for parent

compound and metabolites. The serum half-life of MEK was approximately 270 minutes; all compound was cleared by 12 hours. Only 11 percent of the administered dose was accounted for in the urine. Urinary metabolites were 2-butanol, 3-hydroxy-2-butanone and 2,3-butanediol. Dietz and Traiger (1979) obtained similar results with rats given a single oral dose of 335 mg/kg MEK; serum levels peaked at 4 hours post administration. At the end of 12 hours, only 25 percent of the compound had been accounted for.

Rabbits exposed to MEK reduced the compound to 2-butanol; the main urinary metabolite was the glucuronic acid conjugate (Williams, 1959). Mice eliminated an intravenous dose primarily in the expired air; the remainder was eliminated as the glucuronide (De Castiglia et al., 1972). In dogs, 30-33 percent of a .3-.5/kg dose was eliminated in the expired air (Williams, 1959).

Although methyl ethyl ketone may affect the metabolism of other compounds, results of the studies reviewed were not entirely consistent. Toftgard et al. (1981) exposed rats to 800 ppm MEK in air for up to 14 hours per day over a 4 week period, then sacrificed the animals and used their livers in studies designed to detect effects on the microsomal enzyme system--the system used by the body to metabolize drugs and many other organic molecules. No change in enzyme levels was seen, but some P-450-dependent reactions were decreased. In studies with Wistar rats, Couri et al. (1977) found that continuous or intermittent exposure to 750 ppm MEK in air for 7 hours per day over a 7-day period decreased hexabarbital sleep time in male Wistar rats, presumably by increasing activity of liver enzymes. Traiger et al., (1975) reported that oral administration of a single dose of 1.87 ml MEK/kg body weight also increased liver microsomal enzyme activity in the rat.

Acute Toxicity

MEK is an irritant of the eyes, skin and mucous membranes at concentrations in air of 100 ppm and higher (NIOSH, 1981). Several workers exposed to concentrations of 300-600 ppm complained of numbness in the

fingers and arms; one worker experienced numbness in the legs. Several developed dermatitis from contact with the liquid (Smith and Mayers, 1944). At sufficiently high concentrations, MEK will cause central nervous system depression; the severity of symptoms varies with the absorbed dose (Proctor and Hughes, 1978).

The median lethal oral dose for the rat is approximately 3,400 mg/kg, and the lowest lethal concentration is 2,000 ppm over a 4-hour period (NIOSH, 1981). The major effects of MEK appear to be irritation and central nervous system depression. Guinea pigs exposed to concentrations in air ranging from 10,000 ppm to 100,000 ppm for various durations up to 14 hours exhibited eye irritation, respiratory distress, changes in cardiac function, lack of coordination, and narcosis. Those animals sacrificed immediately after exposure had congested internal organs, indicating extreme irritation; these effects were not observed in animals sacrificed 4 or 8 days after exposure. Exposure for 30 minutes or more to 100,000 ppm produced reversible opacity of the cornea (Patty et al., 1935).

Inhalation of 1 percent, 2 percent and 5 percent concentrations of MEK produced CNS effects, including dose-dependent depression of body temperature, respiratory rate and heart rate (Specht et al., 1940). Increased levels of ornithine carbamyl transferase (OCT) and increased lipid content of the liver were observed in guinea pigs administered a single intraperitoneal dose of 2,000 mg MEK/kg body weight; these findings indicate liver damage (DiVincenzo and Krasavage, 1974).

Chronic Toxicity

No chronic systemic effects have been attributed to exposure to MEK. Although MEK in combination with other solvents has been associated with peripheral neuropathies, exposure to MEK alone has not produced these symptoms. Careful studies have documented peripheral neuropathies in workers exposed to MEK in mixtures with n-hexane or methyl n-butyl ketone; MEK enhances the neurotoxicity of these compounds (Allen et al., 1975), possibly by affecting microsomal enzyme activity (Couri et al., 1977). Case

reports have attributed peripheral neuropathies to exposure to MEK in combination with acetone or toluene (Dyro, 1978) and tetrahydrofuran (Viader et al., 1975).

The most significant chronic effect of MEK exposure is the potentiation of other solvent-induced neuropathies. Rats exposed for 8 hours per day, 7 days per week over a period of 15 weeks to 1,100 ppm MEK and 8,900 ppm n-hexane or 10,000 ppm n-hexane alone developed peripheral neuropathies (muscular weakness of the limbs, etc.); rats exposed to 6,000 ppm MEK alone did not develop signs of neurotoxicity (Altenkirch et al., 1979). Rats exposed for 8 hours per day, 5 days per week over a 6 week period to 200 ppm methyl n-butyl ketone (MBK) and 2,000 ppm MEK developed peripheral neuropathies (Duckett et al., 1974). Rats exposed to 1,125 ppm MEK continuously for 5 months (Saida et al., 1976), exhibited no signs of neurologic injury. Sprague-Dawley rats exposed to 800 ppm MEK for 6 hours per day, 5 days per week for 4 weeks, had increased liver weights and liver weight/body weight ratios, indicating possible damage to the liver. The Chemical Industry Institute of Toxicology (1981) exposed Fischer-344 rats to concentrations of MEK in air of 1,250, 2,500, or 5,000 ppm. No significant toxic effects were seen, and a decision was made to cancel proposed lifetime inhalation toxicity studies. If new data indicate a need, the decision will be reconsidered.

Effects on Genes on Chromosomes

No results of tests for effects on genes and chromosomes were located.

Carcinogenicity

No results of tests for carcinogenicity were located.

Effects on Reproduction

Two tests for teratogenicity have been reported, and results are conflicting. Schewetz et al. (1974) exposed rats to 3,000 ppm for 7 hours

per day on days 6 through 15 during the period of gestation and observed some increased in acaudia, imperforate anus, and brachygnathia. In addition, soft tissue abnormalities, and sternebral variants (not considered teratogenic) were increased, though not to the point of statistical significance. In order to clarify the significance of results, Deacon et al. (1981) of the same laboratory conducted a similar study using 25 pregnant rats per group and exposures of 400, 1,000 or 3,000 ppm MEK in air for 7 hours per day during days 6-15 of gestation. No increases in resorptions or preimplantation losses were observed. At 3,000 ppm, there was a significant increase in the number of animals with extra ribs, and ossification of the skull was delayed. No major malformations were seen .

Carbon Tetrachloride

Absorption and Metabolism

Carbon tetrachloride is rapidly absorbed from the gastrointestinal tract, the lungs, or through injured skin, and is distributed to the liver, fatty tissues, brain, kidney, blood, and bone marrow. Absorption from the GI tract is augmented by the presence of fats and alcohol. Carbon tetrachloride is excreted principally through the lungs unchanged (about 85 percent of absorbed dose) and as carbon dioxide (10 percent) and other metabolites, which (in rabbits) include chloroform and hexachloroethane (in rabbits) (NAS, 1977). Highly reactive free-radical intermediates are thought to be responsible for carbon tetrachloride's toxicity. Such reactive metabolites can bind irreversibly primarily to proteins and lipids in the liver, and may do the same in other tissues (IARC, 1979).

