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AN ASSESSMENT OF THE HEALTH RISKS OF MORPHOLINE AND DIETHYLAMINOETHANOL

Prepared for the

Department of the Navy

by the

COMMITTEE ON TOXICOLOGY

Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
National Research Council

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INTRODUCTION

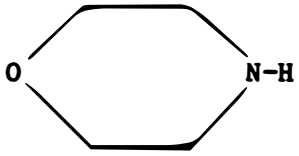
The Committee on Toxicology of the Board on Toxicology and Environmental Health Hazards in the National Research Council's Commission on Life Sciences has a longstanding multiagency contract to provide assistance to its sponsors in matters related to toxicology and environmental health. Under this contract, the Department of the Navy has asked the Committee to assess the health risks of human exposure to morpholine and to diethylaminoethanol (DEAE).

DEAE has been used by the Navy Public Works Center, Great Lakes, IL, to control corrosion in steam-generating and distribution systems. Recently, the Public Works Center indicated that it was planning to substitute morpholine for DEAE. Because live steam is used for humidification of air, sterilization of surgical instruments, and preparation of food in the Naval Regional Medical Center and the major manufacturer of morpholine has recommended that it not be used in food-preparation applications, the Navy has asked the Committee on Toxicology to review the possible adverse health effects of exposure to morpholine and to DEAE. The Committee was also asked to suggest guidelines for airborne exposure if sufficient data were available or, if not, to suggest research that would permit a more complete assessment of the health risks.

ASSESSMENT OF MORPHOLINE

BACKGROUND INFORMATION

Morpholine (tetrahydro-1,4-oxazine) is an oxygen-containing cyclic amine with the following structure:



Morpholine is a colorless, hygroscopic liquid with a characteristic amine odor; it is volatile at room temperature. Its melting point is -4.75°C, and its boiling point, 128.3°C (Weast and Astle, 1978-1979). Morpholine is completely miscible with water in all proportions. It is also miscible with acetone, benzene, ether, castor oil, methanol, ethanol, ethylene glycol, 2-hexanone, linseed oil, turpentine, and pine oil. Morpholine is a strong base (pK_b, 5.6). It reacts with acids to form morpholine salts, and with isocyanates and isothiocyanates to form substituted ureas and thioureas. Morpholine reacts with amides, phenols, ketones, aldehydes, alcohols, olefins, mercaptans, and metallic salts. It is readily alkylated to N-alkylmorpholine and nitrosated to N-nitrosomorpholine. Table 1 provides additional background information on morpholine.

Morpholine is prepared by the dehydration of diethanolamine, $(HOCH_2CH_2)_2NH$, and by the reaction of diethylene glycol, ammonia, and hydrogen. Morpholine is used as an intermediate in chemical syntheses--its largest use is as an intermediate in the production of rubber chemicals. It also serves as a solvent for resins, waxes, casein, and dyes, as well as in the formulation of floor polishes and as a corrosion inhibitor in steam generating systems. The various uses of morpholine are summarized in Table 2. The use of interest in this report--as a corrosion inhibitor in boiler systems--stems from morpholine's neutralizing effects on carbonic acid.

SUMMARY OF TOXICITY INFORMATION

The toxicity of morpholine was recently reviewed by the NRC Committee on Amines (NRC, 1981a).

EFFECTS ON HUMANS

Morpholine is highly irritating; airborne exposure can cause irritation of the skin and eyes. Shea (1939) exposed himself to morpholine at 12,000 ppm (42,000 mg/m^3) in air for 1-1.5 min and reported irritation of the nose and coughing. Ivanov and Germanova

(1973) reported that men exposed to morpholine in the air at 16 mg/m^3 for 1 min showed an irritant effect (determined by the appearance of subjective irritant sensations).

EFFECTS ON ANIMALS

A summary of the acute, subchronic, and chronic toxicity of morpholine is given in Table 3.

Acute toxicity studies conducted by Lam and Van Stee (1978) gave LC_{50} values of 2,250 and 2,150 ppm for male and female rats, respectively, and, 1,450 and 1,900 ppm, for male and female mice, respectively. One study (Migukina, 1973) has indicated that inhalation of morpholine at 8 mg/m^3 (2.3 ppm) for 4 h/d, 5 d/wk, for 2 mo resulted in reversible hypotension and leukopenia in rats. The author also found an increase in the number of chromosomal aberrations of bone cells at this concentration and suggested a maximal permissible concentration of 0.5 mg/m^3 for morpholine. However, these data have not been confirmed.

Carcinogenicity

Shank and Newberne (1976) fed various concentrations of morpholine, sodium nitrite, and N-nitrosomorpholine incorporated into a semipurified diet to pregnant rats and hamsters in a two-generation study. The experimental animals were fed the compounds in the diet from the time of conception until delivery. Offspring of both sexes were then randomly selected for long-term study, which also included use of second-generation rats. Exposures ended at 125 wk for rats and 110 wk for hamsters. Dietary concentrations and tumor incidences for the experimental groups are summarized in Table 4.

Control rats developed no liver or lung tumors, but 3% and 2% of rats maintained on a diet containing morpholine at 1,000 ppm (but no detectable N-nitrosomorpholine) developed hepatocellular carcinomas and lung angiosarcomas, respectively. Morpholine-treated hamsters failed to develop tumors. The data suggest that morpholine may be a weak carcinogen, but the study did not rule out the possibility of intragastric formation of the potent liver and lung carcinogen N-nitrosomorpholine by reaction of dietary morpholine with nitrite of unknown source (the animals were given distilled water and a diet free of nitrate and nitrite). The diet did contain ascorbic acid at 200 mg/kg to decrease the likelihood of in vivo nitrosation of the morpholine (ascorbic acid is known to be a scavenger of nitrosating agents).

In another study, 20 male and 20 female Swiss mice were given morpholine at 6.33 g/kg in the drinking water for 40 wk, but did not develop more lung adenomas than did control animals (Greenblatt et al., 1971).

Mutagenicity

Morpholine, in the absence of nitrite, yielded negative results in three bacterial mutagenicity systems (mouse/Salmonella host-mediated

assays) (Braun et al., 1977; Edwards et al., 1979; Zeiger and Legator, 1971). Cells derived from hamster embryos intubated with morpholine at 500 mg/kg did not show increases in chromosomal aberrations, micronuclei, 8-azaguanine- or ouabain-resistant mutants, or transformation rates (Inui et al., 1979). In contrast, Migukina (1973) exposed rats to morpholine at 8 or 70 mg/m^3 for 4 mo and reported a dose-related increase in chromosomal aberrations due largely to fragmentation. An unpublished finding by the Texaco Chemical Company that morpholine is "weakly mutagenic" in the BALB/3T3 in vitro transformation assay, sister chromatid exchange assay, and possibly the mouse lymphoma forward mutation assay (but not in the Ames assay or the rat hepatocyte primary culture DNA repair assay) prompted that company to recommend that morpholine not be used in food-related applications (Monaghan, 1980).

