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REVIEW OF THE ENVIRONMENTAL FATE OF SELECTED CHEMICALS

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Stanford Research Institute

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A search of the scientific literature and an evaluation of such literature on the environmental fate of the following compounds has been reported: benzidine and its salts; 3,3'-dichlorobenzidine; 1-naphthylamine; -propiolactone; 4,4'-methylenebis(2-chloroaniline); ethylenimine; and bis(chloromethyl)ether. Some intelligent guessing based on structural analogies for the chemicals is made where little information was available. These chemicals are known carcinogens but little is known of their environmental fate. Emphasis is placed on reporting or estimating kinetic values for potentially important pathways of degradation. In cases where no data were available, independent calculations for free radical reactivity were made.

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Task One Report *January 10, 1975*

REVIEW OF THE ENVIRONMENTAL FATE OF SELECTED CHEMICALS

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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SECTION I

INTRODUCTION

The Office of Toxic Substances (OTS), U.S. Environmental Protection Agency (EPA) under Contract No. 68-01-2681 requested that a literature search and evaluation of the results be carried out for the following chemicals: benzidine and its salts, 3,3'-dichlorobenzidine, α-naphythylamine, β-propiolactone, 4,4'-methylenebis(2-chloroaniline), ethylenimine, and bis(chloromethyl)ether. Also at their request, "some intelligent guessing based on structural analogies for the chemicals" is reported in cases where very little information was readily available. Although all of these compounds are known carcinogens, little is known on their fate in the environment. A literature search was instituted to determine what information is available that will help determine potential environmental contamination and fate of these compounds.

The fate of chemicals in the environment depends on a complex variety of chemical, physical, and biological interactions, few of which have been studied in sufficient detail to predict the likely rate of change in concentration of any but the simplest organic compounds. Estimation of the losses of carcinogenic material from manufacturing sites and its eventual fate in the environment cannot be made on the basis of published information. SRI was involved in such an effort recently and was able only to bracket losses as either ≤1%, ≤2%, or ≤3%, on the basis of the major production method. The ability to bracket losses even very approximately is possible only for chemicals in large quantity production (>100 x 10^6 lb/year), where considerable information on the processes, products, and by-products is readily available.

In the chemistry of the compounds considered in this study, emphasis was placed on searching for or estimating kinetic values for potentially important pathways of degradation, including free radical oxidation, photolysis and hydrolytic reactions. With possibly a few exceptions, no attempt was made to catalog or note the wide variety of chemical reactions that these chemicals enter into under "laboratory conditions," inasmuch as this term is vague and not likely to be of general value in assessing the environmental fate of these materials.

In addition to the literature searches accomplished during the study, independent calculations for free radical reactivity were made by Dr. D. G. Hendry, at the request of Dr. T. Mill. In general, the kinetics literature rarely provided rate data for conditions close to those found in the environment.

SECTION II

CONCLUSIONS

Any attempt to quantify losses of a specific product during manufacture or use as an intermediate will require a major effort because of such factors as the wide variations in: (1) production processes, (2) product purification, and (3) product intermediate and end uses. The minimum information required for such an undertaking would be detailed process flow sheets and material balances, together with reaction kinetics data and mixture component vapor pressures and solubilities as a function of temperature and solution composition. The effectiveness of air, water, and solid waste pollution control measures at plant sites should also be examined with some field verification of theoretical losses.

Very few references were found that were of much value in providing rate data for evaluation, and the need for such reliable data has been noted for each compound. The general fate of these compounds in the environment and their toxic effects other than the carcinogenic properties have received little attention in the literature. Basic physical data are frequently unavailable and environmental measurements wholly so. Inferences concerning environmental movement are consequently fragmentary. At best, we can eliminate several of the compounds as probable hazards in freshwaters, but can say little with confidence regarding their decomposition products or their behavior in saltwaters. Nor can we fully appraise their potential biotic impacts, although several compounds are clearly mutagenic as well as carcinogenic. Table 1 summarizes our findings.

To efficiently utilize available resources, we recommend the following sequence of steps be taken:

- Quantify the losses to the environment of the more biologically significant compounds
- Determine the basic physical and chemical properties as related to environmental processes (i.e. oxidation, hydrolysis)
- Reappraise the potential environmental mobility of each compound
- Determine the toxicity, mutagenicity, and teratogenicity of those which appear most hazardous on the basis of mobility and magnitude of release.