Acute Toxicity

In humans, high level exposure has led to severe liver damage and/or kidney failure (Klaassen, 1980b). Accidental poisonings with 14-20 ml have almost always been fatal: the lowest reported fatal dose is 1.5 ml (NAS, 1980; IARC, 1979). Inhaled carbon tetrachloride can cause CNS depression, fatal cardiac arrhythmias, and damage to the lungs (IARC, 1979).

Chronic Toxicity

Chronic exposures to carbon tetrachloride cause liver and kidney damage in humans and animals. Symptoms in humans include nausea, vomiting, headache, drowsiness, and fatigue (NAS, 1977).

Effects on Genes and Chromosomes

Carbon tetrachloride was reportedly negative for mutagenic activity in several bacterial assays (IARC, 1979; NAS, 1980). However, it is possibility that these negative results may have been due to inadequate experimental protocols (EPA, 1982). One report cited by IARC (1979) indicated that carbon tetrachloride could react with DNA of rodent cells under certain conditions (Rocchi et al., 1973). The International Agency for Research on Cancer considers that there is inadequate evidence of carbon tetrachloride's activity in short-term assays (1982).

Carcinogenicity

In 1979, the International Agency for Research on Cancer renewed the 11 bioassays involving oral, inhalational, intratracheal, subcutaneous, and intrarectal administration of carbon tetrachloride in several species (rats, mice, hamsters, trout). It was found to be carcinogenic to rats and mice, producing liver tumors in several strains of both species. In one experiment involving subcutaneous injection of carbon tetrachloride to rats, it produced mammary tumors (IARC, 1979).

There is no conclusive epidemiological evidence of cancer in humans exposed to carbon tetrachloride. However, there are several case reports of liver cancer following carbon tetrachloride poisoning, and of excesses of other types of malignancy among persons occupationally exposed to carbon tetrachloride (IARC, 1979, 1982).

Effects on Reproduction

Pregnant rats exposed to airborne concentrations of 1,800 and 6,300 mg/m^3 (300 and 1,000 ppm) of carbon tetrachloride for 7 hours per day on days 6-15 of gestation produced fetuses with retarded development (Schwetz et al., 1974). Carbon tetrachloride injected in mice at doses of 150 mg/mouse during the final part of pregnancy caused increased fetal mortality, due probably to fetal liver damage and injury to the placenta (Roschlau and Rodenkirchen, 1969). An earlier study reported no teratogenic effect of carbon tetrachloride administered to rats (Wilson, 1954, cited in NAS, 1977). In general, the available evidence is not adeaquate to assess whether carbon tetrachloride can cause teratogenic effects (EPA, 1982). It does, however, appear to be fetotoxic at high doses (such as those noted above). Furthermore, it appears to be capable ot causing testicular generation when injected intraperitoneally at very high doses (i.e., 4,800 mg/kg body weight in rats) (EPA, 1982).

Trichloroethylene

Trichloroethylene is a colorless liquid that is used as a degreaser, a chemical intermediate in organic synthesis and a solvent in various applications. It is highly volatile and is miscible with water and organic solvents. Pure trichloroethylene degrades readily to other toxic organic compounds (IARC, 1979). The stabilizers added to trichloroethylene, e.g., epichlorohydrin or amines, may affect its toxicity.

OSHA has set a PEL of 100 ppm (8-hour time-weighted average concentration with a ceiling of 200 ppm (OSHA, 1981). The ACGIH recommends a TLV of 50 ppm (8-hour time-weighted average) and a Short Term Exposure Limit (STEL) of 200 ppm (ACGIH, 1982).

The liver and the central nervous system are target organs for trichloroethylene; but the compound is reportedly less hepatotoxic than carbon tetrachloride or chloroform. Cats exposed to 20 ppm for 1.5 hours/day for 6 months developed lesions in the liver, kidney and spleen (IARC,

1979). In other investigations, behavioral and histopathologic evidence of neurological damage was seen (Browning, 1965).

Absorption and Metabolism

Trichloroethylene is rapidly absorbed through the lung; about 45 percent of the inhaled dose is excreted unchanged in the expired breath (IARC, 1979). The portion that is not exhaled is metabolized by the hepatic mixed function oxidase system. Monster et al. (1976) exposed four male volunteers to 70 or 140 ppm trichloroethylene in air for 4-hour periods. Concentrations of the parent compound, trichloroethanol and trichloroacetic acid were determined in the blood. Exhaled air was analyzed for trichloroethylene and trichloroethanol and urine was examined for trichloroethanol and trichloroacetic acid. Total recovery was 67 percent. Ten percent was recovered unchanged in the expired breath; in the urine 39 percent was recovered as trichloroethanol and 18 percent was recovered as trichloroacetic acid. The major products of metabolism in dogs, rats, and humans are trichloroethanol (Astrand and Ovrum, 1976), trichloroacetic acid, and trichloroethanol glucuronide (Muller et al., 1974). Humans and rats also produce chloral hydrate (Cole et al., 1975).

Van Duuren and Baneyee (1976) studied the *in vitro* microsomal metabolism of trichloroethylene and covalent binding to rat liver microsomal protein. They hypothesized that TCE is metabolized to its epoxide or other related reactive intermediates that bind to protein and are most likely involved in TCE carcinogenesis. Henschler and Bonse (1978) have also proposed the formation of a reactive epoxide by mixed function oxidases. Scott et al. (1982) studied pharmacokinetics and binding of TCE to macromolecules and DNA in male B6C3FI mice and Osborne Mendel rats *in vivo*. Mice metabolized more inhaled TCE to a metabolite that bind to monomolecules than did rats; liver damage and increased DNA synthesis in mice were noted after repeated doses (2,400 mg/kg/day for 3 days). Only a very low level of alkylation of DNA occurred, the authors suggested that the genotoxic potential of TCE was low, that tumorigenesis probably resulted from an

epigenetic mechanism, and that TCE would be tumorigenic only upon chronic administration of high cytotoxic doses.

Acute Toxicity

Several fatal poisonings have occurred after ingestion of trichloroethylene; signs and symptoms of poisoning are usually those of central nervous system depression, gastrointestinal disturbance, and abnormalities in cardiac function (NAS, 1982). The lowest dose reported to cause inebriation in humans is approximately 300 mg/kg (NAS, 1982).

