Environmental Health Perspectives
Vol. 62, pp. 423-456, 1985

Possibilities of Detecting Health Effects by Studies of Populations Exposed to Chemicals from Waste Disposal Sites

by Patricia A. Buffler,* Martin Crane,* and Marcus M. Key*

Factors affecting the design of an epidemiologic study assessing possible health effects from chemical waste disposal sites are reviewed. Such epidemiologic studies will most likely be prompted either by a known release of chemicals into the environment around the site, or by an unusual disease cluster in a population near the site. In the latter situation, a method for evaluating the health effects is needed, and one possible approach is discussed. In the former situation, it may not be obvious what health outcomes are relevant.

Reported associations between health effects and chemicals in humans were reviewed. Studies from the occupational and environmental literature were classified by chemical and target organ affected and presented in tabular form. No attempt was made to critically evaluate the quality of evidence for each health effect, although bibliographic documentation was provided where possible. Episodes of chemical contamination of food, drinking water and other media were also reviewed and presented in a separate table.

The organ sites likely to be affected by toxic chemicals from waste disposal sites depend heavily on the route of exposure and the dose that is received. Ingestion is the most frequently reported route of exposure in episodes of environmental contamination. These have affected the hepatic, renal, hematopoietic, reproductive, and central nervous systems. The type and severity of effects were dose-dependent. Direct skin contact is important in the occupational environment where dermal and central nervous system effects have been reported but seems less likely as a route of exposure for populations around waste disposal sites. Inhalation, unless at relative high concentrations or as a result of fire, is unlikely to be important, although hematopoietic, reproductive, and central nervous system effects have been reported in occupational studies.

General Considerations

Consideration of the potential human biologic or health effects that might be detected among populations residing near chemical waste disposal sites requires information on the toxicity of the materials disposed and the conditions of exposure of human populations. The issues related to consideration of the potential human health effects will be briefly reviewed.

The design and conduct of an appropriate epidemiologic study requires documentation of the number, type, and volume of chemicals disposed, the time period of operation, and the particular chemicals and quantities currently present. In the absence of such information it is nearly impossible to determine either the necessity for an epidemiologic study or the specific type of health effects to be assessed.

Assuming that information on the type and amounts of toxic materials is assembled, it is then important to consider the potential for human exposure. What are the most likely environmental pathways, e.g, surface water, ground water, air, direct contact? The assessment will depend on several factors, including the structure and integrity of the chemical waste disposal site, the type and quantity of chemicals disposed, the method of containment, the years of disposal, the biological persistence of chemicals, the meteorologic and geologic characteristics of the waste site, and the source of water supply for residents of neighboring communities.

The extent of human exposure also depends on the population sizes and proximity of communities nearby the chemical waste site. In addition, the potential for exposure may be related to human activities in these communities, e.g., farming, fishing, hunting. Other environmental sources for population exposure to chemicals with similar toxic effects, such as area-wide mosquito controls, also need to be considered in assessing the feasibility of a health effects study or the results from such a study. Such population information would enable

*School of Public Health, University of Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX 77225.

one to estimate the acute versus chronic nature of exposure as well as the intensity of such exposures. As a general rule, potential human exposure levels around abandoned waste sites may be much lower than around active sites, unless persistent chemicals are involved. Information indicating exposure to chemicals which persist in human tissue would suggest the potential for continuous and cumulative exposure for individuals long after the environmental exposure has ceased. Exposure to persistent chemicals may be determined objectively by measuring tissue levels (*1*), which provides an opportunity for a more productive epidemiologic study than exposure to transient or nonpersistent chemicals. Studies of persistent chemicals are of particular importance, as most health studies of chemical waste disposal sites may not be undertaken until long after the initial exposures occurred.

Estimating the extent of human exposure may be extremely difficult when groundwater contamination is involved, as is often the case. The use of contaminated aquifers for drinking water by populations quite remote from the waste disposal site could result in a much larger population exposed, but with a lower probability of detecting any adverse health outcome because of the extremely low doses received. Specific health effects associated with chemical contamination of drinking water are discussed elsewhere in this series. Such exposures are mentioned here to stress the importance of this route of exposure and the additional complexity this adds to epidemiologic studies of health effects that may be related to chemical waste disposal sites.

The difficulties in conducting studies to unambiguously assess health effects associated with population exposure to chemical waste disposal sites cannot be sufficiently emphasized. Many of the issues related to the feasibility of such studies are outlined in the CDC draft document entitled System of Prevention, Assessment and Control of Exposures and Health Effects from Hazardous Sites (*2*). Even with a known chemical inventory and population at risk for a community, the ability of a study to detect an effect when it is present (power of study) may be severely limited by numerous factors. Small population sizes, low background rates, long latency periods, and the nonspecificity of many of the potential health effects associated with chemical exposures, especially those which occur with a greater frequency (higher background rates) such as spontaneous abortions, represent such constraining factors. In addition, the actual exposures experienced by the study population may too low to result in detectable increases, even for the nonspecific health outcomes assessed. These limitations have prompted some epidemiologists to consider the role of surveillance or "hypothesis-generating studies" in communities where chemical waste disposal sites are located. In the absence of specific exposure data, exposure is presumed, and selected health indices are examined to determine if there are demonstrable (and statistically significant) increases or decreases in the expected background rates. An essential component of this approach is the selection of an appropriate reference or comparison community for deriving the expected rates.

The need for a health study in a community may be prompted by either of two events. First, there may be evidence of a release of chemicals into the environment. Second, a real or apparent excess in the occurrence of a relevant health outcome such as a "cluster" of cancer cases in the community may be reported (*3*). In the latter situation, the disease "cluster" may be identified by routine health effects monitoring using available statistics or by word of mouth. The relevant health outcome is known (or suspected), and the initial task is to determine if the observed frequency of the disease in time and space represents a significant departure from the number of disease events that would be expected in a population of this size. If the cluster can not be explained by confounding factors, chance, or other factors, then the second, and by far the more difficult, task is to determine if there is an association of chemical exposures from the waste disposal site with the real or apparent disease "cluster." The major difficulty encountered is the uncertainty in estimating individual chemical exposures.

If documented chemical exposures occurred to populations residing in the vicinity of a waste disposal site, all relevant health outcomes should be reviewed intensively for fluctuations of significance in routinely collected health statistics. The need for additional studies can then be determined on the basis of the available exposure data and potential health effects.

A two-step statistical procedure for monitoring routinely reported health events (deaths, births, etc.) in small populations has been outlined for communities adjacent to low-level radioactive waste disposal sites (*3*). Use of this procedure for monitoring calls for an "alert" status when a number of relevant events exceeds a specified level during a given interval of time with followup observation being continued for one more time period. "Action" status is established if the excess continues to be apparent in the second time period. The system also allows for immediate action to be taken if the observed number of events greatly exceeds expectation in the first time period. The procedures outlined only initiate further study and will not provide definitive data regarding the cause of the excess mortality or other health indices. Such a procedure may be useful in assessing the health effects of exposure to chemical waste disposal sites when exposure data are limited or unavailable, the anticipated health effects are unknown, and residents of the community are concerned regarding the perceived health effects of the exposure, e.g., "clusters" of cancer cases, birth defects, or infant deaths.

Potential health effects on target organs or tissues that might be observed in studies of chemical waste disposal sites were identified (Tables 1–9) from reported human exposures to chemicals without regard to the source of exposure. Table 10 presents a list of selected chemicals having the potential to produce effects at con-

centrations sufficiently low that the public is not likely to be aware of their presence. These cross-indexed tables of data are based on a review of the environmental, occupational medicine, and toxicologic literature. It is emphasized that Tables 1–10 are lists of potential health effects from any environmental exposures to the chemicals (not all inclusive of chemicals or effects).

A major factor to consider in assessing the likelihood of observing a potential health effect is the intensity and duration of exposure. Short-term, very low exposures are far less likely to induce any of the health effects identified, whereas chronic exposures of any intensity and acute high exposures may induce a wide range of effects. Population exposures resulting from chemical waste disposal sites are usually much lower than those observed in work environments or accidental environmental exposures. Therefore it may be less likely that some effects associated with environmental exposures in other settings will be observed.

Since few studies of health effects associated with toxic waste disposal sites are available, a review of those studies as well as others in which epidemics resulted from point source release of chemicals into the environment was undertaken. The results of this review can be seen in Table 11.

Thus, three approaches are reported here. First, the adverse health effects that might be seen in clusters and the associated causative agents are identified. Second, the inverse of Tables 1–9 presents selected chemicals and their toxic effects (Table 10). The third is a tabular review of the findings in published and unpublished environmental exposure episodes.

Probable Target Organs Affected by Toxic Wastes

List of chemicals known to have affected those target organs (Tables 1–9) were prepared from a review of recent occupational and toxicologic literature (*246*). Skin and central nervous system conditions were judged to be the most likely effects from direct contact with chemicals. Hepatic, hematopoietic, renal, reproductive, and central nervous system effects were considered to be

Table 1A. Adverse health effects in human target organs reported to be due to exposure to chemicals including metals: skin, pigmentary disturbances.