Table 1

ENVIRONMENTAL DATA NEEDS

Release/Decomposition/Immobilization/Movement	Benzidine	3,3'-Dichlorobenzidine	1-Naphthylamine	β-Propiolactone	4,4'-Methylenebis-(2-chloroaniline)	Ethyleneimine	Bis(chloromethyl)ether
Release to air							
Quantity							
Form (gas, aerosol, particle)							
Release to water							
Quantity							
Form (solution, particle)							
Release to land							
Quantity							
Form (solution, particle)							
Seasonal variations form, quantity or locale of release							
Temporal variation of release (continuous, pulsed)							
Source density--point (+), diffuse (-)	o+	o+	o+	o+	o+	o+	o+
Recipient biomes (deciduous forest, etc.)							
Adsorption							
Humus and other organics--Yes (+), No (-)	o+	o+	o+	o-	o+	o+	o-
Clays	o+	o+	o+	o-	o+	o+	o-
pH dependance of adsorption--Yes (+), No (-)	o+	o+	o+		o+	o+	
Increasing salinity effects on adsorption--greater adsorption (+)	o+	o+	o+		o+	o+	
Vaporization rates--High (+), Low (-)	o-	o-	o-	o+	o-	o+	o+
Solubility in water	•	•	•	•	•	•	
Chemical reactivity in the environment	o	o	o	•	o	•	•
Sensitivity to solar radiation--no sensitivity (-), adsorption in solar region (+)	o+	o+	o+	o-	o+	o-	o-
Identity of decomposition products				•		•	•
Chemical reactivity of decomposition products				o		o	o
Behavior in aerobic/anaerobic environments							
Propensity for microbial degradation--limited (+), none (-)	o-	o-	o-	o+			
Transfer mechanisms							
Identification	o	o		o			o
Quantification							
Efficiency of uptake							
Soil/plants				o			o
Soil/animals							
Water/plants							
Water/animals	o	o	o	o	o	o	o
Air/plants							
Air/animals				o	o	•	•
Propensity to food chain transfers	o	o					
Biological Effects							
Toxicity							
Plants							
Microbes				•			
Animals	•		•	•	•	•	•
Toxicity of products							
Plants							
Microbes							
Animals							
Allergenicity (mammals)	•						
Carcinogenicity							
Plants							
Animals	•	•	•	•	•	•	•
Mutagenicity							
Plants						•	
Microbes	•			•			
Animals				•		•	
Teratogenicity							
Plant							
Animals		•					
Impairment of reproduction							
Physiological						•	
Behavioral							
Indirect impairment of survival							
Dispersal							
Predator avoidance							
Feeding/thermoregulatory behaviors							
Dependancy of biological impact upon medium of occurrence		o		o			

Legend: o = Inferences are possible
• = Some data are available

A

B

SECTION III

LITERATURE SEARCH

Sources and Subject Area

Chemical Abstracts from 1941 through 1974 was searched for the chemical activity of the compounds under study. Biological and environmental information was searched for by using TOXLINE and DIALOG computerized sources; Chemical Abstracts, 1956-1974; Biological Abstracts, 1963-1974; Selected Water Resources Abstracts, 1973-1974; and Current Contents (Biological and Medical Group), 1973-1974.

To some extent these sources are redundant, but the difficulty of finding pertinent references made it necessary to verify the absence or presence of material by hand searching secondary sources such as Chemical Abstracts. Searching was done (1) by the Chemical Abstract Service Number for each compound, (2) on synomyms for each compound, and (3) by such terms as environmental fate, biodegradation, toxicity, and wastewater treatment.

In addition to the abstracts searched, references in pertinent articles were scanned for further information, and selected reviews of the chemistry of classes of compounds were examined for pertinent data or references.

Results

Some references were pulled from all the sources scanned. Those found can be broken down according to compounds: Benzidine and its salts, 73; 3,3'-dichlorobenzidine, 11; α-naphthylamine, 55; β-propiolactone, 64; 4,4'-methylenebis(2-chloroaniline), 9; ethylenimine, 91; and bis(chloromethyl)ether, 18.

The abstracts were read and evaluated by a panel of experts, and full-text copies of articles that seemed to be of interest were ordered. A total of approximately 150 articles was ordered.

SECTION IV

EVALUATION OF DATA AND ESTIMATES OF RATES OF OXIDATION OF ORGANIC COMPOUNDS IN THE ENVIRONMENT

Three important modes of oxidation of organic substances in the environment can be identified. Two apply to the atmosphere, and one applies to the aqueous phase. On the basis of our knowledge of the chemistry of polluted and unpolluted air masses, the reactions of both ozone (O_3) and the hydroxy radical (HO·) are important in the atmosphere. Our knowledge of the chemistry in the aqueous phase is much more uncertain, but concentration estimates of the ubiquitous peroxy radical RO_2· (where R is H or an organic group) indicate its potential involvement.

Estimates of the half-life ($t_{\frac{1}{2}}$) of a substrate (S), assuming disappearance solely by one reaction (for example, reaction with X), can readily be made from the kinetic relation

$$dS = k_x[S][X]$$

$$\int_{100\%}^{50\%} dS/[S] = \int k_x[X]dt$$

under conditions where X is replaced as consumed, resulting in a constant or steady-state concentration,

$$\ln \frac{S_{100}}{S_{50}} = \ln 2 = k_x[X]t_{\frac{1}{2}}$$

$$\ln 2/k_x[X] = t_{\frac{1}{2}}$$

Thus the half-life in the environment for various reactions can be estimated if the concentration of the oxidizing species (X) and the rate constant for a reaction are known. Calculated values of half-lives for the various oxidizing species are given in this report for each compound considered. The values for HO· and O_3 in the gas phase are probably accurate to a factor of 3, while the aqueous phase values for RO_2· are only order-of-magnitude estimates.