The median lethal dose of trichloroethylene in rats is 4920 mg/kg; the median lethal concentration is 5000 ppm. The compound is irritating to the rabbit eye and skin (NIOSH, 1981).

Chronic Toxicity

Chronic exposure to trichloroethylene produces damage to the central nervous system and the liver. Alcohol intolerance, similar to that seen in persons taking Antabuse (disulfiram) or exposed to dimethylformamide, has also been seen in exposed workers (Proctor and Hughes, 1977).

Carcinogenicity

Axelson et al. (1978) reported no statistically significant excesses of tumors associated with exposure to trichloroethylene in an epidemiological study of workers, but problems in the design and conduct of the study (e.g., small number of persons, short period of time since beginning of exposure) limit the usefulness of the results in assessing human risk. Tola et al. (1980) also studied a cohort of workers exposed to trichloroethylene. Both observed total mortality and cancer mortality rates were lower than expected; however, results cannot be considered conclusive because the cohort was young and follow-up has been too short to detect fatal cancers with a long latency period (more than 6-13 years). The cohort will be followed and data will be reanalyzed every 5 years. Studies by Malek et al.

(1979) and Blair (1980) also failed to show an excess of cancers in workers exposed to trichloroethylene.

Trichloroethylene was tested by gavage in an NCI bioassay with Osborne Mendel rats and B6C3F1 mice. The time-weighted average daily doses administered over a period of up to 78 weeks were 1,169 and 2,339 mg/kg for male mice, 869 and 1,739 mg/kg for female mice, and 549 and 1,097 mg/kg for male and female rats. The compound produced hepatocellular carcinomas in both male and female mice, but not in rats (NCI, 1976). The International Agency for Research on Cancer considers that the results of this experiment provide "limited" evidence of the carcinogenicity of trichloroethylene (IARC, 1979). Henschler et al. (1980) exposed NMRI mice, WIST rats, and Syrian hamsters to 0, 100, or 500 ppm TCE for 6 hours per day, 5 days per week for 18 months in an inhalation study. Thirty animals of each sex were used for each dose level. Terminal sacrifice of mice and hamsters occurred at 30 months; surviving rats were maintained until 36 months. The only significant increase in tumor formation was observed in female mice, in which malignant lymphoma incidence was increased twofold in the 100 and 500 ppm groups. The authors suggested that this increase might be due to some effect of TCE on spontaneous rates of a virally induced condition. They conclude that TCE was not carcinogenic and that results of previous tests in which it was found to be carcinogenic were due to the presence of epoxides or other impurities.

The study appears to have been conducted carefully and survival was good. However, the number of animals per group was small, thus limiting the power of the assay. The positive result in female mice may or may not have been due to the action of TCE, but convincing negative evidence has not been presented.

Because the compound used in the original bioassay was contaminated by epichlorohydrin, a second bioassay was undertaken in 1980, using highly purified trichloroethylene. Results corroborate the findings of the first bioassay; the final report was scheduled to be published in late February, 1983, but had not been received as of this writing (Juodeika, 1983).

Effects on Genes and Chromosomes

Results of tests for mutagenicity are conflicting. Trichloroethylene caused unscheduled DNA synthesis, spermhead abnormality in mice and weak or borderline responses in a host-mediated assay and Drosophila (Beliles, 1982). Positive results were also seen in tests with Escherichia coli, Salmonella typhimurum TA 100, and Saccharomyces cerevisiae (NIOSH, 1981). In a mouse host-mediated assay, trichloroethylene induced point mutations and gene conversion in yeast recovered from liver and kidney (IARC, 1982). Negative results were seen in Salmonella typhimurium, a bone marrow cytogenetics assay (IARC, 1979), and dominant lethal assays in rats and mice (IARC, 1982).

Effects on Reproduction

No adverse effects were seen in offspring of rats and mice exposed to 300 ppm trichloroethylene for 7 hours/day on Days 6-15 of gestation (Schwetz et al., 1975). No teratogenic effect, but decreased fetal weight and increased frequency of skeletal anomalies were seen in offspring of pregnant Wistar rats exposed to 100 ppm trichloroethylene in air for 4 hours daily from Days 8 to Day 21 of gestation. Female rats and rabbits were exposed to 0, 100, or 500 ppm trichloroethylene in air for 3 weeks before impregnation and up to 30 days post gestation. No adverse effects in offspring were seen in rats. In one group of rabbits, hydrocephalic fetuses were seen (Beliles, 1982).

Dorfmueller et al. (1979) exposed groups of 30 virgin female Long-Evans rats by inhalation to 1,800 ppm trichloroethylene in air in one of four treatment regimens:

(++)-TCE before mating and during pregnancy

(+-)-TCE before mating, filtered air during pregnancy

(-+)-Filtered air before mating, TCE during pregnancy

(--)-Filtered air before mating and during pregnancy.

TCE with epichlorohydrin as a stabilizer was used. Exposures ended on Day 20 of gestation. On Day 21, 15/30 dams from each group were sacrificed, maternal and fetal liver enzymes were analyzed, and fetuses were examined. Remaining dams were allowed to litter and offspring were subjected to behavioral testing from Day 10 to Day 100 of life.

No significant treatment-related maternal toxicity or embryotoxicity were seen. Skeletal anomalies and displacement of the right ovary were seen in offspring of the (-+) group, but effect might have been strain-specific rather than treatment-related. No true effects were seen. Postnatal behavioral tests revealed no evidence of CNS damage in exposed offspring.

Perchloroethylene

Perchloroethylene (tetrachloroethylene) is a colorless liquid that is used as a dry-cleaning fluid, chemical intermediate, degreaser and as a solvent in various applications. In water it is practically insoluble; it decomposes slowly to trichloroacetic and hydrochloric acids. It is miscible with oils and organic solvents. Perchloroethylene is moderately volatile and has been found in the air of numerous U.S. cities. It may be formed in water as a result of chlorination. It has been detected in domestic water supplies and industrial effluent (IARC, 1979).

The OSHA Permissible Exposure Limit (PEL) for perchloroethylene is 100 ppm (8-hour time-weighted average concentration) with a ceiling of 200 ppm (OSHA, 1981). The ACGIH recommends a threshold limit value (8-hour time-weighted average concentration) of 50 ppm with a short term exposure limit of 200 ppm (ACGIH, 1982).