Teratogenicity

No data on the teratogenicity or reproductive toxicity of morpholine were available to the Committee.

NITROSATION POTENTIAL

Of the approximately 300 N-nitroso compounds that have been tested, 85% of the 209 nitrosamines (including N-nitrosomorpholine) and 92% of the 86 nitrosamides have been shown to produce cancer in laboratory animals (Shank and Magee, 1981; NRC, 1981b). N-Nitroso compounds are readily formed by the interaction of nitrosating agents (nitrous acid, oxides of nitrogen, nitro compounds, and other nitroso compounds) and secondary or tertiary amines and amides. The amines and amides may be nitrosated to nitrosamines and nitrosamides under acidic, neutral, or alkaline conditions. Atmospheric NO_2 may also participate in the nitrosation of amines in aqueous solution (Challis et al., 1982).

Morpholine is a secondary amine and is readily nitrosated by nitrous acid. As with other secondary amines, the nitrosation is acid-catalyzed and proceeds most rapidly at a pH of 3.4 (Ridd, 1961; Mirvish, 1975), but some nitrosation of secondary amines occurs at a pH as high as 6 (Turney and Wright, 1959; Mirvish, 1970). The nitrosation rate is proportional to the morpholine concentration and the square of the nitrite concentration, according to the following equation, where [ ] refers to molar concentration:

$$\text{rate} = k[\text{amine}][\text{nitrite}]^2.$$

The k value, units in $(M^{-2})(s^{-1})$, varies in different amines and is 0.0017 for dimethylamine, 0.42 for morpholine, 83 for piperazine, and 250 for N-methylaniline. Hence, morpholine is nitrosated with moderate ease. The nitrosation of amines is catalyzed by such anions as iodide, bromide, and thiocyanate, and this reaction follows a different equation (Mirvish, 1975).

Nitrosation of morpholine produces N-nitrosomorpholine (NMOR), a potent carcinogen in animals (IARC, 1978). NMOR produces tumors of

the liver, lung, and blood vessels in rats, mice, and hamsters. In addition, several studies have demonstrated clearly that exposure of rats, mice, and hamsters simultaneously to morpholine and nitrite causes cancer of the liver, lung, and blood vessels (Greenblatt et al., 1971; Mirvish et al., 1976; Shank and Newberne, 1976).

In mice, morpholine given orally and nitrogen dioxide given by inhalation were reported to react to form NMOR (Iqbal et al., 1980), which has resulted in a slight excess of lung tumors (adenomas) (Van Stee et al., 1981). It was recently reported that small amounts of NMOR were present in mice exposed to morpholine and atmospheric NO_2 (Van Stee et al., 1983). There is some question about whether NMOR is formed in vivo on exposure to NO_2 or rather that NO_2 exposure produces a nitrosating agent in vivo that reacts with morpholine in tissue homogenates to produce NMOR (Mirvish et al., 1981, 1983). NMOR is mutagenic in a variety of test systems (IARC, 1978), as is the combination of morpholine and nitrite (Braun et al., 1977; Edwards et al., 1979; Inui et al., 1979).

The potential for NMOR formation in steam that contains morpholine is unknown. Although specific data on the presence of morpholine in steam were not available, several authors have speculated that NMOR found in food-related products might have arisen from morpholine in steam. For example, NMOR has been detected in a chicken frankfurter sample (Gray et al., 1981), soy protein concentrate (Fazio and Havery, 1981), packaging material for foods (Hotchkiss and Vecchio, 1983), and utility-steam condensate in a factory (Fajen et al., 1979).

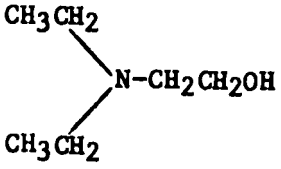
PHARMACOKINETICS

Van Stee et al. (1981) studied the distribution and disposition of morpholine in male New Zealand White rabbits (2-2.5 kg) with reagent-grade (100.0%) morpholine. Thirty minutes after intravenous injection, morpholine was concentrated in the kidney, largely in the medulla. Morpholine was not significantly metabolized to carbon dioxide or conjugated with glucuronic acid, and 90% was excreted unchanged. Sohn and co-workers (1982a) found N-methylmorpholine-N-oxide in the urine of rats, hamsters, and guinea pigs given morpholine.

ASSESSMENT OF DIETHYLAMINOETHANOL (DEAE)

BACKGROUND INFORMATION

DEAE is an aliphatic aminoalcohol that is highly soluble in water and organic solvents. The structure of DEAE is shown below:



DEAE is used as a chemical intermediate in a wide variety of industrial processes. Because of DEAE's neutralizing effects on carbonic acid, it is also used to inhibit corrosion in steam generating and distribution systems. Table 5 provides additional background information on DEAE.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

No data on the effects of human exposure to DEAE are available.

EFFECTS ON ANIMALS

The acute toxicity of DEAE by various routes of administration has been reported by a number of investigators. The data, summarized in Table 6, indicate that neutralized DEAE is mildly toxic and that nonneutralized DEAE (as would be found in steam) is approximately four times more toxic.

DEAE is highly irritating to the eye and skin. The application of 5 mg of DEAE to the rabbit eye produced severe irritation (Lewis and Tatken, 1982), and 10 mg applied to the clipped belly of rabbits produced skin irritation after 24 h (Smyth and Carpenter, 1944).

Cornish (1965) evaluated the inhalation toxicity of DEAE. In one study, 20 male rats were exposed to DEAE at 500 ppm for 6 h/d for 5 d. All animals exhibited nasal and eye irritation after the first day. After 5 d, four animals had died, and many showed marked corneal opacity and had lost 40-80 g in body weight. Autopsies revealed acute purulent bronchiolitis and bronchopneumonia characterized by lymphocytic and large mononuclear cellular infiltration around the lumen of the bronchioles.

In a second study, eight male and eight female rats were exposed to DEAE at 200 ppm for 6 h/d for 5 d. Eye irritation was noted on the first day of exposure, and nasal irritation after 3 d. All exposed animals showed a weight gain equal to that seen in control animals. Histopathologic examination of the major tissues showed no marked differences from the controls.