The half life ($t_{\frac{1}{2}} = \ln 2/k_{HO\cdot}[HO\cdot]$) assumes $[HO\cdot] = 3 \times 10^{-15}$ M (an average value estimated by H. Levy[67]). Values of k_{HO} were estimated from data reported by W. E. Wilson.[101]

Reactions of ozone are important only in air, where typical concentrations are $\sim 2 \times 10^{-9}$ M; in aged polluted air the concentration can reach 10 times this value. Where NO concentrations are high, such as near a combustion source, the concentration of O_3 can be essentially zero. For calculation of half-life ($t_{\frac{1}{2}} = \ln 2/k_{O_3}[O_3]$) the clean air value was used.

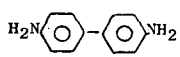
The reactions of peroxy radicals (RO_2·, where R represents any organic radical) are not important in air but might be important in the aqueous phase under some conditions. Concentrations of RO_2· equal to $\sim 10^{-10}$ M are anticipated for water exposed to sunlight containing oxygen and light-sensitive compounds that photodissociate. Half-lives ($t_{\frac{1}{2}} \sim \ln 2/k_{RO_2\cdot}[RO_2\cdot]$) use this concentration. The uncertainty limits range from 1/10 to 10 times reported values. Estimates for $k_{ROO\cdot}$ were based on data given by K. U. Ingold.[44]

In each phase, the important mode of disappearance will be that by the fastest reaction. The reactions of OH undoubtedly contribute to the disappearance of all the compounds under study, to the extent that they occur in the gas phase. Ozone appears to be less important, except in the case of benzidine. In the aqueous phase, the reactions with RO_2· are

relatively slow, and other types of reactions, including biological, may be important.

Although the rates of attack of the various oxidizing species can be estimated, the products of the reactions cannot be predicted with any degree of certainty; only suggestions can be made. Aromatic amines may initially form nitroso amines, amine oxides, hydroxylamines, ring hydroxylated products, and ring cleaved products. The other substances are expected to react by oxidative cleavage reactions. In most cases, all the products will react at rates comparable to those of the parent substrates.

Benzidine



Benzidine has a molecular weight of 184.23, melts at 128°C, is slightly soluble in water, but is readily soluble (1 gm/5 ml) in boiling alcohol or in ether (1 gm/50 ml). Benzidine appears to be resistant to both physical and biological decomposition, and it is sufficiently volatile and soluble to be widely dispersed. Consequently, it appears to model fairly closely the properties of DDT, and should be regarded as a significant hazard until physical properties pertinent to appraisals of environmental transfers have been measured. The major uses of benzidine are based on the conversion of the amino functions to dyestuffs via diazotization with the nitrite ion and coupling with aromatic acceptors, such as napthols, and on the high-temperature reaction of the amino groups with polyurethanes to effect cross-linking, with improvement in physical properties. Both processes offer the possibility of benzidine being introduced into the environment at high local levels, if precautions are not taken. No literature was found that was helpful in evaluating this possible hazard. It is interesting to note, however, that Takemura[96] et al.

hypothesize that benzidine or 8-naphthylamine are possibly produced in river water by the reduction of azo-dye wastes by H_2S or SO_2 in the river water. According to them it is easily demonstrated chromatographically that if H_2S is bubbled for a few minutes through a pure azo dye solution, aromatic amines are liberated from the azo dye.

Air transfers constitute a clear danger, as noted by several authors,[17,58,65,104] but benzidine in water is a probable hazard in the vicinity of dye and pigment factories[96] only.

We would expect the principal chemical reactions of benzidine in air or water to be oxidative degradation via free radical, photochemical, or enzymic processes. On the basis of the foregoing estimates of radical and ozone concentrations in the environment, we estimate that benzidine has half-lives of 1 day for reaction with either HO· or O_3 in the air and 100 days for the reaction with RO_2 radical in water.

We have found no publications concerning the photochemistry of benzidine. By analogy with aniline,[21] benzidine may undergo some cleavage of NH bond, but this is most likely to occur below the solar cutoff at approximately 300 nm. Benzidine absorbs strongly above 350 nm.[15] Two papers discussed the diazotization of waste waters containing benzidine, as a means of removing the amine.[27,38]

Experimental data on the rates of reaction of benzidine with radicals and ozone and on photochemical reactions under environmentally realistic conditions are not available. They would be of value for more reliable estimates of half-lives. Products of such reactions and their toxicity should also be determined.

Decomposition of benzidine in water is probably predominately biologically mediated. However, it is resistant to biological decomposition[70] and can be expected to persist in the environment.

Benzidine is sparingly soluble in water, but considerably more so than DDT and is readily soluble in organic solvents.[45] This suggests that it may readily move through food chains.

No data are available on its movement through soils, although Lahav and Anderson noted changes in benzidine-soil mixtures during freeze-thaw cycles,[65] which might shed light on benzidine's behavior in soils, although the implications are not clear. Benzidine does react readily with plant products, however, which suggests that it would quickly adsorb to either suspended materials in waters or humic materials in soils.[32] Consequently, we can expect fairly rapid immobilization of much of the environmental benzidine in soils or sediments. We have no assurance, however, that biologically significant amounts will not be desorbed in salt waters or the guts of bottom-feeding fishes.