Absorption and Metabolism

Perchloroethylene is readily absorbed from the lung; gastrointestinal absorption is less complete, although the presence of fats may enhance absorption (Lamson et al., 1929). The compound is also absorbed through the skin (Hake and Stewart, 1977). Approximately 70 percent of the inhaled dose

is excreted unchanged or as CO_2 in the expired breath by mice (Yllner, 1961) and rats (Pegg et al., 1978). In mice, urinary metabolites accounted for approximately 20 percent of the radioactive label and were identified as trichloroacetic acid, oxalic acid and dichloroacetic acid. A small percentage was excreted in feces. Induction of the microsomal oxidation system increased hepatotoxicity in rats (Moslen et al., 1977); ethylene oxide, a suspected carcinogen, may be a metabolic intermediate (Henschler and Bonse, 1977). Inhaled perchloroethylene is metabolized very slowly; its biologic half-life ($t_{1/2}$) in humans is 3-5 days, depending on length of exposure. The $t_{1/2}$ in persons exposed to 100 ppm for 8-hours (the OSHA permissible exposure limit) was estimated to be 71.5 hours (Guberan and Fernandez, 1974). Ogata et al. (1971) exposed male volunteers to 87 ppm perchloroethylene in air for 3 hours; after 67 hours, only 1.8 percent of the dose had been excreted in the urine as trichloroacetic acid; no information on concentrations in expired breath was available in the secondary source consulted. Monster et al. (1979) exposed human volunteers to 72-144 ppm perchloroethylene in air for 4-hour periods. Of the absorbed dose, eighty percent was eliminated unchanged in the exposed air; 2 percent was eliminated in the urine as trichloroacetic acid. Concentrations of perchloroethylene in the blood and exhaled air indicated that a long period of time is necessary before elimination is complete (more than 7 days) and therefore, repeated exposures could result in bioaccumulation.

Perchloroethylene in sufficiently high concentrations causes central nervous system depression, liver damage, eye and skin irritation, and pulmonary edema. Volunteers exposed to 100 ppm (the current OSHA PEL) for 7 hours experienced irritation of the eyes, nose and throat, headache, flushing of the face and neck, and lethargy and slurring of speech (Stewart, 1969). Exposure to 600 ppm for 10 minutes produced dizziness, lack of coordination, and numbness around the mouth. Exposures to 2,000 ppm produced mild CNS depression within 5 minutes (Von Oettingen, 1955).

The oral median lethal doses of perchloroethylene in rats and mice are approximately 13 g/kg (Smyth et al., 1969) and 7g/kg (Kohne, 1940), respectively. Acute exposures have produced dose-dependent symptoms of CNS

depression. The inhalation LC50 (median letal concentration) in mice is 5,200 ppm/3 hours (Friberg et al., 1953).

Chronic Toxicity

Chronic exposure to perchloroethylene has caused impaired memory and other CNS symptoms, abdominal pain, and peripheral neuropathies (IARC, 1979; Proctor and Hughes, 1978). Liver and kidney damage have also been reported (Stewart, 1969). There are no published data concerning potential mutagenicity, or adverse reproductive outcomes in humans due to perchloroethylene exposure. Two epidemiologic investigations of dry cleaners, a proportional mortality study and a prospective cohort mortality study, found excess deaths from various cancers: lung, cervix, colon, skin, liver, and leukemia. However, in both studies, mixed exposures probably occurred and IARC (1982) considers results to be inconclusive.

Repeated exposure by inhalation to perchloroethylene has produced liver damage in rats, rabbits and guinea pigs (Proctor and Hughes, 1978). Oral doses have produced liver and kidney damage in dogs and mice (Klaasen and Plaa, 1966, 1967).

Carcinogenicity

Perchloroethylene was tested by gavage in an NCI bioassay in B6C3F1 mice and Osborne-Mendel rats (NCI, 1977). No increases in tumor incidence were observed in rats, but a significant increase in hepatocellular carcinoma incidence was observed in mice. The International Agency for Research on Cancer (1979) considered that these results provided "limited evidence of the carcinogenicity of tetrachloroethylene" (perchloroethylene). NCI/NTP has recently completed a second bioassay of perchloroethylene; the draft report has been requested but not received.

In a study reviewed by IARC, male and female Sprague-Dawley rats exposed by inhalation to 300 or 600 ppm perchloroethylene in air over a 12-month period showed no increased tumor incidence over untreated controls

(Rampy et al., 1977). Schumann et al. investigated the pharmocokinetics and macromolecular interactions of perchloroethylene in Sprague-Dawley rats and B6C3F1 mice in an attempt to explain mechanistically the sensitivity of the mouse and resistance of the rat to perchloroethylene-induced hepatocellular carcinoma. Mice metabolized 8.5 and 1.6 more radiolabelled perchloroethylene than rats after a single inhalation exposure to 10 ppm or a single oral dose of 500 mg/kg, respectively. Greater irreversible binding to hepatic macromolecules also occurred in mice, but no binding to hepatic DNA was detected (the test was sensitive to 10-14.5 alkylations/10^6 nucleotides).

Hepatic DNA synthesis was increased twofold in mice after repeated oral administration of 500 or 1000 mg/kg/day, the approximate levels administered in the NCI gavage bioassay. No significant alterations in hepatic DNA synthesis were seen in rats.

The authors concluded that perchloroethylene induces tumors by cytotoxic mechanisms and that lowering exposure to a level below that at which tissues injury occurs should make tumor production unlikely in both animals and humans.

Effects on Genes and Chromosomes

There are conflicting results regarding the mutagenicity of perchloroethylene. Perchloroethylene caused spermhead abnormality in mice, positive results in host-mediated assay, and weak or borderline responses in tests for unscheduled DNA synthesis and bone marrow aberrations (Belles, 1982). Positive results were seen in Ames Salmonella assay in strain TA 100 and in a host-mediated assay in mice using Salmonella TA 1950, TA 1951, and TA 1952 (Cerna and Kypenova, 1977). Negative results were seen in three screens using E. coli (Greim et al., 1975) and in a bone marrow cytogenetics assay (Cerna and Kypenova, 1977). IARC (1982) considers that there is inadequate evidence of activity in short-term tests.

Effects on Reproduction

No teratogenicity or adverse reproductive outcomes were seen in offspring of rats or mice exposed by inhalation to 300 ppm perchloroethylene for 7 hours daily on Days 6-15 of gestation (Schwetz et al., 1975). Offspring of female Sprague-Dawley rats exposed to 900 ppm or 100 ppm perchloroethylene for 7 hours per day on Days 7-13 or 14-20 of gestation were examined in a series of behavioral tests. No significant differences were observed between offspring of animals exposed to 100 ppm perchloroethylene and control animals on any behavioral tests. Behavior of offspring of animals exposed to 900 ppm varied from controls but in no consistent pattern. Neurochemical analysis of brains of newborn and 21-day-old pups showed reduced levels of acetylcholine significantly different from offspring of controls. Dopamine levels of offspring of dams exposed to 900 ppm from days 7-13 of gestation were significantly lower than those of controls.