In a third study, 50 male rats were exposed to DEAE at 200 ppm for 6 h/d, 5 d/wk, for up to 6 mo. During the first month, seven animals showed progressive weight loss followed by death. One control rat died in the second month. Histopathologic examination showed bronchopneumonia in the animals, but no other tissue abnormalities. The remaining animals showed a 15% depression in weight gain after 1 mo of exposure, but their weights were comparable with those of control animals after 3 mo. After 6 mo, treated and control animals had comparable body and organ weights, blood chemistry, and histopathology. The deaths of animals after 1 mo in this study could have resulted from aggravation of bronchopneumonia by DEAE.

Cornish (1965) also evaluated the oral toxicity of DEAE in rats given 50 and 100 mg/d in the drinking water for 6 mo. Growth rates for control and treated animals were comparable over the first month; however, at 2 mo, the amount of weight gained by the 50- and 100-mg/d-treated animals was less than that seen in controls. At 6 mo, the rats receiving 50 mg/d had recovered to normal body weight, whereas the 100-mg/d group remained 50 g below control. Kidney-to-body-weight ratios of treated animals were higher than those of controls at 1-, 2-, and 6-mo sacrifices. Liver-to-body-weight ratios, clotting time, hemoglobin, liver lipids, serum lipids, serum cholesterol, and histopathology were similar to those of control animals.

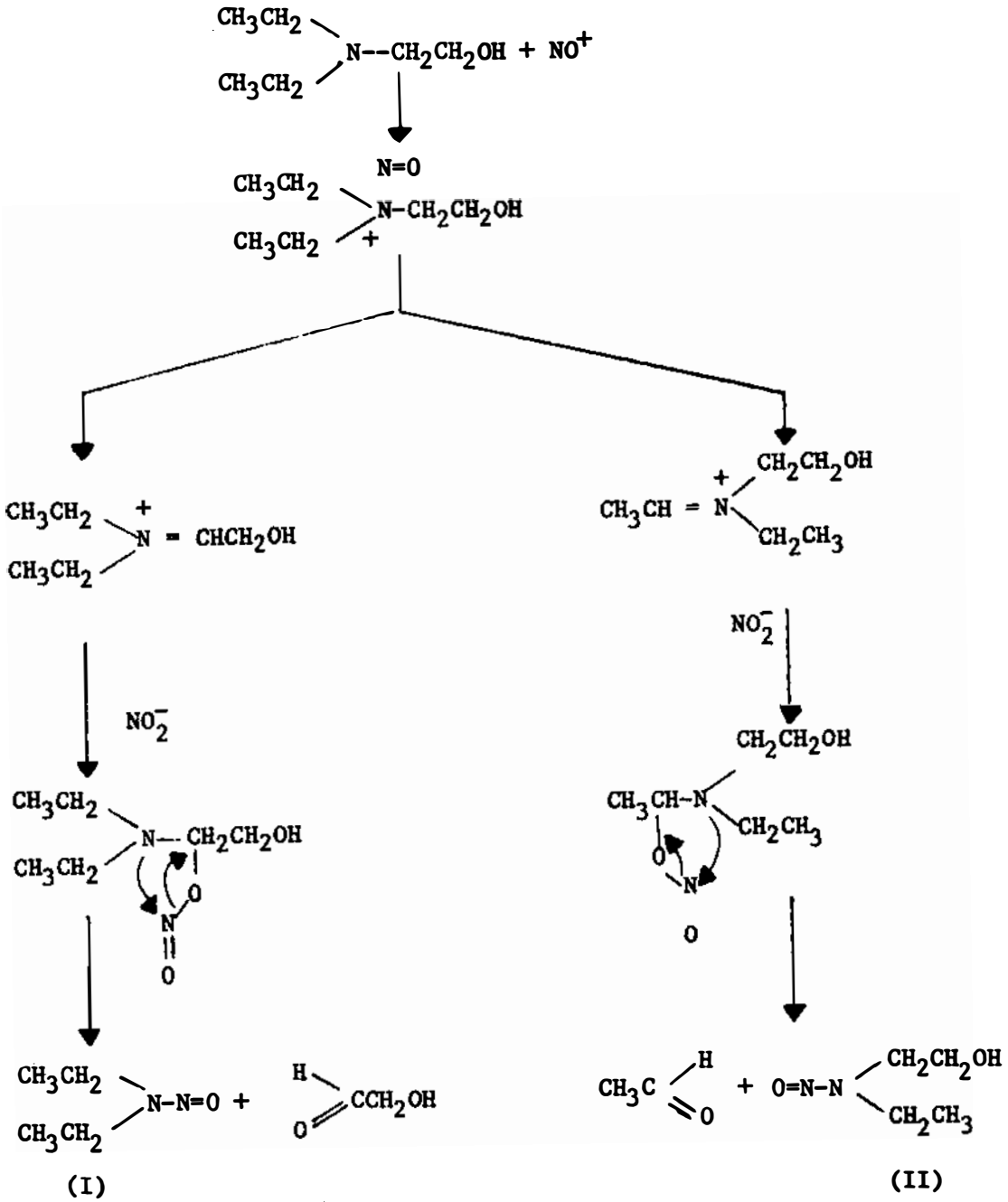
No published studies concerning the carcinogenic, mutagenic, or teratogenic effects of DEAE were available to the Committee.

NITROSATION POTENTIAL

Nitrosation under the usual conditions (by nitrous acid in mild mineral acid) is normally very much slower for tertiary amines, such as DEAE, than for secondary amines (Mirvish, 1975). However, under some conditions, the nitrosation rate can approach or exceed that for secondary amines (Loeppky *et al.*, 1982).

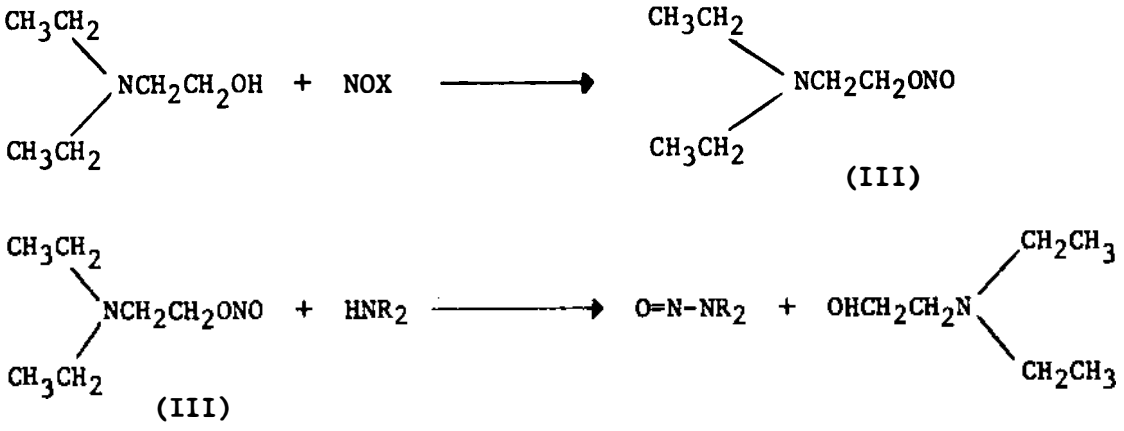
On the basis of its chemical structure, DEAE potentially can be nitrosated to form *N*-nitrosodiethylamine (I) and *N*-nitrosoethylethanolamine (II), two potent carcinogens in animals (IARC, 1978). However, no data concerning the likelihood and kinetics of such reactions are available. This type of reaction is believed to occur through an iminium ion, as shown in Scheme 1 (Ohsima and Kawabata, 1978).