Effect	Chemical	Skin coloration	Reference
Hyperpigmentation	Arsenic	—	(*4–6*)
	Bismuth	—	(*4–6*)
	Mercury	—	(*4–6*)
	Silver	—	(*4–6*)
Hypopigmentation	Dihydroxybenzenes		
	Catechol, *p-tert*-butyl	—	(*7*)
	Catechol, *p*-isopropyl-	—	
	Catechol, *p*-methyl	—	(*8*)
	Hydroquinone	—	(*9*)
	Hydroquinone, monobenzyl ether	—	(*10*)
	Hydroquinone, monoethyl ether	—	(*11*)
	Phenol, amyl-	—	(*12*)
	Phenol, *p-tert*-butyl-	—	(*12,13*)
	Phenol, nonyl-	—	(*14*)
	Phenol, octyl-	—	(*14*)
	Physostigmine (eserine)	—	(*15*)
	N,N',N''-triethylenethiophosphoramide (Thio-TEPA)	—	(*16*)
Pigment discoloration	Organic chemicals		(*4*)
	Acid, picric	Yellow	(*17*)
	Acid, oxalic	Blue	
	Dinobuton (2-(1-methyl-2-propyl)-5,6-dinitrophenyl isopropylcarbonate	Yellow	(*18*)
	4,4'-Methylenedi-aniline	Yellow	(*17*)
	p-Phenylenediamine	Brown	
	Inorganic chemicals		
	Nitric acid	Yellow	
	Sodium nitrate	Yellow	
	Permanganate	Brown	
	Metals		(*4,19*)
	Arsenic salts	Brown	
	Bismuth salts	Blue-gray	
	Bichromates	Yellow	
	Copper salts	Green	
	Lead salts	Blue-gray	
	Mercury salts	Black	
	Silver nitrate	Blue	

Table 1B. Adverse health effects in human target organs reported to be due to exposure to chemicals including metals: skin, contact dermatitis.[a]

Chemical	Irritant[b]	Sensitizer (allergen)	Chemical	Irritant[b]	Sensitizer (allergen)
Organic chemicals			Organic chemicals		
Acetone	X		Phenol	X	
Acid, acetic	X		Phenols, chlorinated	X	
Acid, benzoic	X	X	Phenylhydrazine	X	X
Acid, butyric	X		Polyamides, aliphatic		X
Acid, cinnamic	X		Polyethylene glycol		X
Acid, cresylic	X		Polysorbate		X
Acid, formic	X		Propionate, phenylmercuric		
Acid, lactic	X		Thiazole, amino		X
Acid, oxalic	X		Toluamide, diethyl		X
Acid, picric	X		Toluene, butylhydroxyl		X
Acrylic monomer	X		Trichloroethylene	X	X
Alcohol, amyl		X	Trinitrotoluene		X
Alcohol, benzyl		X	Inorganic chemicals		
Alcohol, butyl	X	X	Acid, chromic	X	X
Alcohol, ethyl	X	X	Acid, hydrofluoric	X	
Alcohol, propyl		X	Acid, nitric	X	
Aldehyde, cinnamic	X		Acid, sulfuric	X	
Amide, oleyl		X	Ammonium compounds	X	
Amine, monoamyl		X	Bromides	X	
Aminophenazone		X	Calcium oxide	X	
Aminothiazole		X	Calcium carbonate	X	
Aniline	X	X	Calcium hypochlorite	X	
Benzene	X		Cyanide, sodium or potassium	X	
Benzene, dichloro-	X	X	Silicate, sodium	X	
Benzene, dinitrochloro-	X	X	Sulfate, sodium		
Benzoate, sodium	X		Metals and their salts		
Benzophenone	X	X	Antimony salts	X	
Carbon disulfide	X	X	Arsenic salts	X	X
Diamine, phenylene	X	X	Arsenical insecticides	X	
Diamine, toluene	X	X	Cobalt chloride	X	
Formaldehyde	X	X	Mercury salts	X	X
Lindane		X	Nickel oxide	X	X
Nitro and nitroso compounds		X	Nickel salts	X	X
Phenazone, amino	X	X	Platinum salts	X	X

[a] Data of Schwartz et al. (*20*), Adams (*4*,*21*) and Maibach and Gellin (*6*).

[b] It should be noted that irritancy is a function of concentration, duration of exposure, and other factors such as occlusion.

the most likely indicators of chronic low-dose exposure by way of ingestion. Both central nervous system and reproductive disorders appeared likely to occur in a number of exposure circumstances, both high and low dose, and also from a variety of chemical agents. Lung, gastrointestinal, and cardiovascular disorders, although important in occupational exposures, were considered unlikely in low-dose exposure situations such as would occur around a toxic waste disposal site.

Chemically Induced Effects in Humans by Target Organ

Once a list of relevant outcomes had been constructed, a review of occupational and human toxicological studies was undertaken, and a list of chemicals that had been associated with each effect was prepared (Tables 1–10). Most of the references are case reports and clinical series, and relatively few associations have been documented in well designed epidemiologic studies. More information is available for dermatologic and central nervous effects than for other target organs, and this is reflected in Tables 1–10.

The immune system was omitted from consideration because it was believed that procedures for evaluation of alterations in immune response were not yet in standard practice in the same way as, for example, hepatic or renal profiles. Similarly, studies of cytogenetic abnormalities of peripheral blood was also considered to still be in the developmental phase.

Review of Environmental Exposure Episodes

Table 11 summarizes point-source epidemics resulting from accidental releases of chemicals into the environment. The chemical or chemicals and circumstances of exposure are described, followed by the study design employed to assess health effects, the method for assessment of exposure, and the results. Included are four episodes involving mixtures from chemical waste disposal sites, seven involving miscellaneous single chem-

Table 1C. Adverse health effects in human target organs reported to be due to exposure to chemicals including metals: skin.

Effect	Chemical	References
Folliculitis and acneform dermatosis (e.g., chloracne)	Polyhalogenated naphthalenes	(*4,22*)
	Polychloronaphthalenes	(*23–25*)
	Polybromonaphthalenes	(*23–25*)
	Polyhalogenated biphenyls	
	Polychlorinated biphenyls (PCBs)	(*26,27*)
	Polybrominated biphenyls (PBBs)	(*26,27*)
	Polyhalogenated dibenzofurans	(*28,29*)
	Polychlorodibenzofurans, especially tri-, tetra-, penta-, and hexachlorodibenzofurans	
	Polybromodibenzofurans, especially tetrabromodibenzofuran	
	Contaminants of polychlorophenol compounds especially herbicides (2,4,5T and pentachlorophenol) and herbicide intermediates (2,4,5-Trichlorophenol) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Hexachlorodibenzo-*p*-dioxin Tetrachlorodibenzofuran	(*30–33*)
	Contaminants of 3,4-dichloroaniline and related herbicides (Propanil, Methazole) 3,4,3′,4′-Tetrachoroazoxybenzene 3,4,3′,4′-Tetrachloroazobenzene	(*34*)
	2,6-Dichlorobenzonitrile	(*35*)
Porphyria cutanea tarda	Chlorinated hydrocarbon intermediates	(*30,36*)
Alopecia	Chloroprene	(*37*)
Neoplasms	Biphenyls, polychlorinated	(*38*)
	Chloroprene	(*38,39*)
	Soots, tars, mineral oils	(*40*)
	Arsenic	(*41*)

icals, five involving polyhalogenated biphenyls, six with organic pesticides, and nine involving heavy metals. The reported effects were very much dose-dependent.

In all situations in which food supplies were contaminated, sequelae were rapid and severe. Symptoms were generally similar to those noted in occupational exposures with skin, gastrointestinal, and central nervous system effects predominating. Contamination of water supplies, in presumably much lower concentrations, did not always result in clear-cut responses. In situations such as the waste disposal sites in which toxic chemicals were not identified in food or water, unequivocal adverse health effects were rarely detected.

Contamination of Food Supplies

Contamination of food supplies by some organic pesticides (endrin, parathion) resulted in severe CNS effects (*271, 272, 275, 276*), whereas others caused either no effect (DDT at low doses) (*266*) or, for hexachlorobenzene, a severe cutaneous porphyria (*273, 274*). Contamination by metallic pesticides such as methylmercury poisoning in Iraq in 1960 and 1971, resulted in severe dose-dependent central nervous system defects (*287*). Other chemical contamination of food supplies resulted in various sequelae, such as 4,4′-diaminodiphenylmethane (liver and CNS disturbances) (*254*), *o*-cresyl phosphate (CNS disturbances, anemia) (*255, 256*), and PCBs (chloracne, reproductive disorders, and other disturbances) (*27, 264, 265*).

Contamination of Water Supplies

Certain areas of Taiwan have very high background levels of arsenic (400–600 ppb) which have been correlated with rates of skin cancer and "black foot disease", a disorder of the peripheral circulation (*278, 279*. Similar studies in the U.S. (*277*) failed to replicate this finding, although mean concentrations were lower (16.5 ppb in rural areas and 4.8 ppb in urban areas) than in Taiwan. A Chilean study which reported arsenic levels in water supplies comparable to those in Taiwan noted a substantial decrease in the frequency of various cutaneous lesions in hospitalized patients after a filtration plant began operations (*280*).

Hematological and peripheral nervous system effects were noted in families in rural areas of Scotland drinking contaminated water from lead-lined pipes in their homes (*282*). These effects were similar to those noted in occupational exposures to lead.