Dichloromethane

Dichloromethane (DCM, methylene chloride) is a large volume solvent used as a paint remover, degreaser, aerosol propellant and extractant; it is also used in the manufacture of plastics, photographic film, and textiles. It is approved for use by FDA in adhesives and in the production of polycarbonate resins intended for use in producing, manufacturing, packaging, processing, preparing and holding food (USFDA, 1977). It is also permitted as a residue in coffee, hops, and various spices. (USFDA, 1977). NIOSH (1980) estimates that approximately 2 million persons per year are occupationally exposed to dichloromethane. OSHA has set an 8-hour time-weighted-average permissible exposure limit (PEL) of 500 ppm (OSHA, 1981). The American Conference of Governmental Industrial Hygienists recommends an 8-hr threshold limit value (TLV) of 100 ppm (ACGIH, 1982).

Dichloromethane is formed during the chlorination of water; chloroform and carbon tetrachloride are also formed. DCM has been found in 1 percent of raw and 8 percent of finished water supplies tested. The mean

concentration found in several samples of finished water was 1 µg/l. DCM was found in 9 of 10 domestic water supplies; the highest concentration detected was 1.6 µg/l. (IARC, 1979)

Absorption and Metabolism

Dichloromethane is absorbed by the lungs and the skin. Ninety-one percent, of a large radiolabelled intraperitoneal dose was eliminated unchanged via the lungs (DiVincenzo and Hamilton, 1975), 2 percent of the dose was eliminated as carbon monoxide, 3 percent as carbon dioxide, and 1 percent as an unidentified volatile compound; 1 percent of radioactivity was detected in urine and 2 percent remained in the carcass. Injection of a small dose (17 mg/kg) apparently resulted in much greater metabolism (Rodkey and Collison, 1977a, 1977b); 47 percent of radioactivity was recovered as carbon monoxide, 29 percent as carbon dioxide, and none was detected in the carcass. These results suggest that dichloromethane metabolism is saturable. Two metabolic pathways have been proposed for dichloromethane in rats. The first is mediated by microsomal mixed-function oxidases and results in the formation of carbon monoxide (Kubic and Anders, 1976). The second is mediated by cytosolic enzymes and is glutathione dependent; the major end products are formaldehyde and carbon dioxide. Formic acid may also be formed (Ahmed and Anders, 1976). In human volunteers exposed to 50-500 ppm for up to 7.5 hours for 5 consecutive days, most DCM was excreted unchanged in the expired breath (Peterson, 1978). Elimination continued for a substantial period beyond the termination of exposure, suggesting a degree of bioaccumulation, probably in lipid tissues (USEPA, 1980). Carboxyhemoglobin blood levels increased with dose up to approximately 10 percent saturation (Stewart and Hake, 1976). Such levels might increase cardiorespiratory stress (USEPA, 1980).

Acute Toxicity

Dichloromethane is a central nervous system depressant (NIOSH, 1976) and irritant of the eyes, skin, and mucous membranes. 2000 ppm did not cause dizziness, but a concentration of 7200 ppm caused numbness of the

extremities after 8 minutes. CNS effects are reversible and the compound has been used as an anesthetic (USEPA, 1980). Skin contact can cause dermatitis (Sax, 1979). Occupation exposure has caused damage to both the CNS and the liver (Hanke et al., 1974; Weiss, 1976). Deaths have occurred after short-and long-term exposures (NIOSH, 1976); death is usually due to cardiac injury and heart failure (USEPA, 1980).

Friedlander et al (1978) conducted two epidemiologic investigations of males occupationally exposed to dichloromethane -- a proportional mortality study of 334 persons and a prospective cohort mortality study of 751 persons. No significant differences were noted in either study between observed and expected deaths from any type of malignancy, circulatory heart disease, ischemic heart disease, or any other cause. However, although both studies were well conducted and analyzed, the cohort studied was young and the follow-up period might not have been sufficiently long to detect even a moderate effect. Further follow-up is scheduled for consecutive 5-year periods.

The oral rat LD_{50} (median lethal does) for dichloromethane is 2136 mg/kg. The mouse inhalation LC_{50} (median lethal concentration) is 16,200 ppm or 56 g/m^3 (Svirbely et al., 1947). The lowest lethal concentration reported for guinea pigs is 5000 ppm/2 hours. Hepatotoxic effects were observed in mice after administration of single lethal doses (Gehring, 1968). Damage to the kidney has been seen in dogs (Klaassen and Plaa, 1967).

Effects on Genes and Chromosomes

Conflicting results have been obtained in various screens for mutagenesis. Positive results were obtained in the Ames test with Salmonella typhimurium strains TA98, TA100, and TA1535 with and without metabolic activation (Simmon et al., 1977; Kanada and Uyeta, 1978; Jongen et al., 1978; Snow et al., 1979; Green, 1980; Gocke et al., 1981). Positive results were also obtained in tests with yeast (Saccharomyces cerevisiae D-7), in a sister chromatid exchange assay with Chinese hamster cells (V79),

in a cell transformation test using rat embryo cell line F1706, and in a sex-linked recessive lethal test with Drosophila melanogaster (Perry and Evans, 1975; USEPA, 1980; Jongen et al., 1981; Gocke et al., 1981). Dichloromethane has not produced genotoxic effects in the following assays: DNA synthesis in human and hamster cells, forward mutation in Chinese hamster cells, mitotic recombination in S. cerevisiae D-3, micronuclei production in NMRI mice.

Carcinogenicity

Dichloromethane is currently being in tested in rats and mice by gavage and inhalation exposure in National Toxicology Program carcinogenesis bioassays. The inhalation assay is in the chronic testing phase and no results will be available for approximately 1 year. The draft report of the gavage bioassay is scheduled for release in March or April of 1983. Rats and mice were administered 0, 500, or 1000 mg/kg DCM in corn oil by oral intubation. Significant increases of neoplastic liver nodules, adrenocortical adenomas, and pancreatic acinar cell adenomas were seen in rats. Significant increases in hepatocellular carcinomas and thyroid c-cell carcinomas were seen in mice. Pancreatic acinar cell adenomas in rats were apparently associated with the corn oil vehicle (Juodeika, 1983). The compound was originally judged to be carcinogenic in male and female animals of both species; the decision regarding carcinogenicity in rats, which was based on the elevated incidence of neoplastic liver nodules, may be revised (Mennear, 1983). Dow Chemical Company conducted a 2-year inhalation study with rats and hamsters exposed to 0, 500, 1500, and 3500 ppm DCM for 6 hours per day, 5 days per week. Preliminary reports indicated a significant increase in benign mammary tumors at all doses in female rats and at 3500 ppm in male rats (USEPA, 1980).

Theiss et al. (1977) conducted a pulmonary tumor assay in male strain A mice. Groups of 20 mice were injected intraperitoneally three times per week for 16 or 17 weeks with 0, 160, 400 or 800 mg/kg DCM. A significant increase in tumors was seen at the 160 ppm dose. Tumors were increased in the two higher dose groups but did not reach statistical significance as a

result of poor survival; only 5/20 animals in the 400 ppm group and 12/20 in the 800 ppm group were examined for tumors.