Scheme 1



Alkanolamines, such as DEAE, can also catalyze the formation of nitrosamines from atmospheric nitrosyl chloride or bromide and secondary amines under exceptionally mild conditions. In such cases, nitrosation occurs through the alkyl nitrite ester (III) shown in Scheme 2.

Scheme 2



Challis and Shuker (1980) found that DEAE catalyzes the formation of N-nitrosopiperidine from piperidine and atmospheric nitrosyl chloride in aqueous solution at 25°C.

In assessing the nitrosation potential of DEAE, one should also consider whether the commercial product is contaminated with secondary amines, such as diethanolamine, ethylethanolamine, and diethylamine. These amines could be nitrosated to produce N-nitrosodiethanolamine, ethylhydroxyethylnitrosamine, and diethylnitrosamine.

PHARMACOKINETICS

The physiological disposition of DEAE was studied by Rosenberg et al. (1949). In humans, they found that approximately 25% of DEAE was excreted in the urine within 8 h after oral dosing. In dogs, DEAE was found in all tissues after intravenous infusion, with the major concentration in the liver and spleen. The major metabolic pathway of DEAE in mammalian systems, however, remains unclear.

DEAE is structurally related to choline (IV), and deficiencies of choline can generate fatty livers. Bell et al. (1964) demonstrated that DEAE can undergo methylation to produce an analog (V) of choline (IV) that is then incorporated into the liver.

ANALYTIC METHODS

Analytic methods for the determination of morpholine and DEAE in air have been developed and evaluated by the National Institute for Occupational Safety and Health (1977, 1978). The general procedure is to trap the volatile amine on silica gel and then desorb it with dilute acid. The acid solution is basified, and the free amine is analyzed by gas chromatography with a flame-ionization detector. The sensitivity of the method has been found to be significantly increased with the use of the nitrogen-phosphorus detector (Sohn et al., 1982b). For morpholine, the above method was validated over a range of 28.5-108.4 mg/m^3; however, the method is capable of measuring much lower concentrations, as long as the desorption efficiency is adequate. Similar validation studies were performed for DEAE over a range of 25-113 mg/m^3 with the potential of detecting much lower concentrations.

CURRENT EXPOSURE LIMITS

The only regulatory guidelines for airborne exposure to morpholine and DEAE in the United States are those recommended by the Occupational Safety and Health Administration (OSHA). OSHA (1982) has established permissible airborne exposure limits of 20 and 10 ppm for morpholine and DEAE, respectively. These guidelines are applicable only to workplace exposures of 8 h/d and 40 h/wk. No guidelines have been suggested for long-term continuous exposures, either for the general population or for sick persons.

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980) has adopted the following threshold limit-time-weighted average values (concentration for a normal 8-h workday and a 40-h workweek to which most workers may be exposed without adverse effect) and threshold limit values-short term exposure limits (concentration to which workers can be exposed continuously for 15 min without suffering irreversible tissue change, narcosis, or irritation) for morpholine and DEAE:

	Morpholine	DEAE
TLV-TWA:	20 ppm (70 mg/m^3)	10 ppm (50 mg/m^3)
TLV-STEL:	30 ppm (105 mg/m^3)	--

The TLVs for both compounds carried a skin notation, indicating that cutaneous absorption can be an important route of exposure. The values for morpholine were judged to be low enough to prevent irritation and harmful effects on the eye and vision. TLVs for morpholine in the USSR and West Germany are 0.13 ppm and 20 ppm, respectively (ACGIH, 1980). On the basis of the acute data derived by Smyth and Carpenter (1944) and Cornish (1965), the ACGIH (1980) stated that the TLV for DEAE would not irritate the skin and eye. Some of the data that were used to arrive at this value were obtained by personal communication and were not available for evaluation.

The Food and Drug Administration (1983a,b) has permitted the use of several amines, including morpholine and DEAE, in some direct and indirect food-additive applications. Among these applications are protective coatings for fresh fruits and vegetables and corrosion inhibitors for steel and tin plate used in food containers. FDA permits the use of several amines in steam that will contact food, as long as they do not exceed specified concentrations--10 ppm for morpholine and 15 ppm for DEAE. Other approved amines are cyclohexylamine (10 ppm) and octadecylamine (3 ppm). Amines are not permitted in steam that will contact milk and milk products.

Although FDA allows the use of morpholine in food processing, the largest producer of morpholine, Texaco Chemical Company, recommended in a letter to its customers in July 1980 that morpholine not be used in food applications (Monaghan, 1980). This recommendation was based on data that suggested that morpholine may be mutagenic. Texaco has also initiated long-term animal studies, but they are not complete.

EXPOSURE INFORMATION

The concentration of amine detected in steam can vary widely, depending on the method of amine addition to the boiler and the time of steam sampling after amine addition. For example, in a study performed by Malaiyandi et al. (1979), the steam condensates from two hospital steam distribution systems were sampled and analyzed for DEAE. The results are shown in Table 7. When DEAE was added as a single daily dose (Hospital No. 1), a high initial concentration that decayed with time was found. When the amine was continuously metered into the system (Hospital No. 3), a fairly constant concentration of DEAE was maintained.

If the concentration of DEAE ranges from 4 to 2,000 ppm in the steam condensate, it is possible to generate room concentrations of 0.05–24 mg/m^3 at 50% relative humidity. (The density of steam is 23 g/m^3 at 25°C, which represents 100% relative humidity. At 50% relative humidity, there would be 12 g of water per cubic meter. With DEAE at 4 ppm, there would be 4 mg of DEAE per liter of water, or 0.048 mg/12 g, which is equivalent to 0.048 mg/m^3. With DEAE at 2,000 ppm, the equivalent concentration of DEAE would be 24 mg/m^3.) If man inhales 10 m^3 of air in 8 h, a total dose of 0.5–240 mg could be expected. If it is assumed that 20 m^3 of air is inhaled over a 24-h period, patients confined to this environment for 24 h would inhale between 1.0 and 480 mg DEAE/d.