Most studies on the toxic effect of benzidine have been related to its carcinogenic activity. It is well known that the incidence of bladder tumors among workers exposed to benzidine is high and that such workers show increased levels of 8-glucuronidase in their blood. In addition to producing bladder tumors, benzidine is reported to induce hepatic tumors in mice,[81] intestinal tumors in rats,[79] and breast cancer in female rats.[40]

Little is known about the oxic effects of benzidine other than its carcinogenic activity. Studies by Christopher and Jairam showed that benzidine can be acutely toxic to rats when administered per os.[23] One gram of benzidine mixed with an unspecified amount of food and fed to six rats killed all the rats within 38 days; the first rat died on day 34. Post-mortem examination of the tissues showed epicardial petichial, hemorrhagic spots and venous congestion.

Rats given a sublethal dose of 100 mg/kg showed leucocytosis, erythrocytopenia, thrombocytopenia and reduced catalase and peroxidase

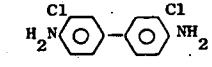
activity after 8 hours.[91] Chronic exposure to benzidine produced excessive proliferation of bile capillaries, an increase in cystine and serine in the liver, mild nephrosis, and a decrease in alkaline phosphatase in the liver.[77]

Cutaneous tests, performed in sensitized patients, showed that benzidine can produce allergic reactions.[85] In this study, a number of amino and nitro compounds related to benzidine were evaluated. It was found that the substituent group exerts a decisive influence on the allergenic properties of aromatic diamines. Allergenicity was intensified by the presence of NH_2 groups; however, NO_2 groups diminished the effect, and CH_3 groups slightly weakened it.

The noncarcinogenic effects of benzidine in nonmammalian species are even less well known. When injected into chick embryos, benzidine prevented neural tube closure and retarded embryonic development and tissue transformation.[74] Trout, bluegill sunfish, and larval lamprey died or showed signs of severe distress when exposed to 5 mg/ℓ benzidine for 14 hours.[5]

According to Ames, benzidine is not only carcinogenic but also mutagenic, causing frame shifts in Salmonella typhimurium histidine mutant.[4]

3,3'-Dicholorbenzidine



3, 3'-Dichlorobenzidine (DCB) has a molecular weight of 253.1, melts at 132-3°C, is insoluble in water, and is readily soluble in ethanol, benzene, and glacial acetic acid. It is slightly soluble in hydrochloric acid. Its major uses appear to be as a dye and pigment intermediate and as a curing agent for polyurethanes.

DCB superficially appears to be a relatively immobile compound, but it is disturbingly similar to DDT. This suggests that it may be concentrated in food chains. It should be regarded as a potentially hazardous pollutant. Like DDT, DCB is readily soluble in organic solvents,[46] is sparingly soluble in water, and should accumulate in organisms.[83] DCB is packaged and distributed as a powder,[1] suggesting that it is minimally volatile. However, this is also true of DDT, which appears to have moved extensively through the atmosphere.[102] Its affinity for suspended particulates in water and for colloids in soils is not clear, but its basic nature suggests that it may be fairly tightly bound to humic materials in soils. Soils may consequently be moderate-to-long-term reservoirs. Because of the halogen substitution, it is likely the DCB has a lesser rate of biodegradation than benzidine. It may be present in the waste streams from plants where it is produced or used for pigment or dye manufacture, but the amount getting into the environment from these sources is believed to be quite small. Since less than stoichoimetric amounts are usually used, unreacted diamine is not normally present in the cured polyurethane elastomers made from dichlorobenzidine. However, the curing agents are often melted before mixing into the elastomer formulations, so dichlorobenzidine could possibly find its way into the waste streams from plants where it is being used as a curing agent.

On balance, the paucity of data and the similarities to DDT indicate that high priority should be given to a more thorough appraisal of environmental release. If release levels are found to be high, studies should be undertaken focusing on atmospheric and aqueous transport, persistence in the soil, and propensity to move through food chains. Changes in toxicity and mobility upon entry into salt waters appear probable and likewise warrant attention (cf. Ref. 3). No literature are uncovered concerning the relevant chemical reactions. We estimate the half-lives

for reactions with HO radicals, O_3, and RO_2 radical, in their respective phases, to be 1, 1-10, and 100 days, respectively. The uv spectrum is similar to that of benzidine, but its photochemistry is unknown.

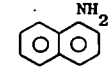
That DCB can cause cancer of the bladder is well known. Less well defined are its effects other than as a carcinogen. No information on its toxicity was found in the Merck Index,[91] Volume II of Industrial Hygiene and Toxicology,[76] or the Handbook of Toxicology, Volume 1.[93] The compound is not listed in Volumes 1, 3, or 5 of the Water Quality Criteria Data Book[32,33,34] or in Water Quality Criteria.[71]

In embryonic kidney tissue, DCB produced a variety of morphological changes after injection of 8 to 10 mg into the embryos.[86] Soloimskaya reported that DCB activates monoamine oxidase and histaminase in rats; however, after repeated doses, the compound inhibits these enzymes.[92]

In monkeys DCB is excreted in the urine almost unchanged, in contrast to benzidine, most of which occurs as various metabolites.[56] In rats, however, DCB undergoes considerable biotransformation. Four metabolites, including benzidine, were identified in rat urine after ingestion of either a single large dose or several small doses over a prolonged period.[2]

Its classification as a carcinogen, in addition to the paucity of information on other effects on biological systems, suggests that DCB requires considerably more study before environmental limits can be set.