One report of phenol in drinking water noted a syndrome consisting of diarrhea, mouth sores, dark urine, and burning in the mouth. No differences in clinical or laboratory findings were noted between exposed individuals and controls 6 months after the episode (*253*). Acrylamide contamination of a well used by a Japanese

Table 2. Adverse health effects in human target organs reported to be due to chemicals including metals: central nervous system.

Effects	Chemical	References
Behavioral changes		
	Organic chemicals	
Neurasthenia, irritability	Acrylamide	(*42*)
Impaired psychomotor function	Organophosphate insecticides	(*43,44*)
Impaired psychomotor function	Perchloroethylene	(*42*)
Neurasthenia, memory impairment	Solvents	(*45*)
Neurasthenia, impaired psychomotor function	Styrene	(*42*)
Memory impairment	Toluene	(*46–48*)
Memory impairment	Xylene	(*46–48*)
	Inorganic chemicals	
Acute psychosis, emotional instability, memory impairment	Carbon disulfide	(*49*)
	Metals	
Neurasthenia, irritability	Arsenic	(*42*)
Neurasthenia, irritability, emotional instability, memory impairment	Lead	(*50,51*)
Neurasthenia, irritability, acute psychosis, emotional instability, memory impairment	Manganese	(*52*)
Neurasthenia, irritability, impaired psychomotor function	Mercury	(*53*)
Central nervous depression		
	Organic chemicals	
	Ethyl alcohol	(*42*)
	Aliphatic alcohols, ketones, aldehydes	(*42*)
	Alkenes, including butadiene	(*54*)
	Alkanes (C_1-C_6)	(*42*)
	Aromatic hydrocarbons (benzene, toluene, xylene)	(*47,54,55*)
	Methylene chloride	(*56*)
	Trichloroethane	(*57–59*)
	Inorganic chemicals	
	Carbon disulfide	(*60*)
Peripheral neuropathies		
	Organic chemicals	
	Acrylamide	(*62–64*)
	DDT	(*42*)
	Hexane	(*65,66*)
	Methyl *n*-butyl ketone	(*67*)
	Methyl chloride	(*42*)
	Solvents	(*47*)
	Trichloroethylene	(*68*)
	Inorganic chemicals	
	Carbon disulfide	(*60*)
	Metals	
	Arsenic	(*69,70*)
	Lead	(*71–75*)
	Manganese	(*76–78*)
	Mercury	(*79,80*)
	Organic chemicals	
Ataxic gait	Acrylamide	(*42,61*)
Myoclonus	Benzene hexachloride	(*42,61*)
Ataxic gait	Chlordane	(*42,61*)
Ataxic gait, opsoclonus, tremors	Chlordecone (Kepone)	(*81–83*)
Ataxic gait, tremors	Chlorophenothane (DDT)	(*42,61*)
Bladder neuropathy	Dimethylaminopropionitrile	(*84,85*)
Ataxic gait, impaired visual acuity	Hexane	(*65,66,86*)
Impaired visual acuity	Methanol	(*42,61*)
Ataxic gait	Methyl *n*-butyl ketone	(*87*)
Seizures	Organochlorine insecticides	(*42,61*)
Palsy, Guillain-Barre syndrome	Organophosphate insecticides	(*88–91*)
Ataxic gait	Toluene	(*92,93*)
Cranial neuropathy	Trichloroethylene	(*50,68,94*)
	Inorganic chemicals	

Table 2 (continued)

Effects	Chemical	References
Acute psychosis, cranial neuropathy, headache	Carbon disulfide	(*95*)
	Metals	
Seizures, Parkinsonism	Lead	(*42,61*)
Tremors, headache	Manganese	(*52,77*)
Ataxic gait, myoclonus, tremors, impaired visual acuity, intracranial pressure	Mercury	(*96*)
Neoplasm	Vinyl chloride	(*39*)
	Chlordane, heptachlor	(*97*)

Table 3. Adverse health effects in human target organs reported to be due to chemicals including metals: liver.

Effect	Chemical	References
Acute hepatocellular injury (hepatitis)	Organic chemicals	
	Chlorinated benzenes	(*98,99*)
	Biphenyls, polychlorinated (PCB)	(*98,99*)
	Carbon tetrachloride	(*100–103*)
	Chlordecone (Kepone)	(*104*)
	Chloroform	(*98,99*)
	Dioxin	(*105*)
	Ethylene dibromide	(*98,99*)
	Ethylene dichloride	(*98,99*)
	Naphthalenes, chlorinated	(*98,99*)
	Nitrosamine, dimethyl	(*106*)
	Inorganic	
	Phosphorus compounds	(*98,99*)
	Metals	
	Arsenic	(*107*)
	Copper	(*98,99*)
Subacute necrosis and cirrhosis	Organic	
	Biphenyls, polychlorinated (PCB)	(*108*)
	DDT	(*109*)
	Tetrachloroethane (perchlorethylene)	(*100*)
	Toluene	(*110*)
	Trinitrotoluene	(*111,112*)
	Vinyl chloride	(*113*)
	Metals	
	Arsenic	(*107*)
Cirrhosis	Organic	
	Biphenyls, polychlorinated (PCB)	(*108*)
	Carbon tetrachloride	(*102*)
	Hexachlorobenzene	(*98,99*)
	Naphthalene, chlorinated	(*108,114,115*)
	Metals	
	Beryllium	(*116*)
Neoplasms		
	Carbon tetrachloride	(*97*)
	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	(*39*)
	Vinyl chloride	(*97*)
	Arsenic	(*39*)

family was reported to cause severe CNS disturbances, although blood values and liver function were apparently within normal limits (*257*).

Several heavy metals, including cadmium, were released from a Japanese chemical factory into a river that was subsequently used as a source of drinking water and for irrigation of crops. Individuals who consumed this water developed a syndrome involving bone pain ("itai-itai" or "ouch-ouch"), and proteinuria, and glucosuria. It is unclear, in spite of a number of investigations, to what extent this condition is attributable to cadmium alone, or to an interaction between nutritional status and cadmium exposure (*281*).

Contamination Due to Unusual Environmental Circumstances

In Seveso, Italy, a chemical manufacturing plant experienced an explosion in a reactor where trichlorophenol was being produced. Dioxin (2,3,7,8-

Table 4. Adverse health effects reported to be due to chemicals including metals: reproductive system and fetus.[a]

Effect	Chemical	References
Germ cell mutation	Vinyl chloride (suspected)	(*125*)
Infertility, male (includes decreased spermatogenesis)	Organic chemicals	
	Carbaryl (suspected)	(*126*)
	Carbon disulfide (suspected)	(*127*)
	DDT (cyclodiene group of chlorinated insecticides)	
	Dibromochloropropane	(*128–130*)
	Epichlorohydrin (suspected)	(*131*)
	Ethylene dibromide (suspected)	(d*132*)
	Kepone (suspected)	(*133,134*)
	Polychlorinated biphenyls (PCB)	(*135*)
	Chloroprene	(*136*)
	Metals	
	Cadmium (suspected)	(*137*)
	Lead	(*138,139*)
	Manganese (suspected)	(*140*)
Infertility, female	Organic chemicals	
	Benzene (suspected)	(*137*)
	Carbon disulfide (suspected)	(*127*)
	Chloroprene (2-chlorobutadiene) (suspected)	(*141*)
	Dibromochloropropane (suspected)	(*142*)
	Ethylene dibromide (suspected)	(*143*)
	Kepone (suspected)	(*134*)
	PCB (suspected)	(*144*)
	Metals	
	Cadmium	(*139*)
	Lead	(*139*)
Embryotoxicity	Organic chemicals	
	Benzene (suspected)	(*137*)
	PCB	(*145,146*)
	Metals	
	Lead	(*140*)
	Arsenic (suspected)	(*140*)
	Mercury (suspected)	(*137*)
Teratogenesis (congenital anomalies/malformations)	Organic chemicals	
	Aldrin (suspected)	(*124*)
	Benzene (suspected)	(*124*)
	Captan (suspected)	(*124*)
	Carbaryl (suspected)	(*124*)
	Dimethyl sulfoxide (suspected)	(*124*)
	Dioxin (suspected)	(*147*)
	Ethylene dibromide (suspected)	(*143*)
	Ethylene thiourea (suspected)	(*148*)
	Hexachlorophene (suspected)	(*149*)
	Malathion (suspected)	(*124*)
	PCB	(*150*)
	Perchloroethylene (suspected)	(*151*)
	Propylene glycol (suspected)	(*124*)
	2,4,5-Trichlorophenoxyl acetic acid (suspected)	(*152,153*)
	Vinyl chloride (suspected)	(*154–156*)
	Metals	
	Arsenic (suspected)	(*124*)
	Cadmium (suspected)	(*157*)
	Lead (suspected)	(*124*)
	Mercury	(*158*)
Spontaneous abortion/fetal death	Organic chemicals	
	Chloroprene (suspected)	(*136,159*)
	Dibromochloropropane	(*160*)
	2,4,5-Trichlorophenoxyacetic acid (suspected)	(*161*)
	Dioxin (suspected)	(*147*)
	Ethylene dibromide (suspected)	(*143*)
	PCB	(*150*)
	Vinyl chloride (suspected)	(*125,162*)
	Inorganic chemicals	
	Carbon disulfide (suspected)	(*127*)
	Metals	
	Arsenic (suspected)	(*140*)
	Cadmium (suspected)	(*140*)
	Lead	(*139,163,164*)
	Mercury (suspected)	(*140*)