The Navy Public Works Center, Great Lakes, has instituted a program to monitor the concentration of DEAE in steam. The results of analysis with a gas chromatograph using an NP (nitrogen-phosphorus) detector are as follows:

Sample	Day 1	Day 2
Condensate, Bldg 200H	17.7 ppm	12.9 ppm
Boiler #6 steam	16.5 ppm	12.0 ppm
Feed water	6.4 ppm	3.4 ppm

Thus, on the basis of the average concentration found in steam condensate and the method described above, DEAE would be present at approximately 0.2 mg/m^3 in air at 50% relative humidity. This would result in exposure of hospital patients to DEAE at 4 mg/d.

Malaiyandi et al. (1979) also analyzed the steam condensate in one hospital for the presence of morpholine. A mixture of morpholine and cyclohexylamine was continuously metered into the steam generator. Over a 12-h sampling period, the average concentration of morpholine in steam condensate was 2.41 ppm. According to the method described above, this would be equivalent to an airborne morpholine concentration of 0.03 mg/m^3 at 50% relative humidity. No other exposure information from use of morpholine as a boiler water additive was available to the Committee.

The Committee has not attempted to estimate nitrosamine exposures that could occur from airborne DEAE or morpholine at the concentrations estimated above.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The Committee has reviewed the available toxicity and exposure information pertinent to the application described above and has reached the following conclusions concerning DEAE and morpholine:

- DEAE and morpholine are both strong irritants. In addition, each has the capacity to be converted to a nitrosamine, and nitrosamines are suspected of being carcinogenic in humans.

- Amines, such as piperazine (Hagmar et al., 1982), have been shown to trigger asthmatic attacks in factory workers who handled amines and other chemicals. Although no reports of asthmatic attacks after exposure to either morpholine or DEAE were identified by the Committee, it is possible that patients in a hospital, particularly those with asthmatic conditions or prior occupational exposure to amines, might be at higher risk of adverse effects from exposure to these amines.

- Data on human health risks of long-term, low-level airborne exposure of morpholine and DEAE are lacking. In addition, animal data on low-level exposures that could be extrapolated to humans are also limited. Finally, no data exist on airborne concentrations of morpholine or DEAE in indoor environments humidified by steam that contains these amines. Because of these critical gaps in the information base, the Committee cannot suggest guidelines for long-term continuous exposure to morpholine or DEAE in naval health-care facilities, nor can it quantitatively estimate what the health risks might be from such exposures.

- The Committee also observes that, although current FDA regulations permit the use of morpholine in steam that contacts foods, FDA has considered rescinding its approval, because of the nitrosation potential of this amine. That potential, combined with the recent recommendation from Texaco Chemical Company that morpholine not be used in food-preparation applications and the finding of NMOR in foods and food packaging presumably exposed to steam that contains morpholine, suggested to the Committee that the substitution of morpholine for DEAE may not now be prudent.

RECOMMENDATIONS

The OSHA and FDA standards for DEAE and morpholine are apparently based on their irritant and acute toxic effects. In making the following recommendations, the Committee has considered the possible adverse health effects of exposure to nitrosamines that may be formed from either DEAE or morpholine and the likelihood of their formation. This basis for its recommendations is consistent with the conclusion

of the NRC Committee on Amines that morpholine should be considered to be as hazardous as the nitroso compound formed from it (NRC, 1981a). In addition, the Committee emphasizes that the following recommendations are based entirely on the assessment of possible risks to human health and do not take technologic feasibility and economic costs into consideration. Furthermore, the Committee did not review the toxicity of alternatives to the use of DEAE or morpholine.

- The Navy should use boiler additives that are least likely to be nitrosated and that do not have other adverse effects on health that would preclude their use.

Morpholine (a secondary amine) can be nitrosated in vitro or in vivo to N-nitrosomorpholine (NMOR), a potent animal carcinogen and, according to IARC (1978), presumably a human carcinogen. Although DEAE (a tertiary amine) can potentially be nitrosated to N-nitrosodiethylamine and N-nitrosoethylethanolamine, also potent animal carcinogens and presumably human carcinogens, data that demonstrate the extent to which this reaction can occur are not available. Cyclohexylamine (a primary amine) is another neutralizing amine that is approved for use in boiler water by the FDA, and it is less likely than either morpholine or DEAE to form a stable nitrosamine. However, the Committee has not reviewed other toxic effects of this amine and thus cannot recommend that it be used as a substitute for DEAE or morpholine. The Committee does recommend that morpholine not be used to replace DEAE in systems where the latter chemical is already in use.

- Morpholine and DEAE should not be used in concert in a steam generating system when human exposure to the steam may occur.

Under a given set of conditions, DEAE can catalyze the nitrosation reaction and presumably could increase the likelihood of NMOR formation from morpholine.

- When amines are used in steam generating systems, the air in rooms where the steam is used and the steam condensate should be monitored for the presence of amines and nitrosamines.

A major gap in the information available to the Committee concerned the concentrations of DEAE in the ambient air in naval health-care facilities. Such information is necessary to estimate patient exposure to the chemical. In addition, little is known about the presence of nitrosamines in steam treated with amines. The presence of any N-nitroso compound should be considered sufficient cause to discontinue the use of the amine in the steam. The absence of nitrosamines, of course, would not necessarily rule out the possibility of in vivo formation.

- If DEAE, morpholine, or other nitrosatable volatile amines are used in steam generating systems where humans may be exposed to the steam, the amounts of amines added should be reduced as much as possible.

Evidence on acute effects stemming from the inhalation of amines has indicated that persons with asthma or prior occupational exposure to amines are at greater risk of adverse health effects than healthy persons. Thus, the prudent course would be to reduce patient exposure to amines as much as possible. In addition, nitrosation can occur in vivo as well as in vitro; thus, even if nitrosamines are not detected in ambient air, inhalation of nitrosatable amines presumably could lead to the formation of carcinogenic nitrosamines in the body. The Committee cannot estimate an acceptable exposure to such agents. Until more is known about the frequency and biologic importance of in vivo nitrosation, the Committee believes it prudent to assume that such reactions can occur and that the nitrosated products could cause cancer in persons so exposed. Thus, reducing the likelihood of their formation by reducing the concentration of the substrate would reduce the risks of cancer from this source.