The EPA Carcinogen Assessment Group states that there is "suggestive evidence" for the carcinogenicity of dichloromethane; this opinion is based on the results of mutagenicity screens as well as rodent tests. The International Agency for Research on Cancer (1982) considers that there is inadequate evidence for the carcinogenicity of DCM in animals and humans, and limited evidence for genotoxic activity in short-term tests. These judgments were made before preliminary results of the NTP bioassay were made available.

Effects on Reproduction

Schwetz et al. (1975) exposed pregnant rats and mice to 1250 ppm DCM in air for 7 hours daily on Days 6-15 of gestation. No treatment-related effects on litter size, resorptions, or fetal development were seen. Hardin and Manson (1980) exposed pregnant Long-Evans rats to 4,500 ppm DCM by inhalation and found no teratogenic effects.

Organic Tin Compounds

Absorption and Metabolism

Dialkyl and trialkyl tins may be absorbed from the gastrointestinal tract, although the fractional absorption differs among species. Most organotin compounds are poorly absorbed from the GI tract, except trimethyl-, triethyl-, and dimethyl tin (Krmbrough, 1976). Such alkyl tin compounds are distributed to the liver and, in the case of trialkyl tins, to the central nervous sytem. After injection in animals, dibutyl tin concentrates in the liver, with smaller amounts in the kidney. Dibutyl tin is excreted unchanged in the bile (Barnes and Stoner, 1959).

Acute toxicity

There are few published data on isooctylthioglycolate derivates of organic tin compounds. The acute toxicity of these compounds, however, is reportedly similar to that of other dimethyl and dibutyl organotin derivatives (Barnes and Stoner, 1958, 1959). The following discussion is therefore based on experiments performed principally with dialkyl tin dichlorides or diacetates, or trimethyl tin chloride. There are major qualitative differences in the toxicity of dialkyl versus trialkyl tin derivatives.

The principal toxic effects of acute exposure to dialkyl tin componds are a generalized illness and, in the case of dibutyl tin, a severe, potentially fatal injury to the bile duct (Barnes and Stoner, 1958). Such bile duct lesions have been produced in rats and mice, but not rabbits, guinea pigs, cats, or hens (Barnes and Stoner, 1959). This phenomenon has reportedly been observed only in species in which the pancreatic and bile ducts follow a common course (Kimbrough, 1976). In humans, these ducts are separate.

Dimethyl tin salts, while also toxic to rodents, do not appear to cause bile duct lesions. Applied to the skin of rats and guinea pigs, there can be marked necrosis and scar formation. An oral no-observed-effect-level for a single dose of dimethyl tin dichloride to rats was reportedly 40 mg/kg, whereas for dibutyl tin dichloride such a level was 10 mg/kg, reflecting the latter compounds's greater oral toxicity (Barnes and Stoner, 1958).

Trialkyl tins, particularly triethyl and trimethyl tin, exert their principal toxic effects on the central nervous system, causing weakness, tremors, convulsions, paralysis, and death from respiratory failure.

Chronic Toxicity

There are very few chronic toxicity data on dimethyl or dibutyl tin bis isooctylthioglycolates. The Food and Drug Administration (FDA) recently

approved the use of a mixture of dimethyl and monomethyl tin isooctyl mercaptoacetate (thioglycolate) as a stabilizer in PVC water pipe used in food processing plants (21 CFR 178; 46 Fed. Reg. 10461, Feb. 3, 1981). SRI requested documentation (by telephone and written request) supporting this regulation, but has not yet received anything from the FDA.

Dibutyl tin dichloride (DBTC), but not dimethyl tin dichloride, caused dose-related atrophy of lymphoid tissue (thymus and lymph nodes) in rats fed 50 and 150 ppm of this substance in their diets for 2 or 4 weeks (Seinen et al., 1977a). This was also observed in rats fed 20 ppm in their diet for 2 weeks. A no-observed-effect level was not determined. However, these effects on the thymus were reversible. Subsequent experiments indicated that DBTC selectively inhibits T-lymphocyte-dependent immune functions (Seinen et al., 1977b) in rats fed 50 or 150 ppm in the diet for 5 to 9 weeks or exposed prenatally, then postnatally, by gavage to doses of 1 to 3 mg/kg.

Effects on Genes and Chromosomes

Dibutyl tin dichloride was reported to be mutagenic in Chinese hamster ovary (CHO) cells, but not in the Ames test (Li et al., 1982). The concentration range in which mutagenicity was observed in CHO cells was at least 50 to 200 ppb.

Carcinogenicity

Dibutyl tin diacetate was tested for carcinogenicity using the standard protocol of the National Toxicology Program (NTP, 1979). Although there was a dose-related trend in liver tumor incidence in mice, there was no statistically significant increase in tumors in rats or mice of either sex. This assessment must be qualified in that more than one-third of the tissues from high-dose female rats were lost prior to examination.

A mixture of 75 percent dimethyl tin bis (isooctylthioglycolate) and 25 percent monomethyltin tris (isooctylthioglycolate) ("Advastab TM-181FS")

was tested for chronic toxicity using a protocol that would not be acceptable for investigating carcinogenicity by current standards (Mosinger, undated). Twenty male and twenty female Wistar rats were fed ADVASTAB at 100 mg/kg in the diet. The author concluded that the absence of tumors in the experimental animals showed that "the product tested is not cancer-causing at the doses given." Since this test includes only one species, with less than half the number of experimental animals that are required to detect an increase of even 5 to 10 percent in tumor incidence, and a dose level that is not clearly the maximum tolerated dose (MTD), the author's generalized conclusion is unwarranted. The oral intake study of dimethyl/monoethyl tin isooctylthioglycolate is inadequate to assess the carcinogenicity of this mixture.

Effects on Reproduction

A mixture of 75 percent dimethyl tin isooctylthioglycolate and 25 percent monomethyl tin isooctylthioglycolate was tested for reproductive effects in Wistar rats. (Mosinger, undated) Little experimental data is provided, other than that 5 females and 1 male were treated. In view of the small sample size, the author's inference that "the product tested is not teratogenic," is not justified. Even without additional description of experimental protocol, this study is inadequate to assess the effects of the chemical mixture on reproduction.

Substances Associated with Polybutylene Plastic Pipe

Irganox 1010

Irganox 1010 is a hindered phenolic compound that is used as an antioxidant and stabilizer for various polymers. It is a constituent of polybutylene piping.