Table 4 (continued)

Effect	Chemical	References
Neonatal death	Organic chemicals	
	PCB (suspected)	(*144*)
	Metals	
	Cadmium (suspected)	(*165*)
	Lead	(*137*)
	Mercury (suspected)	(*137*)
Low birth weight	Organic chemicals	
	Chloroprene (suspected)	(*136*)
	Perchloroethylene (suspected)	(*151*)
	PCB	(*150*)
	Metals	
	Cadmium (suspected)	(*166*)
	Lead	(*167,168*)
	Mercury (suspected)	(*139*)
Developmental disabilities	Organic chemicals	
	PCB (suspected)	(*144*)
	Metals	
	Arsenic (suspected)	(*140*)
	Cadmium (suspected)	(*169*)
	Lead	(*170,171*)
	Mercury	(*158*)
Childhood cancer (cancer in offspring)	Organic chemicals	
	Hydrocarbons (suspected)	(*172–174*)
	Metals	
	Lead	(*175*)

[a] Attention was directed at identifying chemicals or other environmental agents shown or suspected to be capable of inducing reproductive effects in humans, excluding the effects of maternal use of drugs, smoking, and ethanol during conception and pregnancy, exposure of hospital personnel to anesthetic gases and the effects of radiation exposures. The reproductive effects of these exposures are well known and extensively documented (*117–124*). Chemicals are identified as "suspected" as capable of inducing a health effect in humans when the human evidence is deficient or when only animal (experimental) data are available.

Table 5. Adverse health effects in human target organs reported to be due to chemicals including metals: hematopoietic and lymphatic system.

Effect	Chemical	References
Anemia	Organic chemicals	
	Nitrobenzene	(*176*)
	Naphthalene	(*177–179*)
	Naphthol	(*180*)
	Phenol derivatives	(*181*)
	Phenylhydrazine	(*180*)
	Quinones	(*180*)
	Metals	
	Arsenic trioxide	(*180*)
	Arsine	(*182,183*)
	Copper sulfate	(*184*)
	Lead	(*185–187*)
Marrow depression		
	Benzene	(*188,189*)
	Lead	(*180*)
Immune suppression		
	Polychlorinated biphenyls (suspected)	(*180*)
Aplastic anemia		
	Benzene	(*190*)
	Benzene hexachloride (Lindane)	(*191,192*)
	Trinitrotoluene	(*193*)
Leukemia and lymphoma		
	Benzene	(*194*)
	Chlordane and heptachlor (uncertain)	(*97*)
	Chloroprene (uncertain)	(*97*)
	Dichlorobenzene (uncertain)	(*97*)
	Epichlorohydrin (uncertain)	(*97*)
	Ethylene oxide (uncertain)	(*97*)
	Hexachlorcyclohexane (uncertain)	(*97*)
	Trichloroethylene (uncertain)	(*97*)
	Vinyl chloride (uncertain)	(*97*)

Table 6. Adverse health effects in human target organs reported to be due to chemicals including metals: genitourinary system.

Effect	Chemical	References
Acute renal failure	Organic chemicals	
Prerenal ischemia	Aniline	(*198*)
Secondary effects of hemolytic agents	Carbon tetrachloride	(*199,200*)
Direct tissue injury	Chlordane	(*201*)
	Ethylene glycol	(*202,203*)
	Parathion	(*204*)
	Paraquat	(*205*)
	Toluene	(*206*)
	Trichloroethylene	(*207,208*)
	Metals	
	Mercury	(*209–211*)
Chronic renal disease	Carbon disulfide	(*195–197*)
Tubal or interstitial disease	Cadmium	(*212*)
	Lead	(*213–215*)
Glomerulonephritis	Gasoline (?)	(*216*)
	Solvents	(*216–219*)
Neoplasia, kidney	Cadmium (uncertain)	(*97*)
	Lead (uncertain)	(*97*)
Neoplasia, bladder	4-Aminobiphenyl	(*220*)
	Benzidine	(*220*)
	2-Naphthylamine	(*221*)
	N-Phenyl-2-naphthylamine (uncertain)	(*97*)
	Soots, tars, oils	(*222*)
	o-, *p*-Toluidine	(*223*)
	Lead (uncertain)	(*97*)
Neoplasia, prostate	Cadmium (uncertain)	(*97*)

Table 7. Adverse health effects in human target organs reported to be due to chemicals including metals: lung and respiratory tract.

Effect	Chemical	References
Asphyxiation (mechanism of action)	Organic chemicals	(*224,225*)
	Ethane (simple)	
	Methane (simple)	
	Inorganic	
	Carbon dioxide (simple)	
	Carbon monoxide (chemical)	
	Hydrogen cyanide (chemical)	
	Hydrogen sulfide (chemical)	
	Nitrogen (simple)	
Irritation	Organic chemicals	(*226,227*)
	Inorganic chemicals	(*226,227*)
	Ammonia	
	Halogen gases	
	H-X (any concentrated acid mist where X is a halogen	
	Nitrogen oxides	
	Ozone	
	Phosgene	
	Sulfur oxides	
Sensitization, asthma	Organic chemicals	(*228*)
	Anhydride, phthalic	
	Anhydride, trimetallic	
	Anhydride, tetrachlorophthalic	
	Amine, phenylene-	
	Chloramine	
	Formaldehyde	
	Isocyanates, organic	
	Phenol	
	Piperazine formaldehyde	
	Pyrethrins	
	Sulfonechloramine	
	Tannic acid	
	Inorganic chemicals	
	Isocyanates, inorganic	

Table 7 (continued)

Effect	Chemical	References
Sensitization, asthma (cont'd)	Metals	
	Chromium	
	Cobalt	
	Nickel sulfate	
	Platinum salts (complexed)	
	Vanadium pentoxide, trioxide	
Hypersensitivity pneumonitis	Phthalic anhydride	(*229*)
	Trimetallic anhydride	(*229*)
	Toluene diisocyanate	(*229*)
	Organic dusts	(*229*)
Pneumoconioses	Oil shale	(*230*)
	Minerals	(*230*)
	Asbestos	(*287*)
	Coal	
	Silica	
	Talc	
	Metals	(*230*)
	Antimony	
	Cerium oxide	
	Tungsten carbide	
Fibrosis	Asbestos	(*230,287*)
	Silica	(*230*)
Edema	Smoke (products of pyrolysis)	(*230*)
	Inorganic chemicals	(*230*)
	Ammonia	
	Chlorine gas	
	Nitrogen oxides	
	Phosgene	
	Metals	
	Cadmium	(*230*)
Granulomatous disease	Inorganic chemicals	(*230*)
	Talc	
	Metals	(*230*)
	Aluminum	
	Beryllium	
	Zirconium	
Mesothelioma	Asbestos	(*97,287*)
	Radon	(*97*)
Cancer	Organic chemicals	(*97*)
	Acrylonitrile (uncertain)	
	Amitrole (uncertain)	
	Bischloromethyl ether	
	Chloroprene (uncertain)	
	Epichlorohydrin (uncertain, IARC, 1979)	
	Hexachlorocyclohexane (uncertain)	
	Mustard gas	
	Soots, tars, mineral oils	
	TCDD	
	Vinyl chloride	
	Vinylidene chloride (uncertain)	
	Minerals	(*97*)
	Asbestos	(*287*)
	Hematite (uncertain)	
	Metals	(*97*)
	Arsenic	
	Beryllium (uncertain)	
	Cadmium (uncertain)	
	Chromium	
	Lead (uncertain)	
	Nickel (uncertain)	

tetrachlorodibenzodioxin, TCDD), one of the by-products resulting from the conditions in the reactor, was identified in soil samples taken from several areas around the plant. The population around the plant experienced immediate effects, such as burns and contact dermatitis from exposure to trichlorophenol, followed within a few weeks by comedones and epidermal cysts typical of chloracne associated with dioxin. Dermatological prob-

lems were not correlated with environmental dioxin concentrations except in the immediate vicinity of the plant (*259*). Cytogenetic studies of subsets of exposed persons revealed no differences from unexposed control subjects (*261*), and results from immunologic studies were equivocal (*260*). Studies of reproductive effects were also equivocal due to difficulties in establishing appropriate comparison groups, reporting biases and small numbers of events (*262*). A registry has been established for long-term morbidity and mortality studies but, other than the initial dermatological problems, no unusual problems had been reported as of three years after the incident.

Another incident involving dioxin occurred in Missouri, when waste oils containing dioxin were sprayed for dust control on residential, recreational, and work areas. Once the problem was discovered, a case-control study was initiated to examine health effects in a group of individuals at high risk of exposure as compared to controls. No cases of chloracne or porphyria cutanea tarda were noted, nor were any discernible differences in immune, renal, or hepatic function noted between exposed and control subjects. The authors emphasized that this should be considered a pilot study, and also noted that a method for measuring the body burden of TCDD would be extremely helpful in studies of this sort (*258*).