One possible method of reducing the concentration of volatile amines in steam would be to use a combination of a "filming" amine, such as the FDA-approved octadecylamine, and a neutralizing amine, such as DEAE. Presumably, the filming amine would not be released to the air, and a lower concentration of the volatile amine would be needed to inhibit corrosion. The feasibility of this approach would, of course, need to be determined by engineering and economic considerations, as well as according to the likelihood of adverse health effects.

- When amines are added to a steam generating system, they should be added continuously in small amounts, rather than in one large daily dose.

When amines are added in a single daily dose, a high initial concentration is found that decays with time. When they are continuously metered into the system, fairly constant concentrations are maintained. Thus, the possibility of short-term exposures to amines at higher concentrations is minimized, as is the likelihood of nitrosamine formation (the kinetics of nitrosation reactions depend on the concentrations of the reactants).

RESEARCH RECOMMENDATIONS

The Committee notes that its recommendations are limited by a number of scientific uncertainties and gaps in data, including the following:

- The absence of data on concentrations of amines and nitrosamines in the air of institutions humidified by live steam that contains amines.

- A lack of knowledge concerning the likelihood of in vivo formation of nitrosamines after inhalation of amines and the conditions necessary for such reactions to occur.

- The absence of data on the ease of nitrosation of DEAE under various conditions.

- The lack of detailed analyses of commercial DEAE samples for their content of secondary amines.

- The absence of animal or human data on the effects of long-term, low-level airborne exposure to morpholine and DEAE.

- The lack of understanding concerning the mechanism(s) by which morpholine itself might be mutagenic and carcinogenic in experimental animals and the significance of these findings to humans.

- The absence of data on the mutagenic and carcinogenic potential of DEAE and on its ability to be nitrosated to N-nitrosodiethylamine and N-nitrosoethylethanolamine.

Research aimed at eliminating these uncertainities would improve the basis for recommending exposure limits and is encouraged by the Committee.

Table 1. BACKGROUND INFORMATION ON MORPHOLINE[a]

Molecular formula:	C_4H_9NO
CAS number:	110-91-8
Chemical name:	Tetrahydro-1,4-oxazine
Synonyms:	Morpholine; diethyleneimide oxide; diethylene oximide
Common name:	Morpholine
Molecular weight:	87.12
Melting point, °C:	-4.75
Boiling point, °C:	128.3
Density (20°/4°):	1.0005
Refractive index (n_D):	1.4548

[a] Weast and Astle, 1978-1979; Windholz et al., 1976.

Table 2. USES OF MORPHOLINE[a]

Uses	Amount Used, metric tons/yr	Percentage of Total
Rubber chemicals	3,600	33
Corrosion inhibitors	2,700	25
Optical brighteners	1,100	10
Alkyl morpholines	1,100	10
Waxes and polishes	900	8
Exports	800	7
Miscellaneous uses	800	7

[a]Adapted from National Research Council, 1981a.

Table 3. TOXICITY OF MORPHOLINE[a]

Species	Dose/Concentration	Duration	Effects	Reference
Rat, M	2,250 ppm	NG[b]	LC_{50}	Lam & Van Stee, 1978
Rat, F	2,150 ppm		LC_{50}	
Mouse, M	1,450 ppm		LC_{50}	
Mouse, F	1,900 ppm		LC_{50}	
Rat	450 ppm	6 h/d, 5 d/wk, 8 wk	Food consumption and body weight gain decreased; changes in sensory areas, such as eyes and nose	
Mouse	1,391 ppm (4,869 mg/m^3)	NG[b]	LC_{50}	Zaeva et al., 1968
Rat	1.05 g/kg	Single, oral	LD_{50}	Smyth et al., 1954
	0.5 ml/kg	Single, skin (24-h contact)	LD_{50}	
Rat, M	11.48 mmol/kg (1,000 mg/kg) pH, 7	Single, oral; killed 48 h later	Normal SGOT and SGPT, no liver necrosis	Borzsonyi et al., 1981
Rat	6,285 ppm (22,000 mg/m^3)	1 h	Lacrimation, rhinitis, inactivity	Indust. Bio-Test Lab., Inc., 1970
Rat	3, 40, or 260 mg/m^3	4 h	260 mg/m^3 increased respiratory rate and decreased ability of lung cells to excrete dye; 40 mg/m^3 did not alter respiratory rate, but did decrease ability to excrete dye	Ivanov et al., 1973
Rat	6,734 ppm	4 h (23,569 mg/m^3)	Irritation	Internatl. Labour Office, 1972
Rat	8,497 ppm	8 h (29,740 mg/m^3)	1/6 died	
Rat	8,000 ppm	8 h (28,000 mg/m^3)	No deaths	Smyth et al., 1954

Table 3. (continued)

Species	Dose/Concentration	Duration	Effects	Reference
Rat	12,000 ppm	8 h	Dilation of blood vessels in lung, cellular reaction and debris in bronchioles, cloudy swelling of liver and kidney tubules with full recovery 16 d after exposure	Shea, 1939
Rat, Guinea pig	18,000 ppm (63,000 mg/m^3)	8 h/d contin. or intermitt. for up to 42 h	Some deaths, irritation of eyes and nose, hemorrhage in lungs, congestion of liver and kidneys	Shea, 1939
Rat, M	80 mg/m^3	4 h/d, for 2, 4, or 8 d	Hypersecretion by thyroid cells, greater accumulation of I-131 by thyroid	Grodetskaya and Karamzina, 1973
Rabbit, Guinea pig	Nondiluted, not neutralized; or diluted aqueous soln nondiluted, neutralized	1-13 daily applications to shaven skin	Skin burns, necrosis, inflamed edematous derma, congestion of liver and spleen, fatty degeneration and necrosis of liver, renal tubular necrosis, death	Shea, 1939
	Nondiluted, neutralized	30 daily applications to shaven skin	Thickening of derma	

Table 3. (continued)

Species	Dose/Concentration	Duration	Effects	Reference
Rabbit	250 ppm	6 h/d, 31 d	300% increase in lung macrophage α-mannosidase, acid phosphatase, and β-N-acetylglucosaminidase activity; decreased binding of lectins to macrophages after exposure; most changes were not detectable 48 h after exposure	Tombropoulos et al.,1979
Rat	8 mg/m^3	4 h/d, 5 d/wk, 4 mo	Nervous system activity increased through 1st month, hypotension and leukopenia by 2nd month; size of lymph nodes of spleen decreased (no longer detectable 1 mo after exposure terminated)	Migukina, 1973
Guinea pig	8 mg/m^3	4 h/d, 5 d/wk, 4 mo	Same splenic lymph node changes as in rat	Migukina, 1973

Table 3. (continued)

Species	Dose/Concentration	Duration	Effects	Reference
Rat	70 mg/m^3	4h/d, 5d/w, 4 mo	Transient increase in nervous system activity, hypertension followed by hypotension by 2nd month; increase in hemoglobin and erythrocyte count and decrease in leukocyte count at 1st and 4th months; no detectable changes in ECG or function of liver, kidneys or testes; alveolar swelling and atrophy of respiratory lymphatics and splenic lymphoid elements (even in animals 1 mo after exposure terminated); number of chromosomal aberrations due to fragmentation increased	Migukina, 1973
Guinea pig	70 mg/m^3	4 h/d, 5 d/wk, 4 mo	Transient increase in nervous system activity; decrease in hemoglobin and leukocyte count; alveolar swelling and atrophy of respiratory lymphatics and splenic lymphoid elements (even 1 mo after exposure ended)	Migukina, 1973

[a]Except where otherwise noted, exposure is by inhalation.
[b]NG = not given.