There is no OSHA PEL or ACGIH TLV for Irganox 1010. A repeated insult patch test was conducted on 50 human subjects according to the method of

Shelanski and Shelanski. No primary irritation or sensitization occurred (Ciba-Geigy, 1982). Based on animal testing, the compound would be considered nontoxic to slightly toxic in the Gosselin et al. (1976) rating system.

Absorption and Metabolism*

Radiolabelled (^{14}C) Irganox was administered to rats (dose and route unspecified) to determine gastrointestinal absorption and metabolic fate. Of the radioactive carbon, 1.5 percent was recovered in the expired breath, 0.5 to 1.0 percent was detected in the urine and unspecified "minute" quantities were found in the blood. The feces contained approximately 80 to 84 percent of the labelled species. In a second study of metabolic fate "no measurable radioactivity was found in the urine, expired air, blood, livers, or kidneys." The only significant activity was found in the feces (Ciba-Geigy, 1982).

Acute Toxicity

The acute oral LD_{50} in rats was not determined, but it is greater than 5,000 mg/kg. At this dose animals did not exhibit any signs of toxicity, and no gross pathology was detected at necropsy. Drake (1979) reported that the LD_{50} in mice also exceeded 5,000 mg/kg. Irganox in corn oil was administered by oral intubation to albino rats at doses of approximately 3,000, 4,000, 7,000, and 10,000 mg/kg. Treatment-related effects included hypoactivity and "ruffed" fur. No gross pathological changes were seen at necropsy. The acute dermal LD_{50} in rabbits is greater than 3,160 mg/kg, the highest level tested; at this level no observable effects occurred. Rats exposed to an airborne concentration of 46 mg/l for 1 hour showed no "significant" signs of irritation. There were

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* Because only two citations were obtained from a computerized literature search, virtually all of the following information was excerpted from toxicology data supplied by Ciba-Geigy Corporation.

no treatment-related deaths, and at necropsy no pathological changes were detected. Rats and dogs were fed Irganox in the diet for 90 and 91 days, respectively. The no-observable-effect levels in the two species were the highest concentrations administered: 50,000 ppm in rats and 10,000 ppm in dogs (Ciba-Geigy, 1982).

Drake (1979) reported that Irganox 1010 was not irritating to rabbit skin. A mild and transitory effect was seen when the compound was applied to the rabbit eye. Irganox (dosage and route unspecified) did not produce sensitization in guinea pigs.

Chronic Toxicity

Irganox 1010 was fed to Sprague-Dawley CFY rats in dietary concentrations of 1,000, 3,000, and 10,000 ppm for 104 weeks. No observable effects were seen at any concentration. The "no-observable-effect level" was estimated to be 446-547 mg/kg day. No treatment-related increases in tumor incidence were seen in MAGF (SPF) mice fed 0, 100, 300, and 1,000 ppm Irganox 1010 in the diet for 24 months. These concentrations correspond to an approximate mean daily dose of 0, 11, 35, and 107 mg/kg for female animals and 12, 41, and 126 mg/kg for male animals (Ciba-Geigy, 1982).

Effects on Genes and Chromosomes

Irganox was reported to be nonmutagenic in a mouse dominant lethal assay at doses of 1,000 and 3,000 mg/kg. No significant increases in anomalies of interphase nuclei and no chromatid or chromosomal aberrations were detected in cytogenetic assays of the bone marrow of hamsters intubated on two consecutive days with 500, 1,000 or 2,000 mg/kg Irganox in corn oil. Geigy reported that "no evidence of the induction of point mutations by Irganox 1010 or by the metabolites formed as a result of microsomal activation was detectable in the strains of Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537) used in the experiment" at concentrations ranging from 10 to 250 µg/0.1 ml without activation and from 5 to 100 µg/0.1 ml with activation (Ciba-Geigy, 1982). Wang and Smith (1980) also reported that

Irganox was nonmutagenic in an Ames Salmonella test using strains TA 1535, TA 1537, TA 98, and TA 100 with and without metabolic activation.

Carcinogenicity

As noted above, 2-year feeding studies were conducted in Sprague-Dawley rats and MAGF mice. No treatment-related increases in tumor incidence were seen in animals of either species.

Irganox was nonmutagenic in an Ames Salmonella assay, a short-term test used to predict carcinogenicity (Wang and Smith, 1980).

Effects on Reproduction

Irganox was administered orally to pregnant rats at doses of 150, 500, and 1,000 mg/kg on days 6-15 of gestation; no embryotoxic or teratogenic effects were observed. Pregnant mice were dosed at the same levels according to the same schedule. No adverse effects were seen in offspring of dams dosed at 150 or 500 mg/kg. Delayed ossification of sternebrae was seen in offspring of females dosed at 1,000 mg/kg; no teratogenic effects were observed (Ciba-Geigy, 1982).

Substances Associated with Metal Pipes

Lead

Absorption and Metabolism

Absorption of lead from the gastrointestinal tract varies with the age of the individual, the chemical form of the lead, and the dietary levels of iron, calcium, fats, and proteins. Children absorb a much higher percentage of dietary lead (about 40 percent) than do adults (about 8-10 percent) (Hammond and Beliles, 1980; IARC, 1980). Lead is rapidly transferred to bone, a cumulative process that occurs throughout life. Lead in other

tissues rises during childhood and adolescence, and reaches a steady state by early adulthood (Hammond and Beliles, 1980). Adults excrete lead primarily in the urine, but also in feces, sweat, and breast milk, and through deposition in the hair and nails. In infants the principal route of excretion is gastrointestinal.

Acute toxicity

Acute lead poisoning is uncommon. Symptoms and signs inlcude thirst, nausea, severe abdominal pain, diarrhea or constipation, muscle pain and weakness, tingling of the skin, anemia, and hemcglobin in the urine. The kidneys can be damaged and urinary output decreased. Death may occur in 1 or 2 days (Klaassen, 1980).

Chronic Toxicity

Chronic low-level exposure to inorganic lead can give rise to a variety of syndromes involving different organ systems (see below). Because of the cumulative nature of lead absorption in children, they (including unborn children) should be considered the most sensitive population. In evaluating the risk of lead in drinking water, it should be borne in mind that the average daily oral intake of lead (through food and water) is 120 to 350 µg, of which about 25 µg is aborbed by adults, while a greater amount is absorbed by children (Klaassen, 1980).

Several studies have provided suggestive evidence that tap-water lead levels are correlated with blood levels (NAS, 1977, 1982; EPA, 1980c). Lead concentrations greater than 50 µg/liter may, according to one study cited by the NAS, raise and sustain blood levels above 30 µg/100 ml of whole blood. An analysis discussed by EPA indicates that blood-lead levels approximate a cube root function of water-lead levels (EPA, 1980c). Other minerals in the water can affect the extent to which lead is absorbed. For example, increased calcium intake can interfere with lead absorption. Another study investigating the epidemiology of mental retardation in Glasgow, Scotland,

suggested that tap-water lead concentrations greater than 100 µg/liter may raise the risk of childhood retardation (NAS, 1977).