Table 8. Adverse health effects in human target organs: gastrointestinal tract.[a]

Effect	Chemical
Esophagitis	Inorganic chemicals
	Acids, mineral
	Alkalis
Ulcer	None
Gastritis, acute or chronic	Ethyl alcohol
Neoplasia, pharyngeal-esophageal-laryngeal	Organic chemicals
	Formaldehyde
	Isopropyl oils
	Mustard gas
	Soots, oils, tars
	Metals, minerals
	Chromium (uncertain)
	Nickel (uncertain)
	Asbestos (uncertain)
Neoplasia, stomach	Organic chemicals
	Chloroprene (uncertain)
	Ethylene oxide (uncertain)
	Soots, tars, and mineral oils
	Vinyl chloride (uncertain)
	Minerals, metals
	Asbestos (uncertain)
	Lead (uncertain)
Neoplasia, colon	Organic chemicals
	Acrylonitrile (uncertain)
	Chloroprene (uncertain)
	Ethylene oxide (uncertain)
	Soots, tars, and mineral oils
	Vinyl chloride (uncertain)
	Minerals, metals
	Asbestos (uncertain)
	Lead (uncertain)

[a]Data of Schedl (*231*), Tolman (*232*), and IARC (*97*).

Polyhalogenated biphenyls have been released into the environment by contamination of animal feed in Michigan (*268*), sewage sludge later used as fertilizer (*267*) and presumably as by-products of pesticide manufacturing released into a stream (*266*). In each of these instances, a direct measure of exposure, in the form of serum levels of the chemical, was available. In none of the three studies were serum PBB or PCB levels associated with overt adverse health effects. However, immunologic studies on a subset of the exposed population in Michigan were conflicting, with an early study showing decreases in T-cell function, as measured by E-rosette formation, and increases in number of null cells (*269*), but a subsequent study failed to confirm this result (*268*).

Bioconcentration of organic mercury in Minimata Bay, Japan resulted in an epidemic of neurologic disease in adults and severe neurologic sequelae in children exposed *in utero* who ate fish and shellfish from the bay (*79, 158*). Other episodes of heavy metal poisoning have included exposure to lead from smelters that resulted in high blood lead levels in children living near the smelters (*283, 284*). Although no physiological deficits were noted in the children with elevated blood lead levels, performance on several scales within a battery of IQ tests was said to be compromised in the exposed children (*285*).

Exposures Resulting from Chemical Waste Disposal Sites

The prototypical episode for exposure to toxic chemicals from chemical waste disposal sites is Love Canal. Although much has been written, very little data have been published. One carefully controlled study of cytogenetic abnormalities noted no differences in frequency of chromosomal aberrations or sister chromatid exchanges between exposed and control subjects (*247*). An ecological study which examined incidence rates of cancer in the Love Canal area versus the rest of upstate New York noted no excesses of any site except possibly lung (*248*). The lung cancer excess was not consistent across age groups. Few additional data are available for review, although a summary of other clinical investigations noted: "... Information was sought on a wide range of conditions. No unusual patterns were noted, except possibly with respect to certain reproductive effects.... Although an increased frequency of low birth weight in women from homes with possible seepage risk suggested a toxic effect, the finding does not correspond well with NYSDH [New York State Department of Health] environmental test results" (*1*).

Leachate from an abandoned chemical waste disposal site in Chester, Pennsylvania, caught on fire in February, 1978. The CDC subsequently investigated the site to determine health effects in residents around the site or in the firemen who extinguished the fire. At the time of the CDC investigation in October, 1979, several

Table 9. Adverse health effects in human target organs: cardiovascular system.

Effect	Chemical	References
Hypertension	Metals	
	Cadmium	(*233*)
	Lead (uncertain)	(*97*)
Heart disease, indirect effect	Organic chemicals	
	Dinitro benzene	(*234*)
	Methylene chloride	(*235*)
	Trinitro toluene	(*234,236*)
Heart disease, direct effect	Organic chemicals	
	Ethylene glycol fluorocarbons	(*237*)
	1,1,1-Trichloroethane	(*238,239*)
	Inorganic chemicals	
	Carbon disulfide	(*240,241*)
	Metals	
	Arsenic	(*242,243*)
	Cobalt	(*244*)

Table 10. Selected waste chemicals and their adverse health effects.

Compound	Effect	References
Acetone	Skin irritant	(*4*)
Benzene	Skin irritant	(*4*)
	Female infertility (suspected)	(*137*)
	Embryotoxicity (suspected)	(*137*)
	Teratogenesis (suspected)	(*124*)
	CNS depression	(*47,54*)
	Bone marrow depression	(*188,189*)
	Aplastic anemia	(*190*)
	Leukemia	
	Lymphoma (suspected)	(*194*)
Carbon tetrachloride	Acute hepatocellular injury (hepatitis)	(*101–103*)
	Hepatic cirrhosis	(*102*)
	Hepatic neoplasia (uncertain)	(*97*)
	Acute renal failure (direct tissue injury)	(*199,200*)
DDT	Peripheral neuropathies	(*109*)
	Ataxic gait	
	Tremors	
	Subacute hepatic necrosis with possible cirrhosis	
	Male infertility	
Dichlorobenzene (unspecified)	Leukemia and lymphoma (uncertain)	(*97*)
Dichloromethane	CNS depression	(*56*)
	Heart disease; indirect effect	(*235*)
Naphthalene	Anemia	(*177,178*)
Phenol	Skin irritant	(*5*)
	Asthma	
Polychlorinated biphenyls	Chloracne	(*26,27*)
	Skin neoplasia (uncertain)	(*39,97*)
	Acute hepatocellular injury (hepatitis)	(*108,135*)
	Subacute hepatic necrosis with possible cirrhosis	
	Male infertility	(*144*)
	Female infertility (suspected)	
	Embryotoxicity	(*145,146*)
	Teratogenesis	(*150*)
	Spontaneous abortion/fetal death	(*150*)
	Neonatal death (suspected)	(*144*
	Low birth weight	(*150*)
	Developmental disabilities (suspected)	(*144*)
	Immune suppression (suspected)	
TCDD	Chloracne	(*4*)
	Acute hepatocellular injury (hepatitis)	
	Hepatic neoplasia (uncertain)	(*39*)
	Teratogenesis (suspected)	(*147*)
	Spontaneous abortion/fetal death (suspected)	(*147*)
1,1,2,2-Tetrachloroethane	Acute hepatocellular injury (hepatitis)	(*100*)
	Subacute hepatic necrosis with possible cirrhosis	

Table 10. (Continued)

Compound	Effect	References
Tetrachlorethylene	Impaired psychomotor function	
	Teratogenesis (suspected)	
	Teratogenesis (suspected)	(*151*)
	Low birth weight (suspected)	(*151*)
	Cardiac toxicity, direct effect	(*238*)
Toluene	Memory impairment	(*46–48*)
	CNS depression	(*54*)
	Ataxic gait	(*92,93*)
	Subacute hepatic necrosis with possible cirrhosis	(*110*)
	Acute renal failure	(*206*)
1,1,1-Trichloroethane	Heart disease; direct effect	(*239*)
Trichloroethane: (unspecified)	CNS depression	(*57,59*)
Trichloroethylene	Skin irritant	(*4*)
	CNS depression	(*58*)
	Peripheral neuropathies	(*68*)
	Miscellaneous neurological conditions	(*50,68,94*)
	Leukemia and lymphoma (uncertain)	(*97*)
	Acute renal failure	(*207,208*)
Vinyl chloride	CNS neoplasia	(*39*)
	Subacute necrosis with possible cirrhosis	(*113*)
	Hepatic neoplasia	(*97*)
	Germ cell mutation (suspected)	(*125*)
	Teratogenesis (suspected)	(*154–156*)
	Spontaneous abortion/fetal death (suspected)	(*125,159*)
	Leukemia and lymphoma (uncertain)	(*97*)
	Lung and respiratory tract neoplasia	(*97*)
	Stomach and colon neoplasia (uncertain)	(*97*)
Vinylidene chloride	Lung and respiratory tract neoplasia	(*97*)
Xylene	Memory impairment	(*46–48,54*)
	CNS depression	
Inorganic compounds		
Arsenic and arsenic compounds	Hyperpigmentation	
	Pigment discoloration (brown)	(*4,19*)
	Skin irritant and contact allergen	(*4*)
	Skin neoplasia	(*41*)
	Neurasthenia, irritability, other mild CNS symptoms	
	Peripheral neuropathies	(*69,70*)
	Acute hepatocellular injury	(*107*)
	Subacute hepatic necrosis with possible cirrhosis	(*107*)
	Hepatic neoplasia (uncertain)	(*39*)
	Embryotoxicity (suspected)	(*140*)
	Teratogenesis (suspected)	(*124*)
	Spontaneous abortion/fetal death (suspected)	(*140*)
	Development disabilities (suspected)	(*140*)
	Anemia, arsenic trioxide	(*182,183*)
	Anemia, arsine	
	Heart disease; direct effect	(*242,243*)
Asbestos	Pneumoconioses	(*287*)
	Fibrosis	(*287*)
	Mesothelioma	(*287*)
	Other lung and respiratory tract neoplasia	(*287*)
	Pharyngeal, esophageal, laryngeal neoplasia (uncertain)	(*287*)
	Stomach and colon neoplasia (uncertain)	(*287*)
Cadmium		
	Male infertility (suspected)	(*137*)
	Female infertility	(*137*)
	Teratogenesis (suspected)	(*157*)
	Spontaneous abortion/fetal death (suspected)	(*140*)
	Neonatal death (suspected)	(*165*)
	Low birth weight (suspected)	(*166*)
	Developmental disabilities (suspected)	(*169*)
	Chronic tubal or interstitial renal disease	(*212*)
	Kidney and prostate neoplasia (uncertain)	(*97*)
	Pulmonary edema	
	Lung and respiratory tract neoplasia (uncertain)	(*97*)
	Hypertension	(*233*)
Chromium and chromium compounds	Pigment discoloration (yellow), bichromate	(*19*)
	Skin irritant and contact allergen	(*4*)
	Asthma	