1-Naphthylamine



1-Naphthylamine has a molecular weight of 143.2 and a melting point of 50°C; it is insoluble in water (at 25°C), readily soluble in ether and other solvents, and volatile.

This amine is used as an intermediate for dyes and herbicides and directly as an antioxidant in oils. Extensive listings in Chemical Abstracts on naphthylamine failed to reveal much information relevant to its environmental chemistry.

We estimate the half-life of 1-naphthylamine towards HO radical, O_3, and RO_2 radical, in their respective phases, to be <1, 1-10, and ~100 days, respectively.

Like benzidine, 1-naphthylamine absorbs light in the solar region out to nearly 350 nm; however, no evidence indicates that this absorption leads to significant photochemistry. Ashkinazi reported that sensitized photoxidation with chlorophyll leads to colored intermediates with free electron spin.[6]

1-Naphthylamine is potentially a significant, generalized hazard in the environment. This is suggested by its occurrence as a derivative of azo-dye wastes in anaerobic waters[96] and its heat tolerance.[47,48] As a substance that dissolves readily in organic solvents,[60,61,62,63] it has a high probability of movement through aquatic food chains, although this uptake may be particularly sensitive to pH and salinity. The data bearing on this are only suggestive, however, and were available only as abstracts (cf. Refs. 60,61,62,63,81).

It is probable that movement through soils will be minimal if the substance is introduced at the surface rather than at deeper layers. As a weak base, 1-naphthylamine can be expected to combine with humic acids possibly being immobilized.

Little information was found on the biological effect of 1-naphthylamine except for its role as a carcinogen. Early work performed by Pitini reported in the Handbook of Toxicology[93] results in lethal dose estimates of 300 to 400 mg/kg for rabbits and dogs via subcutaneous administration. Applegate reported that trout, bluegill sunfish, and

larval lamprey did not survive exposure to 5 mg/ℓ of 1-naphthylamine in water for more than 12 hours.[5]

The compound is reported to affect various biochemical and physiological processes in laboratory animals. Increases in aryl hydrocarbon hydroxylase were observed in rat liver, lung, and kidney homogenates and microsome preparations.[3] A well-known effect of 1-naphthylamine and almost all aromatic nitro and amine compounds is its ability to produce methemoglobenimia.

1-Naphthylamine does not appear to affect biological systems as much as other compounds of the same class. When equal doses of 1- and 2-naphthylamine were administered repeatedly to mice, 1-naphthylamine produced focal adiposity in the liver, whereas 2-naphthylamine caused diffused hyperplasia and edematous growth.[59] 1-Naphthylamine did not inhibit incorporation of amino acids into proteins of rat liver slices; however, marked inhibition was produced by 2-aminofluorene, 2-acetylaminofluorene, and 2-naphthylamine.[7]

1-Naphthylamine as well as 2-naphthylamine is oxidized by a mixed-function amine oxidase. This enzyme was isolated from pig liver microsomes by Ziegler and coworkers.[105] The compound is metabolized to various products such as unconjugated N-(1-naphthyl)hydroxylamine[18] and 1-amino-2-naphthylglucosiduronide.[24] N-(1-Naphthyl)hydroxylamine is a more potent carcinogenic agent than 1-naphthylamine.[12]

Its high toxicity to fish, as indicated by the preliminary study of Applegate and co-workers, suggests that more comprehensive studies should be performed to determine maximum acceptable concentrations for natural water bodies with respect to protection of aquatic species if it is released in significant amounts into the environment.

<u>β-Propiolactone</u>

$$\underline{OCH_2CH_2CO}$$

β-Propiolactone (BPL) has a molecular weight of 72.06, melts at -33.4°C, boils at 162°C with decomposition, and is soluble in water, oils,

or physiological media. It has a high chemical reactivity and readily hydrolyzes in water.

This reactive lactone was formerly used as a sterilant, but currently its use is limited to production of acrylic acid and its esters and polymers. Despite the high reactivity toward water, alcohols, amines, and other nucleophilic agents, we have been unable to find recent data on the kinetics of the hydrolysis of BPL from which to evaluate the half-life of the lactone under environmental conditions. A further check of older literature and the holdings of the Chemical Kinetics Center at the National Bureau of Stand is (under Dr. David Garvin) might be worthwhile.

We estimate that the half-lives of BPL toward HO radical, O_3, and RO_2 radical, in their appropriate phases, are 1-10 days, >1 year, and >1 year, respectively. These results, even in the absence of hydrolytic data, fairly certainly indicate that radical oxidation or ozonization are not important pathways for degradation in the environment.