Table 4. DIETARY CONCENTRATIONS OF COMPOUNDS GIVEN TO RATS AND HAMSTERS AND INCIDENCES OF CANCER[a]

Dietary Concentration, ppm				Incidence of Cancer, %					
				Rat				Hamster	
Test Group	Sodium Nitrite	Morpholine	N-Nitroso-morpholine	Number of Animals[b]	Liver Cell Cancer	Liver Angio-cancer	Lung Angio-sarcoma	Number of Animals	Liver Cell Cancer
1	0	0	0	156	0	0	0	23	4
2	1,000	0	0	96	1	0	0	30	0
3	0	1,000	0	104	3	0	2	22	0
4	1,000	1,000	0	159	97	14	23	16	31
5	1,000	50	0	117	59	5	6	32	0
6	1,000	5	0	154	28	12	8	40	0
7	50	1,000	0	109	3	2	1	22	0
8	5	1,000	0	172	1	2	1	19	0
9	50	50	0	152	2	1	1	30	0
10	5	5	0	125	1	2	2	40	0
11	0	0	5	128	58	15	9	35	0
12	0	0	50	94	93	21	20	18	6

[a]Adapted from Shank and Newberne, 1976.
[b]F_1 and F_2 generations combined.

Table 5. BACKGROUND INFORMATION ON DEAE

CAS No.:	100-37-8
Synonyms:	β-Diethylaminoethyl alcohol; 2-hydroxytriethylamine; N,N-diethylethanolamine; 2-(diethylamino)-ethanol
Molecular formula:	$C_6H_{15}NO$
Molecular weight:	117.19
Specific gravity:	0.88 @ 25°C
Boiling point:	163°C
Vapor pressure:	1 mm Hg @ 20°C
Flammable Limits in Air:	6.7 to 11.7%
Solubility:	Water, infinite Alcohol, soluble Ether, soluble Acetone, soluble Benzene, soluble

Table 6. ACUTE TOXICITY OF DEAE

Route	Animal	LD_{50}, mg/kg	Reference
Oral	Rat	1,300[a]	Smyth and Carpenter, 1944
Oral	Rat	5,600[b]	Cornish, 1965
Intraperitoneal	Rat	1,220	Lewis and Tatken, 1982
Intraperitoneal	Mouse	308	Lewis and Tatken, 1982
Subcutaneous	Mouse	1,561	Lewis and Tatken, 1982
Intravenous	Mouse	188	Lewis and Tatken, 1982
Intramuscular	Mouse	416	Lewis and Tatken, 1982
Skin	Rabbit	1,260	ACGIH, 1980
Skin	Guinea pig	1,000	Smyth and Carpenter, 1944

[a] Nonneutralized.
[b] Neutralized.

Table 7. ANALYSIS OF STEAM CONDENSATES FROM HOSPITAL DISTRIBUTION SYSTEMS[a]

Hospital No. 1 (DEAE added as single daily dose)		Hospital No. 3 (DEAE continuously metered into the system)	
Sampling Time	DEAE, mg/L	Sampling Time	DEAE, mg/L
3:45 p.m.[b]	6.8	9:15 a.m.	4.6
4:15 p.m.[c]	2,090.0	10:00 a.m.	5.2
8:00 a.m.	198.4	11:00 a.m.	4.5
9:00 a.m.	97.2	12:00 noon	4.2
10:00 a.m.	106.0	1:00 p.m.	4.0
11:00 a.m.	72.2	3:00 p.m.	4.5
12:00 noon	58.7	4:00 p.m.	3.4
3:30 p.m.[c]	15.2	5:00 p.m.	3.6
4:15 p.m.	310.0	7:00 p.m.	4.0

[a] Adapted from Malaiyandi et al., 1979.
[b] Pretreatment.
[c] 30 min after treatment.

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BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

Richard R. Bates is Senior Staff Scientist, Health Effects Institute, Cambridge, Massachusetts. Dr. Bates received an M.D. in 1958 from McGill University. He has previously served as Associate Commissioner of Science, Food and Drug Administration, and Assistant to the Director for Risk Assessment, National Institute for Environmental Health Sciences. Dr. Bates is a member of the American Association of Pathologists, American Association for Cancer Research, and Society of Toxicology. His research has focused on clinical carcinogenesis and toxicology and he is an expert in risk assessment and experimental pathology.

Donald J. Ecobichon is a Professor of Pharmacology at McGill University, Montreal, Quebec. He received a B.Sc.Phm. in 1960, M.A. in 1962, and Ph.D. in pharmacology in 1964 from the University of Toronto. Dr. Ecobichon's research has focused on the toxicology of chlorinated hydrocarbons and organophosphorus insecticides and drug hydrolysis by tissue esterases of various mammalian species. Dr. Ecobichon's professional affiliations include the Society of Toxicology, Pharmacology Society of Canada, and New York Academy of Sciences.

David W. Gaylor is Director of the Division of Biometry of the National Center for Toxicological Research, Jefferson, Arkansas. He received a B.S. in 1951 and M.S. in 1953 from Iowa State University and a Ph.D. in statistics in 1960 from North Carolina State University. He holds a concurrent position as Adjunct Professor at the University of Arkansas Medical School. Dr. Gaylor is a Fellow of the American Statistical Association and a member of the Biometry Society. He is an expert in statistical design and analysis of experiments and in biostatistics.

Peter Greenwald is Director of Resources, Centers, and Community Activities of the National Cancer Institute, Bethesda, Maryland, and Editor-in-Chief of the Journal of the National Cancer Institute. He received his M.D. in 1961 from the State University of New York at Syracuse and an M.P.H. in 1967 and D.P.H. in 1974 from Harvard University. Dr. Greenwald is board certified in internal medicine and preventive medicine. He previously served as Director of Cancer Control and of Epidemiology for the New York State Department of Health. He currently chairs the Epidemiology Section of the American Public Health Association, is on the Board of Directors of the American College of Epidemiology, and is on the Food and Nutrition Board of the National Academy of Sciences/National Research Council. Dr. Greenwald is an expert in the field of cancer prevention and control.