Table 10. (Continued)

Compound	Effect	References
	Lung and respiratory tract neoplasia	
	Pharyngeal, esophageal, laryngeal neoplasia (uncertain)	(*97*)
Copper and copper compounds		
Copper salts	Pigment discoloration (green)	(*19*)
Copper sulfate	Anemia	(*184*)
Cyanide (free cyanide ion)		
Sodium or potassium cyanide	Skin irritant	(*245*)
Hydrogen cyanide	Asphyxiation	
Isocyanates	Asthma	
Toluene diisocyanate	Hypersensitivity pneumonitis	(*229*)
Lead and lead compounds		
	Pigment discoloration (blue-gray), lead salts	(*19*)
	Neurasthenia, irritability, other mild CNS symptoms	(*50,51*)
	Emotional instability	(*50,51*)
	Memory impairment	(*50,51*)
	Peripheral neuropathies	(*71–75*)
	Seizures	
	Intracranial pressure	
	Male infertility	(*137,138*)
	Female infertility	(*137*)
	Embryotoxicity	(*140*)
	Teratogenesis (suspected)	(*124*)
	Spontaneous abortion/fetal death	(*137,163,164*)
	Neonatal death	(*137*)
	Low birth weight	(*167,168*)
	Developmental disabilities	(*170,171*)
	Childhood neoplasia (cancer in offspring of exposed individuals)	(*175*)
	Anemia	(*185–187*)
	Bone marrow depression	
	Chronic tubal or interstitial renal disease	(*213–215*)
	Kidney and bladder neoplasia (uncertain)	(*97*)
	Lung and respiratory tract neoplasia (uncertain)	(*97*)
	Stomach neoplasia	
	Colon neoplasia (uncertain)	(*97*)
	Hypertension (uncertain)	
Mercury and mercury compounds	Pigment discoloration (black), mercury salts	(*19*)
	Skin irritant and contact alllergen, mercury salts	(*4*)
	Neurasthenia, irritability, other mild CNS symptoms	(*53*)
	Impaired psychomotor function	(*53*)
	Peripheral neuropathies	(*79,80*)
	Ataxic gait	(*96*)
	Myoclonus	(*96*)
	Tremors	(*96*)
	Impaired visual acuity	(*96*)
	Other behavioral changes	(*96*)
	Embryotoxicity (suspected)	(*137*)
	Teratogenesis	(*158*)
	Spontaneous abortion/fetal death (suspected)	(*140*)
	Neonatal death (suspected)	(*137*)
	Low birth weight (suspected)	(*137*)
	Developmental disabilities	(*158*)
	Acute renal failure	(*209–211*)
Nickel and nickel compounds	Skin irritant and contact allergen, nickel salts and oxide	(*4*)
	Asthma, nickel sulfate	
	Lung and respiratory tract neoplasia (uncertain)	(*97*)
	Pharyngeal, esophageal, laryngeal neoplasia (uncertain)	(*97*)

firemen reported cough, headache, and a skin rash as the major symptoms resulting from contact with smoke and fumes at the site, although they had not been examined at the time of the incident. Eighty-six residents in 31 households around the dump were queried concerning illness connected to the site. Although most were aware of the waste site, none reported any ill effects associated with it. Fourteen neighborhood children who had been examined as part of a National Health Service Corps clinic study showed no unusual dermatological, nervous or liver function abnormalities (*249*).

Groundwater used as a source of drinking water in Hardeman County, Tennessee, was contaminated by leachate from a chemical waste dump that contained

Table 11. Episodes of environmental exposure to chemical and heavy metal pollutants from point sources.

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
			Mixtures of chemicals		
1a	Mixture of organics and metals	New York, 1978	Leachate from an abandoned chemical waste disposal site	Inhalation, ingestion, contact	Survey
1b	Mixture of organics and metals	New York, 1978	Leachate from an abandoned chemical waste disposal site	Inhalation, ingestion, contact	Case-control
1c	Mixture of organics and metals	New York, 1978	Leachate from an abandoned chemical waste disposal site	Inhalation, ingestion, contact	Ecological
2	Mixture of organics and metals	Pennsylvania, 1979	Leachate from abandoned chemical waste disposal site	Inhalation, contact	Survey
3a	Mixture of organics and metals (esp. arsenic)	Massachusetts, 1982	Abandoned toxic waste disposal site. Chlorinated organics discovered in two town water wells	Ingestion, contact, inhalation	
3b	As above	As above	As above	As above	
4	Mixture of chemicals, primarily chlorinated hydrocarbons.	Tennessee, 1978	Leachate from abandoned waste disposal site into groundwater used as drinking water	Ingestion	Case-control
			Single organic chemicals		

Table 11. (continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
1a	N = unknown	Surrogate measure based on proximity of residence to site	No unusual patterns of disease except possibly reproductive problems, which did not, however, correlate with preliminary environmental exposure	(*1*)
1b	Group I: Exp N = 29 Cont N = 25 Group II: Exp N = 16 Cont N = 8 Group II in previous uncontrolled cytogenetic study; neighborhood controls	Indirect; based on levels of chemicals in the air of homes of residents	Frequencies of chromosomal aberrations and sister chromatid exchanges did not differ from control levels. Blinded study. Outcome was evaluated without knowledge of exposure status	(*247*)
1c	Cancer rates by census tract in Love Canal area	Surrogate measure based on proximity of residence to site	No excessive cancer in census tracts near site. Lung cancer excessive in the local population, but not consistent across age groups.	(*248*)
2	N = 86 residents questioned N = 14 children examined N = 35 firemen questioned	Surrogate measure Based on proximity to site. Children admitted playing at the site. Firemen put out a fire there.	No neurologic or hematologic abnormalities. Liver function tests were normal.	(*249*)
3a	3257 households were surveyed by phone, interviewers were volunteers from citizen action groups.	Surrogate measure Amount of water from two contaminanted wells per household, 1960–82 (estimated).	"The major finding . . . is a consistent pattern of positive associations between availability of water from [contaminated wells] and the incidence of childhood leukemia, perinatal deaths, and some classes of birth defects and childhood disorders."	(*250*)
3b	N = 12 (Leukemia) N = 10 (Kidney cancer) N = 5 (Liver cancer) Neighborhood controls (1:2 matching)	Indirect measure; Asked re: water and air quality; also other environmental exposures	Significantly elevated incidence of childhood leukemia for 1969–79. "Few cases had contact with the site . . ." Interviews with parents of leukemia cases, two groups of matched controls, and family members of renal and liver cancer cases revealed ". . . no associations between environmental factors and the disease."	(*251*)
4	High exposure (N = 49) Moderate (N = 33) Controls (N = 57)	Indirect Based on concentration of chemicals in the drinking water.	Liver: some values increased in exposed (Alk phos, total bilirubin, SGOT); SGPT and SGGT similar. Slight hepatomegaly in exposed. Renal: function similar in exposed and controls. No skin or eye abnormalities. Results consistent with transient liver injury to exposed population.	(*252*)

Table 11 (Continued)

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
5	Phenol	Wisconsin, 1974	Railroad accident led to spill of phenol. Later detected in well water consumed by residents.	Ingestion	Case-control
6	4,4′-Diaminodiphenylmethane (4,4′-DAPM)	U.K., 1965	Flour was transported in a truck in which a canister of 4,4′-DAPM had been spilled.	Ingestion	Case series
7	*o*-Cresyl-phosphate (OCP)	Bombay, 1960	Mustard oil; means of contamination not established.	Ingestion	Case series
8	*o*-Cresyl-phosphate (OCP)	Morocco, 1959	OCP was present in oil sold as "olive oil" and consumed by residents in several cities.	Ingestion	Case series
9	Acrylamide	Japan, 1974	Acrylamide used in construction of a sewage system near patients' residence. Well water was contaminated.	Ingestion	Case series
10	Dioxin (TCDD) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	Missouri, 1982	Dioxin was an ingredient in waste oils from a chemical plant sprayed on residential, recreational, and work areas for dust control.	Dermatic, inhalation, ingestion	Case-control