Effects on Genes and Chromosomes

Whether lead affects genetic material depends in part on the nature of the lead compound being tested. Neither lead chloride nor lead acetate appears to induce mutations or similar effects in multiple bacterial tests (IARC, 1980). Lead chloride has interfered with the fidelity of DNA synthesis *in vitro*. Lead acetate transformed hamster cells, giving them the ability to produce tumors when injected into other rodents (IARC, 1980). Various *in vivo* and *in vitro* tests produced different kinds of chromosome damage, although there have been reports of negative results as well. Chromosomal abnormalities in humans have been reported in nine studies involving occupational exposure to lead. In six other studies no such effects were reported (IARC, 1980). Overall, because of differences in experimental protocols and in the quality of data, it cannot be said unequivocally that lead *per se* is mutagenic (Gerber et al., 1980).

Effects on Reproduction

Adverse effects of lead on reproduction have been known for centuries. Lead compounds used to be used to induce abortion. High levels of maternal exposure to lead are associated with menstrual disorders, impaired fertility, miscarriages and stillbirths (Gerber et al., 1980; Damstra, 1977). Several sperm abnormalities have been reported in men occupationally exposed to lead, with substantially elevated blood lead levels (IARC, 1980). Similar effects have been reported in rodents at lower blood leads (Damstra, 1977).

Numerous studies in animals implicate lead as a fetotoxic, fetolethal and teratogenic agent (see IARC, 1980). In addition to causing resorption (the rodent equivalent of miscarriage) and fetal deaths, high doses of lead have caused a variety of birth defects in different strains and species of experimental animals. Lead affected the development of the brain and

nervous system, the eyes, the skeleton and tail, the teeth, and the gastrointestinal system (IARC, 1980). Also reported have been decreased birth weight, retardation, and lower post-natal survival (Damstra, 1977).

The offspring of human pregnancies during which the mother suffered lead intoxication have been observed to have retarded intrauterine and postnatal growth, and damage to the nervous sytem (Gerber et al., 1980). At high maternal doses, it is clear that lead can adversely effect the outcome of pregnancy; however, there is no published evidence that lead causes birth defects in humans at lower levels of exposure (EPA, 1980). While lead can be transferred to the fetus, the human placenta appears to act as a partial barrier to such transfer (Gerber, 1980).

Carcinogenicity

The International Agency for Research on Cancer reported three relevant epidemiologic studies on men occupationally exposed to lead. Each study was subject to different limitations, but none reported any excess cancer due to lead exposure (IARC, 1980).

At least 25 bioassays of lead compounds have been conducted. Reviewing this evidence, the International Agency for Research on Cancer concluded that, "[l]ead acetate, lead subacetate and lead phosphate are carcinogenic to rats and lead subacetate to mice. These compounds induced benign and malignant tumors of the kidney following oral or parenteral administration. Gliomas occurred in rats given lead acetate or lead subacetate parenterally or by the oral route" (IARC, 1980). The carcinogenicity of lead arsenate, lead carbonate, lead oxide, metallic lead, lead naphthenate, and lead nitrate could not be evaluated because of inadequate or insufficient data.

If one assumes that absorbed lead circulates in a dissociated ionic form, and that the lead ion induces the experimental tumors, then lead in drinking water may pose a risk of cancer to humans. However, the nature of

the animal experiments is such that the potential human risk cannot be calculated (NAS, 1982).

Other Chronic Toxicity

Chronic effects of lead exposure can be classified according the system affected: it is not uncommon for there to be some overlap. Except as otherwise noted, these effects only occur at high levels of exposure.

Central nervous system effects are common in children, and are often of insidious onset. Symptoms include clumsiness, irritability, insomnia, dizziness, falling, progressing to delirium, seizures, vomiting, coma, and death. The mortality rate is 25 percent. Nearly half of the survivors have a neurologic deficit (e.g., retardation, seizures, cerebral palsy) (Klaassen, 1980).

This severe form of lead poisoning is unlikely in children exposed to the lead levels described elsewhere in this report. Of greater concern are more subtle effects on the CNS in terms of mental deterioration. Symptoms and signs of low-level poisoning inlcude impaired learning, hyperactivity, loss of motor skills and sensory perception, aggressive behavior, and convulsions. Such effects are seen when blood lead levels exceed 60 µg/100 ml whole blood, though it may occur at lower levels (Klaassen, 1980). Indeed, the apparent threshold for CNS effects in children has been progressively lowered on the basis of the results of more recent studies (Landrigan et al., 1980; Needleman, 1980).

It has been estimated that there is a threshold of about 55-60 µg/100 ml whole blood with respect to effects on the CNS. The estimate has more recently been lowered to 50 µg/100 ml whole blood (NAS, 1977, 1982). Animal evidence suggests that adverse biochemical effects occur at blood lead concentrations below 30 µg/100 ml (Needleman, 1980; Averill and Needleman, 1980). Otherwise asymptomatic children have been reported to have subtle neurologic impairment (Landrigan et al., 1980; Needleman, 1980).

Neuromuscular effects include "lead palsy." This syndrome of muscle weakness and fatigue is due to advanced chronic lead poisoning and is uncommon (Klaassen, 1980). It is not considered important for purposes of this Environmental Review.

Lead interferes with several biochemical steps in the synthesis of heme, a component of various oxygen-utilizing proteins (e.g., hemoglobin, myoglobin, cytochromes). Lead poisoning also causes anemia. The effect on heme synthesis is relatively easy to measure in the laboratory through analysis for heme precursors. The threshold blood-lead levels for accumulation of such precursors is below 20 µg/100 ml whole blood, or less than the average "normal" value for lead in blood (Piomelli, 1980). Lead's actions on heme synthesis has been considered the most sensitive effect in humans (NAS, 1977).

Two types of kidney injury have been reported in humans: reversible defects in reabsorption of certain nutrients and irreversible, progressive kidney failure usually found in persons with prolonged high-level lead exposure (Hammond and Beliles, 1980). Such kidney damage is not considered significant for the purposes of this Environmental Review.

Gastrointestinal effects are the most common syndrome of chronic lead intoxication among adults, and are characterized by loss of appetite, malaise, headache, constipation, and, in advanced cases, severe abdominal pain (Klaassen, 1980).

Copper

Absorption and Metabolism

About 30 percent of dietary copper is absorbed from the gastrointestinal tract. The fraction absorbed depends on the chemical form (salt or metal complex, water solubility) and on the presence of other substances (leucine increases absorption, while various ions of molybdenum, sulfur, iron and zinc decrease absorption) (Venugopal and Luckey, 1978).