In transit through the air, however, BPL may be a significant hazard, although even here it appears that its reactivity would result in localization of the hazard. It can be expected to predominantly decompose to ethylene and carbon dioxide, both essentially harmless compounds. Ethylene is a plant hormone that affects flower and fruit development; the quantities produced by this pathway should be a trivial component of the anthropogenic release of ethylene to the environment. The volatility of BPL is sufficient, however, to suggest that atmospheric dispersal would be rapid.[50,54]

BPL has no significant absorption above 270 nm; therefore we would not expect this lactone to exhibit any significant photochemistry in the solar region. No citations were found concerning the occurrence or disposal of BPL in waste water. It reacts readily with biological material,[16] so unhydrolyzed material should be rapidly adsorbed to suspended particulates, particularly in eutrophic waters. Upon entry into salt waters,

it apparently reacts with chloride ions to form 3-chloropropionic acid, which seemingly is far less hazardous than BPL.[50] Alterations of its activity in fresh waters of varying acidity may occur, but the limited data available suggest that such interactions would be minimal in the vicinity of neutrality (pH 7-8).[28]

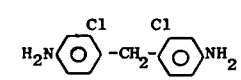
In view of its reactivity and rapidity of hydrolysis, it is unlikely that BPL will be a significant hazard if released to soils or transported to them through the air. Nor is it likely to be accumulated in biological materials and transferred through food chains.

BPL was commonly used in cold sterilization of blood, plasma, and various tissues for grafts. Its viricidal, bacteriocidal, carcinogenic, and mutagenic properties are relatively well known. A large percentage of the published articles pertaining to the biological action of BPL have been devoted to its use as a sterilant and its effects on tissues in vitro. Most of the other articles have concerned carcinogenesis and mutagenesis. No information was found concerning the toxicity of BPL to plants or to terrestrial and aquatic wildlife.

BPL is highly toxic to laboratory animals. In rats the estimated oral LD_{50} is 50-100 mg/kg; when the substance is administered intraperitonially, the LD_{50} is about the same. In guinea pigs the LD_{50} is less than 5 ml/kg for application to the skin.

Its high toxicity to viruses, bacteria, and laboratory mammals, as well as its relatively high solubility in water, suggests that BPL could be highly toxic to aquatic life.

4,4'-Methylenebis(2-chloroaniline)



This compound has a molecular weight of 267 and a melting point of 110°C.

The only commercial use of this amine is as curing agent for polyurethanes. Since less than stoichiometric amounts are usually used, unreacted diamine is not normally present in the cured polyethane elastomers made from 4,4'-methylenebis(2-chloroaniline). However, the diamine is often melted before mixing into the elastomer formulations, so it could possibly find its way into the waste streams from plants where it is being used as a curing agent.

No information was uncovered concerning spectral or photochemical properties. By analogy the compound should behave much like dichlorobenzidine. We have estimated the half-lives of this amine toward HO radical, O_3, and RO_2 radical in the appropriate phase to be similar to those of 3,3'-dichlorobenzidine: <1, 1-10, and ~100 days, respectively.

4,4'-Methylenebis(2-chloroaniline)(MOCA) resembles DDT both structually and physically. It is almost insoluble in water, but soluble in organic solvents, and apparently it has a low vapor pressure.[47] The most pertinent evaluation of its hazards, that of Linch et al.[69] noted that absorption through the skin is more important than inhalation in industrial settings, but this does not preclude the possibility that inhalation is the dominant mode of uptake in nonindustrial settings.

Sound appraisals of the propensity of MOCA to move through food chains, to reside in soils, or to move through water are not possible with the present data. In view of the experience with DDT and the similarity of the two compounds, however, caution is warranted. High priority should be given to appraisals of air and water transport, the potential for food-chain accumulation, and residence times in soils if the release rate to the environment proves to be significant.

The status of MOCA as a carcinogen is in question. Grundmann and Steinhoff reported that rats maintained on a low protein diet containing

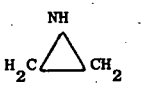
0.1% MOCA developed lung, liver, brain, and mammary tumors.[42,94] The survival of treated animals was less than that of controls.

On the other hand, Linch and coworkers did not find any clinical evidence of malignancy in dogs during the third year of a 6-year MOCA feeding study; the dosage was not specified.[69] These authors also stated that surveillance of workers exposed to MOCA for 16 years showed no symptoms of toxic effect.

The acute toxicity of MOCA, administered orally, to mice or rats, is relatively low. The LD_{50} is 880 mg/kg and 2100 mg/kg in mice and rats, respectively.[57] The toxicity of MOCA to nonmammalian organisms and plants is unknown.

The U.S. FDA has disallowed MOCA as a component of food-contacting adhesive and polyurethane resins, basing this decision on the work of Grundmann and Steinhoff. The status of MOCA as a carcinogen should be reevaluated, and its toxicity to wildlife, relative to amounts that occur in the environment, should be determined.

Ethylenimine



Ethylenimine has a molecular weight of 43.07 and a boiling point of 56-7°C; it is miscible with water, flammable, and readily polymerizable. It is used principally for treatment of paper; to a lesser extent, it is used in high-energy fuels and as a chemotherapeutic agent.