Table 11 (Continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
5	Exposed (N = 39) Controls (N = 119)	Indirect; concentration of phenol in well water and proximity of residence.	Syndrome: diarrhea, mouth sores, dark urine, burning mouth. Findings 6 months after the incident revealed no clinical (skin rashes, mouth lesions, conjunctivitis, sensation) or laboratory (liver enzymes, urinanalysis, urinary phenol) differences. Blinded study, clinical exam and lab tests performed without knowledge of exposure status.	(*253*)
6	N = 84	Indirect; all patients had eaten bread from the bakery to which the contaminated flour had been delivered.	CNS disturbances noted in most cases: convulsions (30 patients), dizziness, weakness in legs. Liver involvement revealed by severe jaundice in 5 patients, and mild jaundice in others; also increased total bilirubin. Stomach pain (50 patients), nausea, flu-like symptoms.	(*254*)
7	N = 58 (32 examined)	Indirect; most patients had purchased oil from one shop. OCP not detected in several batches during citywide samplings.	CNS disturbances: cramps or heaviness in lower extremities (23 patients) followed by paralysis (17), sensations of touch, pain, temperature impaired (27); high-stepping gait (32). Other: diarrhea (9), anemia (18), and EKG abnormalities (in 4 of 12 patients).	(*255*)
8	N = 2000	Indirect; self-reported history of consumption of "dark" oil	CNS: illness began with pain in calves, followed by parathesis and loss of sensation, motor weakness, and occasional weakness of hands. Occasional bradycardia, fever, and diarrhea. No deaths reported.	(*256*)
9	N = 5	Indirect; high concentrations of acrylamide in well water.	CNS disturbances: subacute mental confusion and truncal ataxia. More severe in 3 adults than in 2 children. Liver function normal. Blood values normal.	(*257*)
10	Exposed (N = 82) Controls (N = 40) Controls from low risk area.	Indirect; residence or employment in exposed areas.	CNS disturbances: no differences. Liver: no differences. Skin: no differences. Immune status: no differences. No differences between exposed and controls both by physical exam and laboratory measurements. The study was blind in that subjects were evaluated without knowledge of exposure status. Authors note that this should be considered a pilot study.	(*258*)

Table 11 (Continued)

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
11a	Dioxin (TCDD)	Italy, 1976	Dioxin was spread over a large area around a chemical plant after an explosion in the plant.	Inhalation, dermatic, ingestion	Survey Case-control
11b	As above	As above	As above	As above	Case-control
11c	As above	As above	As above	As above	Case-control
11d	As above	As above	As above	As above	
12	PCB	Japan, 1968	PCBs were present in rice oil used for cooking. Contamination occurred during manufacture of the oil.	Ingestion	Case series

Table 11 (Continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
11a	Residents near the plant (N = 786) and those with dermatological problems.	Indirect; residence near the plant.	Higher frequency of skin problems and chloracne in residents nearest the plant, but no gradient beyond the immediate area.	(*259*)
	Cases were children with chloacne (N = 163); controls were children without skin problems (N = 51)	History of residence in contaminated area during and after the explosion, animal deaths, eating from own or neighbor's garden, playing or working outdoors.	Both groups were equally likely to have a history of exposures as defined by proximity to plant, deaths of animals at home, consumption of locally grown food.	
11b	Exposed children (N = 48) Plant workers (N = 103) Soldiers (N = 75) involved with quarantine of area. Controls were apparently healthy individuals from a nearby city.	Indirect; residence near plant, employment in the plant, or temporary employment in exposed area.	Ten tests of immunologic function were performed (without knowledge of exposure) Total serum complement hemolytic values were higher in exposed children than controls, and higher in children with than without chloracne. Response to mitogens was higher in exposed children than controls, but chloracne was not related to this finding. Results were not anticipated since TCDD experiments in animals suggest an immunosuppressant effect.	(*260*)
11c	Induced abortions in exposed (N = 13) and unexposed (N = 11). Examined maternal blood, placenta, and fetal tissue.	Indirect; as above	Cytogenetic abnormalities occurred with equal frequency in all groups studied. In some cases the presence of at least one aberrant cell was higher in exposed than non-exposed subjects. "The results so far do not suggest a straightforward conclusion." Aberrations were scored blindly, i.e., without knowledge of exposure status.	(*261*)
	Peripheral lymphocytes from residents near the plant (N = 145), workers in the plant (N = 69) and controls (N = 87).			
11d	Birth defects registry. Rates of defects born in children before and after the accident are compared.	Indirect	Possible increase in malformations but authors note severe problems in the comparison group. Rates appear similar to those reported elsewhere in Europe.	(*262*)
12	N = 189 adults N = 12 babies	Indirect; based on reported use of rice oil.	Skin: brown pigmentation of nails, acnelike skin eruptions, hyperpigmentation of skin. Eye: discharge, swelling of lids. CNS: feeling of weakness. Reproductive: 12 births to exposed mothers, 1 was stillborn; all with unusual pigmentation. Several case-control studies suggested that the problem was diet, and particularly a contaminated batch of cooking oil.	(*27*)

Table 11 (Continued)

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
13	PCB	Taiwan	PCBs present in rice oil contaminated by PCBs.	Ingestion	Case series
14	PCB	Alabama, 1978	PCBs were observed in environmental samples downstream from a chemical plant.	Ingestion	Survey
15	PCB	Indiana, 1977	PCB in sewage sludge which was later used as fertilizer.	Ingestion	Survey
16a	PCB	Michigan, 1973	PCB spilled into cattle feed during transportation accident. Dairy cattle and dairy products were contaminated.	Ingestion	Survey
16b	As above	As above	As above	As above	Case-control
			Organic pesticides		
17	DDT	Alabama, 1978	DDT was detected in fish downstream from a pesticide plant.	Ingestion	Survey

Table 11 (Continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
13	Approximately 1900 persons.	Direct; serum PCB levels	Skin: acneform and follicular keratotic changes were widespread. Also altered pigmentation but not chloracne. Eye: discharge was an early symptom. CNS: sensory and motor neuropathy in a few patients who were examined. Liver: abnormal function in some patients. Symptoms and level of severity always correlated with serum levels.	(*263*) (*264*) (*265*)
14	A majority of residents who lived near the stream were examined.	Direct; serum PCB levels	Liver: positive association between serum PCB and SGOT. SGPT and total bilirubin showed no association. Cardiovascular: positive association between blood pressure and serum PCB levels. Reproductive: no relation to serum PCB levels.	(*266*)
15	Four groups with varying exposures were defined (N = 148)	Direct; serum PCB levels	Skin: no chloracne. Renal: no relation to serum PCB. Liver: no relation to serum PCB. Blood: no relation to serum PCB. Plasma triglycerides correlated with serum PCB, suggesting that PCB may alter lipid metabolism.	(*267*)
16a	Six groups with varying exposures identified. Some were unexposed (N = 4545)	Direct; serum PCB levels	Skin: no chloracne. Liver: no excess hepatitis. Immune status: no clear differences in immune function among any of the exposure groups. The cohort identified is to be followed for chronic effects.	(*268*)
16b	Exposed	Direct; serum PCB levels	Immune status: exposed persons showed significant decreases in T-cell function (sheep erythrocyte rosette), and numbers of null T-cells. A significant proportion of the exposed showed abnormal lymphoblastogenesis.	(*269*)
17	All individuals living in the area were invited to participate. N = 499	Direct; serum DDT levels	CNS: no data. Renal: creatinine levels and history of renal disease not associated with serum DDT. Liver: SGOT was positively associated with serum DDT but SGPT and total bilirubin were not. CVD: no relationship between history of cardiovascular disease and serum DDT was noted. Reproductive: no effects.	(*270*)

Table 11 (Continued)

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
18	Endrin	Egypt, 1967	Bread was made from treated seed intended exclusively for planting.	Ingestion	Case series
19	Endrin	UK, 1956	Endrin leaked into flour while being transported.	Ingestion	Case series
20	Hexachlorobenzene (perchlorobenzene)	Turkey, 1956	Hexachlorobenzene was used to treat seed for planting. The seed was made into flour and eaten.	Ingestion	Case series
21	Parathion	Singapore, 1959	Parathion probably leached into barley while being transported from Europe.	Ingestion	Case series
22	Parathion	Jamaica, 1976	Parathion in flour contaminated during transport from Europe.	Ingestion	Case series
23	Arsenic	Oregon, 1958–71	High background levels of arsenic in well water.	Ingestion	Ecological
24	Arsenic	An area of SW Taiwan, endemic since 1920s. Investigated 1965–67.	High background levels of arsenic in well water.	Ingestion	Survey

Table 11 (Continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
18	One family ($N = 4$)	Indirect; history of bread consumption.	CNS: dizziness, headache, convulsions. Other: abdominal discomfort and nausea. Recovery was rapid and complete.	(*271*)
19	$N = 59$	Indirect; all cases purchased from one bakery. The flour was shown to be contaminated.	CNS: convulsions (30 subjects), dizziness, weakness in legs. Other: nausea, abdominal discomfort. Recovery was rapid and apparently complete.	(*272*)
20	$N = 5000$	Indirect; history of use of seed for planting, residence in area where seed was distributed.	Skin: cutaneous porphyria with blistering and epidermolysis of skin; hyperpigmentation. Liver: chronic cases with hepatosplenomegaly. Renal: red urine. CNS: no effects noted.	(*273*) (*274*)
21	$N = 38$	Indirect; most cases ate barley which was purchased at one shop.	CNS: coma, convulsions (7 subjects), constricted pupils (10 subjects). Respiratory: dyspnea (13 subjects). CVD: hypertension (3 of 4 examined). Other: mild cases with abdominal discomfort, nausea, general malaise.	(*275*)
22	$N = 79$	Direct: paranitrophenol in urine in 9 during first 48 hr, not present later. Indirect: history of ingestion of baked goods from the flour.	CNS: convulsions, coma, pinpoint pupils. Respiratory: dyspnea. CV: bradycardia Other: nausea, vomiting. Plasma cholinesterase levels depressed for patients in which they measured.	(*276*)
23	Census track rates of skin cancer were correlated with arsenic water levels.	Surrogate measures; residence in tracts with high arsenic levels.	No relationship between rates of skin cancer (basal cell and squamous cell) and water arsenic levels. Arsenic levels were lower in water supplies than in other studies. Cancer rates were lower than those reported in the Third National Cancer Survey. Mean arsenic levels in rural areas was 0.016 ppm (range 0–2.15) and in urban areas, was 0.048 ppm (range 0–0.860).	(*277*)
24	Inhabitants of the area with high arsenic levels were visited ($N = 40,421$)	Indirect; arsenic concentrations in the well water of study subjects was used to estimate exposure. Arsenic concentration in well water ranged from 0.01 to 1.82 ppm	Skin: hyperpigmentation (prevalence 18.4%), keratosis (7.1%), cancer (1.1%). CVD: "blackfoot disease" (0.9%) (compromised peripheral circulation) Clear dose-response gradient for all conditions above. No data re other systems.	(*278*) (*279*)