Leonard T. Kurland is Professor of Epidemiology at Mayo Graduate School of Medicine and Chairman of the Department of Epidemiology and Medical Statistics at Mayo Clinic, Rochester, Minnesota. He received a B.A. in 1942 and Dr.P.H. in 1951 from The Johns Hopkins University, M.D. from the University of Maryland in 1945, M.P.H.

from Harvard University in 1948, and completed a Fellowship in Neurology at Mayo Clinic in 1955. Dr. Kurland is a past president of the American Epidemiological Society and a member of the Armed Forces Epidemiology Board. Other professional affiliations include the American Neurological Association and American Society of Human Genetics. He is an expert in medical record systems and the epidemiology of neurological diseases and cancer.

Howard I. Maibach is Professor of Dermatology at the University of California School of Medicine, San Francisco. He received his A.B. in 1950 and M.D. in 1955 from Tulane University. Dr. Maibach is a diplomate of the American Board of Dermatology. Among his affiliations are the Society of Investigative Dermatology, American Academy of Dermatology, and the American Federation of Clinical Research. Dr. Maibach is an expert on the biologic effects of chemicals from dermal exposure.

Roger O. McClellan is Director and Toxicologist of the Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. Dr. McClellan received his D.V.M. in 1960 from Washington State University, is a diplomate of the American Board of Veterinary Toxicology, and is certified by the American Board of Toxicology. Dr. McClellan is an expert in the metabolism and toxicity of inhaled materials, especially materials released from the use of different energy technologies. He has served on numerous government committees dealing with radiation protection and environmental health including the Department of Energy, Environmental Protection Agency, and National Institutes of Health. Dr. McClellan's professional affiliations include the Society of Toxicology, American College of Veterinary Toxicology, Radiation Research Society, Health Physics Society, and Society of Risk Analysis.

Robert E. Menzer is Professor of Entomology, Director of the Water Resources Research Center, and Chairman of the Graduate Program in Marine-Estuarine Environmental Sciences at the University of Maryland, College Park. He received his B.S. in 1960 from the University of Pennsylvania and Ph.D. in entomology in 1964 from the University of Wisconsin. He is a member of the Society of Toxicology, Entomological Society of America, and American Chemical Society. Dr. Menzer's research has focused on pesticide chemistry and toxicology with emphasis on the metabolism of organophosphorus insecticides.

Ronald C. Shank is Professor of Toxicology and Director of the Program on Environmental Toxicology at the University of California at Irvine. Dr. Shank received an Sc.B. in 1959, an Sc.M. in 1961, and a Ph.D. in nutrition and biochemistry in 1964 from MIT. Dr. Shank has previously served as Director of the MIT Mycotoxin Research Project in Southeast Asia. Dr. Shank's research has been devoted to studying the alkylation of nucleic acids and proteins from exposure to toxic substances and the toxicology of food-borne substances. He is a member of the Society of Toxicology.

Edward A. Smuckler is Professor and Chairman of the Department of Pathology at the University of California School of Medicine, San Francisco. He received his A.B. in 1952 from Dartmouth College, an M.D. in 1956 from Tufts University, and his Ph.D. in pathology in 1963 from the University of Washington. He is a member of the American Association of Pathologists, American Society of Biological Chemists, Federation of the American Society for Experimental Biology, and Society of Toxicology. He is an expert in cellular alterations as a result exposure to toxic substances, with emphasis on the liver cell. Dr. Smuckler has served as a consultant to numerous state/federal governmental advisory committees on matters related to environmental health.

Robert Snyder is Professor and Chairman of the Department of Pharmacology at Rutgers University School of Pharmacy and Director of the Toxicology Program at Rutgers University, Piscataway, New Jersey. He received a B.S. in 1957 from Queens College and a Ph.D. in biochemistry in 1961 from the State University of New York. Dr. Snyder's affiliations include the New York Academy of Sciences, American Society of Pharmacology and Experimental Therapeutics, and Society of Toxicology. His research has been devoted to drug metabolism and the relationship of metabolism of xenobiotics to toxicologic activity.

Ronald J. Spanggord is Director, Bio-Analytical Chemistry Program, SRI International, Menlo Park, California. He received a B.S. in 1965 from San Francisco State College and a Ph.D. in chemistry in 1971 from the University of Arizona. Dr. Spanggord is a member of the American Chemical Society and Alpha Chi Sigma. He is an expert in qualitative and quantitative analysis of organic compounds in water, soil, and biological systems; biological and chemical mechanisms of organic compound transformations; and chromatographic and spectroscopic methods of analysis.

Peter Spencer is Associate Professor of Neurosciences and Pathology and Director of the Institute of Neurotoxicology at Albert Einstein College of Medicine, Bronx, New York. He received a B.S. and Ph.D. in medicine from the University of London. He is a recipient of the Joseph P. Kennedy, Jr. Fellowship in the Neurosiences and has been inducted into membership of the Royal College of Pathologists, U.K.. His research has been devoted to effects in the nervous system of exposure to toxic substances and the study of nerve fiber development, degeneration, and regeneration. Dr. Spencer is a member of various professional societies including the American Society of Cell Biology, American Association of Neuropathologists, Society of Neuroscience, and Society of Toxicology.

Lloyd B. Tepper is Corporate Medical Director, Air Products and Chemicals, Inc., Allentown, Pennsylvania. He received an A.B. in 1954 from Dartmouth College and an M.D in 1957 and Sc.D. in occupational medicine in 1962 from Harvard University. Dr. Tepper previously served as Associate Commissioner of Science for the

Food and Drug Administration. He is a Fellow and past President of the American Academy of Occupational Medicine, Adjunct Professor of Environmental Medicine at the University of Pennsylvania, and Editor of the Journal of Occupational Medicine. Dr. Tepper's research has focused on industrial and environmental toxicology and environmental and medical standards.

Clarence J. Terhaar is Supervisor of Toxicology, Eastman Kodak Company, Rochester, New York. Dr. Terhaar received a B.S. in 1953 from the University of Idaho and a Ph.D. in parasitology in 1957 from Kansas State College. He is a Diplomate of the American Board of Toxicology and a member of the Society of Toxicology, Entomological Society of America, and American Society of Pharmacology and Experimental Therapeutics. Dr. Terhaar's research has focused on invertebrate and mammalian toxicology.