It is volatile, highly toxic, flammable, and mutagenic in plants.[11] Two observations suggest that it is stable in the air. First, it is one of the products of the photodecomposition of methylamine, suggesting that it is itself stable.[72] Second, it retains its biological activity at

room temperature for extended periods.[8] Consequently, it is probably capable of broad aerial dispersal, although one report suggests it undergoes eventual photo-decomposition.[39]

Hydrolysis of ethylenimine has been studied in acidic and basic aqueous systems near 25°C. From the data of Bunnett and McDonald[19] we estimated the half-life in 1 M perchloric acid to be about 160 hours at 29.5°C. Pomonis and coworkers measured the rate in nearly neutral phosphate buffers at 27°C.[79] The rate of hydrolysis of ethylenimine at pH 7, with 0.2 M HPO_2^{2-}, gives an estimated half-life of about 700 minutes; with 0.1 M HPO^{2-}, the half-life increases to 1300 minutes; extrapolating to zero HPO_2^{2-} at pH 7, the estimated half-life is over 2500 minutes or 41 hours. At pH 8, the half-life would be about ten times longer if the same mechanism for hydrolysis was important.

In the gas phase the half-lives of ethylenimine for reactions with HO radical and O_3 are estimated to be <1 day and >1 year, respectively; in water, reaction with RO_2 radical has an estimated half-life of >1 year. Thus we conclude that the major pathway for chemical degradation will be via hydrolytic decompositions in water or possibly by moisture in the air. Ethylenimine does not absorb in the solar uv region; therefore we would not expect any significant photochemical reaction.

There is no solid basis for inference concerning the propensity of ethylenimine to move through and be concentrated in food chains. However, the possibility that it does so is strong, if all the foregoing suppositions regarding aqueous hazards are correct.

Direct hazard to man potentially extends to impairment of reproductive ability, although the concentrations used in the pertinent experiments with rats were far in excess of any to be expected outside an industrial setting.[103]

Direct effects on plants are frequently reported to be beneficial, although we question the generality of beneficial mutations. The species and families in which mutagenic action has been reported are:

Graineae:	Barley[87]
	Wheat[80]
Leguminosaea:	Kidney bean[100]
	Bean, common[10]
	Pea[68]
Solanaceae:	Tomato[20]
Malvaceae:	Cotton[30]
Compositae:	Cosmos, Zinnia, Crysanthemum[35]
Oleaceae:	Red ash[84]

Mutagenic effects have been observed in a number of plants, including tomato, cotton, wheat, lupine, barley, kidney bean, and ash. In tomato, treatment of seeds increased germination, flowering, plant height, and pollen fertility. The mutation frequency was higher in the M_2 generation than in the M_1 generation. In cotton, the compound produced mutants with larger cotton balls, thicker fibers, greater branching, and longer growing period. Barley mutants were of higher protein content and larger kernels. Exposure of pea seeds to ethylenimine inhibited plant growth and development.

Ethylenimine, administered orally or by percutaneous absorption, is highly toxic to laboratory mammals. It is extremely toxic when inhaled. The compound has not been investigated extensively for carcinogenecity. As a mutagen, it is relatively potent, and it has been used to treat seeds of commercially important plants to produce high-yield mutants.

According to Sutton, the LD_{50} is 15 mg/kg in rats via oral adminstration.[95] As little as 0.014 ml/kg applied to the skin of the guinea pig produced severe skin necrosis, and as little as 0.005 ml applied to the eye of the rabbit resulted in severe corneal damage and death. The LD_{50} in mice exposed to ethylenimine in air was reported as 3.93 mg/ℓ.[89] Death after inhalation is usually delayed. Irritation to the eyes and nasal passages is a frequent observation.

Although human subjects were not able to detect the presence of 0.05 mg/M^3 of ethylenimine in air, EEG measurements showed desynchronization of the α-rhythm in the cerebral cortex.[14] Berzina also found that exposure of rats to 0.001, 0.01, and 0.1 mg/M^3 of ethylenimine for 95 days resulted in decreases in blood nucleic acid levels at 0.01 and 0.1 mg/M^3, but not at 0.001 mg/M^3.[13] He hypothesized that the reduction of nucleic acids in blood was due to denaturation by ethylenimine.

Ethylenimine is reported to affect mammalian endocrine systems. One- to 8-day exposure to 0.6 to 0,8 μg/l decreased thyroid activity and increased slightly the weight coefficients of the hypophysis and adrenal glands.[41] Ultramicroscopic examination of the adrenal medulla, following a single injection of ethylenimine, showed endothelial rupture of the medullary blood vessels 2 hours after the injection, followed by complete arrest of medullary circulation 8 to 9 hours after the injection.[26]

Inhalation of the compound results in delayed lung injury with congestion, edema, and hemorrhage. Kidney damage is almost always observed after absorption of ethylenimine. Proteinuria, hematuria, and elevated blood urea are frequently observed.

Effects of ethylenimine on renal function have been studied extensively by James and Jackson.[51,52,53] The compound and certain of its derivatives cause intense and prolonged diuresis in rats.