Table 11 (Continued)

Episode	Chemical	Location and date	Exposure circumstances	Route of exposure	Study design
25	Arsenic	Chile, 1968–69	High background levels of arsenic in city water supply. Reduced by filtration plant in 1970.	Ingestion	Case series
26	Cadmium	Japan, 1960s	Cadmium, lead, and zinc discharged into a river by a chemical plant. Downstream water used for drinking and irrigation.	Ingestion	Surveys and case-control series
27	Lead	Scotland, 1971	Lead in drinking water from lead-lined pipes in older housing.	Ingestion	Case series
28	Lead	Idaho, 1974	Lead emitted from stacks at a large smelter.	Inhalation	Survey
29a	Lead	Texas, 1971	Particulate lead emitted from smelter	Inhalation, ingestion	Survey
29b	As above	As above	As above	As above	Case control
30	Methylmercury	Japan, 1953	Methylmercury was discharged into Minimata Bay by a plastics factory.	Ingestion	Survey
30b	As above	As above	As above	As above	Case series
31	Organomercury	Iraq, 1970s	Organic mercury compounds used as pesticides on seeds intended for planting only. Flour and bread were made from the seeds.	Ingestion	Case series

Table 11 (Continued)

Episode	No. of subjects	Exposure variable	Findings	Reference
25	Cases presented to the regional hospital for evaluation (N = 457)	Direct; hair content of As compared with nonexposed persons. Indirect; residence in high arsenic area of city.	Admission rates for persons with cutaneous lesions decreased after filtration plant initiated operations. Hair content or arsenic in exposed ten times higher than nonexposed. Skin cancer fairly rare in exposed population. Arsenic content of water was 0.6 ppm (range 0.05–0.96)	(*280*)
26		Direct; urinary excretion of cadmium. Indirect; residence in vicinity of polluted area.	Musculoskeletal: severe back pain ("itai-itai"), multiple fractures. Renal: proteinuria, glycosuria (presumed renal tubular dysfunction). Some uncertainty as to whether cadmium alone, or cadmium with other heavy metals is the cause. Interaction with nutritional status is likely.	(*281*)
27	Four families referred by their physicians (N = 20)	Direct; blood lead (PbB) erythrocyte protoporphyrin (EP), urinary δ-aminolevulinic acid (ALA)	CNS: tremor (5 patients), peripheral neuropathy (5 patients) Blood: anemia (3/12), increased EP (12/12), PbB (11/14) Other: abdominal pain, vomiting.	(*282*)
28	Children living around the smelter were examined (N = 1056)	Direct; blood lead (PbB)	Blood: 20% of high risk children were anemic; 1% of low risk. CNS: peripheral nerve conducting velocity decreased with increasing PbB (r = 0.39)	(*283*)
29a	A random sample of children residing in proximity to the smelter was chosen (N = 1369)	Direct; blood lead (PbB)	Blood-PbB was elevated (40 μg/100 mL) in approximately 50% of children near the smelter.	(*284*)
29b	(PbB 40 μg/100 mL) (N = 46) Controls similar in age, ethnicity, SES (N = 78); blinded	Direct; blood lead	CNS: performance of exposed children was significantly decreased in 2 scales from an intelligence test; exposed children also showed significant slowing in finger-wrist tapping test. Full-scale IQ, verbal IQ, and behavioral and hyperactivity ratings were similar in both groups.	(*285*)
30a	Examination of residents around the bay revealed 83 cases.	Indirect; proximity to bay and source of food supply. Direct; mercury measured in tissues of dead patients.	CNS: peripheral neuropathies and intellectual impairment were present in most cases; severe cases resulted in coma and death.	(*79*)
30b	Children born to patients with Minamata disease (N = 40)	No data	Reproductive: children exposed in utero with palsy, other CNS problems.	(*158*)
31	Adults and children determined from hospital admissions (N = 6530)	Indirect; residence in areas where the contaminated seed had been distributed. Direct; blood mercury.	CNS: ataxia (dose-dependent), blurred vision and constriction of visual field; slurred speech and hearing difficulties; coma and death. CV, GI, and GU symptoms were rare	(*286*)

predominantly chlorinated pesticides. Residents in the area were classified as having a high, intermediate or low exposure based on well water concentration of organics. No chlorinated organic chemicals or likely metabolites were detected in the urine of any subjects. Liver function tests (alkaline phosphatase, SGOT) were elevated in exposed individuals, but a subset who were retested 3 months later had returned to normal levels. The medical examination showed no significant differences between any of the exposure groups except for borderline hepatomegaly in the exposure groups. Renal function was normal in all groups. The authors concluded that transitory liver injury probably occurred in this population as a result of drinking the contaminated water (*252*).

One other episode involving toxic chemical wastes was reported from Woburn, Massachusetts. The residents of Woburn had complained about the quality of the municipal water supply for many years, and the discovery of waste disposal sites and contamination of well and ground water aroused community concern. A cluster of childhood leukemias was subsequently described and investigated by the state health department and CDC. The parents of juvenile leukemia ($N = 12$), adult kidney cancer ($N = 10$), and adult liver cancer ($N = 5$) cases from the time period 1969–1978 were incorporated into a case-control study. An extensive interview that dealt with environmental exposures was conducted with each case and two controls. The report concluded that the "... information gathered thus far fails to provide evidence establishing an association between environmental hazards and the increased incidence of childhood leukemia and renal cancer in Woburn" (*251*). A subsequent study by a different team of investigators was directed at reproductive and childhood disorders in residents of Woburn. A telephone survey using a questionnaire administered by local community volunteers was used to determine health data for members of households in the city. Rates of reproductive events and childhood cancer were computed by geographical area of the city, and these areas were chosen to correspond to those served by the water wells. Two of these wells had been contaminated by leachate, and the authors concluded that a consistent pattern of increased childhood leukemia, perinatal deaths and certain birth defects and childhood disorders was associated with the availability of water from the contaminated wells (*250*).

From this brief review of environmental exposure episodes, the following conclusions appear warranted.

The severity and immediacy of responses are dose-related, and are directly related to route of exposure. Episodes in which food was directly or indirectly contaminated resulted in the most severe response. Water as a route of exposure was not inconsequential, but only in relatively high dose situations were clear clinical illnesses apparent. In low dose situations, many exposed individuals were asymptomatic or showed only transient subclinical illness.

Although inhalation is a possible route of exposure, in only two episodes did it occur. In Seveso, Italy, no respiratory symptoms were mentioned, although an explosion had occurred. In Chester, Pennsylvania, a fire in a dump caused cough, headache, and skin problems in firemen responsible for extinguishing the blaze.

Direct contact was more likely to have sequelae than inhalation, but neither route was as important as ingestion.

Direct measures of exposure were rarely available, the exceptions being serum levels of PBBs, PCBs, DDT, and lead. In the absence of direct methods of ascertaining exposure, it was extremely difficult to observe a dose-response relationship in exposed populations, and thus difficult to show an association with the putative exposure.

In low-dose situations, detectable health effects were rarely reported, especially if health outcomes were evaluated without knowledge of exposure status. The predominant health effects reported in these low exposure situations were more likely to be nonspecific (neurobehavioral, reproductive, hepatic, renal).

Predominant health effects were predictable on the basis of data from occupational health studies. In high-dose situations, skin, central nervous system, liver, kidney, and reproductive outcomes predominated. In moderate exposure situations, hematologic abnormalities were frequent. In low dose situations, CNS, liver, and reproductive abnormalities were observed.

Tables 1–10 should serve as useful starting points for identification of health effects possibly induced by exposure to toxic chemicals from waste disposal sites. Any future review should include attention to the route of exposure, the concentration of the substances, the biological measure of exposure employed (if any such measure was used), the ascertainment and assessment of disease, the study design (cases alone or control group as well) and study methods (blind assessment of disease and/or exposure) and attention to confounding by the authors in analyzing and interpreting their results. This activity should lead to a more compact guide of likely effects attributable to chemical exposure from chemical waste disposal sites.

The authors wish to thank Mr. Francis Williams for his technical help in the preparation of this manuscript.

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