In rats, Zaeva and coworkers found that exposure for 1.5 months to 19 mg/M^3 produced testicular atrophy, deformation of spermatozoa, and decreased sperm mobility.[103] Pregnant rats exposed to 0.007-0.01 mg/ℓ of ethylenimine in air for 20 days produced high embryo mortality.[88]

Ethylenimine has been reported to produce chromosomal abberations in human cell cultures,[22,75] and hamster cell cultures.[29] Chromosomal abberations have also been observed in bone marrow cells of rats exposed to 0.0006 to 0.024 mg/ℓ in air for 2 to 30 days.[36]

The effect of ethylenimine on terrestrial and aquatic wildlife is not known. It is unlikely that terrestrial mammals, and perhaps avian species, will respond differently to ethylenimine than laboratory species. The response of aquatic wildlife may be different because of differences in environment. It is likely, however, that the compound may be more toxic to aquatic organisms than to terrestrial forms if it is stable in water; aquatic life forms are generally less tolerant of chemical pollutants than mammalian organisms.

Bis(chloromethyl)ether

$ClCH_2OCH_2Cl$

Bis(chloromethyl)ether (BCME) has a molecular weight of 115 and a boiling point of 104°C; it is miscible with ethanol, ether, and other organic solvents.

This ether is used only as an intermediate in preparation of textile aids and anion exchange resins.

The high reactivity of BCME in alkylation reactions is also reflected in a high solvolytic reactivity in aqueous systems. A report[73] on the relative reactivity of BCME to chloromethyl methyl ether (CME), which is 1:5000 in MeOH/H_2O, also included some data of Van Durren[99] on the solvolysis of BCME in DMF/H_2O at 0°C with a rate constant 1, ~0.35 min^{-1},

which is equivalent to a 2-minute half-life. However, CME solvolyzes in i-PrOH at 0°C with a rate constant of $7.4 \cdot 10^{-3}$ sec^{-1} or 1.6-minute half-life. Assuming that BCME solvolyzes at $2 \cdot 10^{-5}$ of this rate at 0°C or $1.5 \cdot 10^{-7}$ sec^{-1}, the half-life would be 1300 hours at 0°C or about 200 hours at 25°C. This estimate is at least consistent with observations of Collier (private communication quoted in the Nichols and Merritt paper)[73] that CME has a half-life of 6 minutes in moist air, whereas BCME is stable for this time period.

We estimate that BCME has half-lives toward HO radical, O_3, and RO_2 radical in corresponding phases of <1 day, >1 year, and >1 year, respectively. In aqueous systems it is clear that solvolysis (hydrolysis) will far outweight radical oxidation as a significant route for removal of BCME in the environment. No photochemistry was noted in Chemical Abstracts citations on BCME; there is little or no absorption in the solar region.

Two important papers by Kallos[55] and Frankel[37] described the formation of BCME from the reaction of HCHO and HCl in the air in low ppb levels when both HCHO and HCl are present in 500-10,000 ppm. A paper by Collier described detection of BCME in the environment at ppb levels using mass spectrometry.[25]

BCME is highly volatile[49] and is moderately stable in humid air,[97] and significant atmospheric movement should be expected. It is unlikely, however, that its dispersal will ever be more than a local problem. Even though fractions of any release might reasonably be expected to travel as much as 200 miles, dilution to unmeasurable levels should occur within a few miles or tens of miles at most. In very humid climates, such as the Pacific Northwest, the high humidity and frequent rains can be expected to enhance this localization, although the intensity of the enhancement may be highly variable (cf. Ref. 37). Optimal dispersal should occur in cool, humid regions, such as southern Canada and New England. The hazard

might consequently be in the order: New England >Southeastern United States >Pacific Northwest >Southwest. Formation of BCME in the atmosphere by reaction of formaldehyde and hydrogen chloride is improbable at atmospheric concentrations.[55]

In contrast, BCME is extremely unstable in water. It decomposes with a half-life of 10-40 seconds. Fortunately, it fails to move from water to air in measurable amounts prior to decomposition, even within small reaction vessels where the ratio of surface area to volume is considerably larger than in natural waters.[55] It is probable that half-lives in soils or organisms are comparably short and that food-chain transfers are consequently nonexistent.

BCME is very irritating to the eyes and skin. When it is inhaled, death can occur due to lung edema or secondary pneumonia. Hake and Roe, reporting unpublished data from the Biochemical Research Laboratory (Dow Chemical Company), stated that 1.0 g/kg, fed to rats caused death, whereas 0.3g/kg allowed survival.[43] The estimated LD_{50} by oral administration is 0.5g/kg. Severe eye irritation and necrosis developed when a 1% solution in ethylene glycol was placed in the eyes of rabbits. Rabbit skin tests with the full strength material produced severe hyperemia, edema, and even complete skin destruction.

Exposure to 2000 ppm of the vapor for over 30 minutes can be lethal; so can exposure to 100 ppm for 4 hours. These conclusions are based on studies (Dow Chemical Company) with rats. Death due to inhalation of the vapors is often delayed, occurring several days to several weeks after exposure.

Chloromethyl ether concentrations high enough to be acutely toxic to wildlife are unlikely to be found in the environment, unless an accidental spill occurs. The highly irritating vapors would probably be avoided by mobile terrestrial organisms. The toxicity to fish and other aquatic

organisms is not known. By direct contact or by contact with decomposition products such as chlorine, the toxicity could be considerable.

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