

## ENVIRONMENTAL PROTECTION AGENCY

[OPTS-42032 TSH-FPL 2348-4]

### Formamide; Response to the Interagency Testing Committee

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

**SUMMARY:** The Tenth Report of the Interagency Testing Committee (ITC) designated the chemical formamide for health effects testing consideration. Subsequent to the designation, BASF Wyandotte Corporation, the sole importer of formamide, presented to EPA plans for subchronic effects testing of formamide. In addition, the National Toxicology Program (NTP) initiated a testing program to define formamide's genotoxic potential. The Agency has concluded that these combined programs are sufficient to evaluate chronic effects, other than oncogenicity, and genotoxic effects, as recommended for testing by the ITC. Further, the Agency believes that oncogenicity testing recommended by the ITC is not warranted based on the available data. Consequently, the EPA is not initiating rulemaking under section 4(a) of the Toxic Substances Control Act (TSCA) to require additional health effects testing of formamide. This notice constitutes the Agency's response to the ITC's designation of formamide, as mandated by section 4(e) of TSCA.

**DATE:** Interested persons are invited to comment on this proposed decision. All comments should be submitted on or before July 7, 1983.

**ADDRESS:** Written comments should bear the document control number [OPTS-42032] and should be submitted in triplicate to: TSCA Public Information Officer (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Room E-108, 401 M St. SW., Washington, D.C. 20460.

**FOR FURTHER INFORMATION CONTACT:** Jack P. McCarthy, Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-511, Washington, D.C. 20460, Toll Free: (800-424-9065), In Washington, D.C.: (554-1404), Outside the USA: (Operator 202-554-1404).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Section 4(a) (Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*) of the Toxic Substances Control Act (TSCA) authorizes EPA to promulgate regulations which require manufacturers

and processors to test chemical substances and mixtures. Data developed through these test programs are used by EPA to determine the risks that these chemicals may present to health and the environment. Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for the promulgation of testing rules under section 4(a) of the Act. The ITC may designate up to 50 of its recommendations at any one time for priority consideration by EPA. EPA is required to respond within 12 months of the date of designation, either by initiating rulemaking under section 4(a) or publishing in the Federal Register reasons for not doing so.

On May 10, 1982, the ITC forwarded to EPA its Tenth Report which designated formamide for priority consideration by EPA (Ref. 29). It recommended that formamide be considered for testing for genotoxic effects, carcinogenicity, and other chronic effects. The reasons for the ITC's recommendations were: (1) The presumed high worker exposure resulting from formamide's widespread use as a solvent and chemical intermediate, (2) insufficient data to determine its genotoxic potential, (3) observed teratogenic effects in laboratory animals, and (4) the lack of data on chronic and carcinogenic effects.

Subsequent to the ITC Report, BASF Wyandotte Corporation, the sole importer of formamide, submitted to EPA market information, industrial and consumer use descriptions, and health effects data (Refs. 3, 4, 5, 7 thru 15). EPA also considered the data reported by BASF under TSCA section 8(a) which includes importation volume, use, exposure, and release information. EPA has used these data, in conjunction with other information, to reach its decision not to initiate rulemaking on formamide under section 4(a).

#### II. Assessment of Exposure and Health Effects

##### A. Production, Use, and Exposure

Formamide (CAS No. 75-12-7), or methanamide, is a clear, viscous, hygroscopic liquid with low volatility and a faint ammonia-like odor. Production of formamide in the United States ceased in 1979 (Ref. 22). BASF Wyandotte Corporation, Wyandotte, Michigan, imports formamide in volumes between 1 and 11 million pounds per year from BASF Aktiengesellschaft (Federal Republic of Germany) (Ref. 3).

About 82 percent of the imported formamide is used as a chemical intermediate, primarily by the pharmaceutical industry, in the production of antibacterial, antiviral, and antiulcer drugs for human and animal health (Ref. 22). About 1.0 percent of the formamide imported from Germany is exported to countries outside the United States (Ref. 3). The major TSCA use of formamide (13 percent) is in petroleum production, where it acts as a carrier for the corrosion inhibiting additives pumped into wells during drilling operations. In this capacity, formamide is expected to be quickly hydrolyzed because of the high temperature, high pressure, and low pH conditions of the well (Ref. 3 and 4). Other non-consumptive TSCA uses include soil stabilization (1.0 percent), polymerization (0.5 percent), laboratory (1.0 percent), and ink solvent (1.5 percent) uses (Ref. 3). Consumer products containing formamide as a result of its use as an ink solvent include a number of porous-tip writing instruments (fiber, plastic, and felt-tip pens and markers) (Ref. 5).

The National Occupational Hazard Survey conducted between 1972 and 1974 by the National Institute for Occupational Safety and Health (NIOSH) estimated that 8,516 workers in 1,010 plants or businesses were exposed to formamide (Ref. 25). This exposure estimate was cited by the ITC as the number of workers exposed to formamide (Ref. 29). However, these numbers reflect worker exposure when formamide was still being produced in the United States. Since over 50 percent of the workers included in the survey were employed in plants producing either the chemical or allied products, EPA has concluded that the NIOSH figure cited by the ITC substantially overstates the number of workers currently being exposed to formamide.

BASF Wyandotte, using data from a customer survey, estimates that about 400 workers are currently being exposed to formamide (Ref. 4). A representative sample of BASF's large and small customers from every market segment was interviewed to determine their handling procedures and the number of potentially exposed workers. The following is excerpted from that survey. When formamide is used as a chemical intermediate or polymerization solvent the reactions take place in enclosed systems resulting in low worker exposure. Points of potential exposure appear to occur on an intermittent basis from loading, mixing or drumming operations. Formamide's use in oil production would also result in low

worker exposure due to controlled use conditions. In this process drummed formamide is pumped into closed mixing tanks and combined with other additives. The drummed additive package is injected into the well by pumping. Exposure in the production area and at the wells occurs on an intermittent basis. Potential for exposure to formamide from its use as a solvent in water soluble inks occurs both in the formulation of the ink and in the loading of the ink into the writing instrument. The larger manufacturers of these instruments use automated equipment which approach enclosed systems. In less automated equipment, some inhalation of formamide could occur, although dermal exposure to the inks is expected to be minimal. One percent of the imported volume of formamide is used as a laboratory chemical for end uses in life science research. BASF's customers indicated that hazard warnings are clearly indicated on their bottles. In addition, BASF reported that company labels advise the use of protective equipment, such as gloves, respirators, and goggles. A special warning to pregnant workers to avoid contact with formamide unless adequate precautions are observed to minimize exposure is also given.

Based on the above information, EPA believes that the number of workers exposed to formamide is not substantial. Although no data on the levels of exposure in any of the industries using formamide was submitted, EPA has no evidence which might suggest that the levels of exposure are significant given the use of proper protective equipment recommended on existing labels.

Consumer exposure to formamide may result from its use in water soluble ink formulations. Formamide is used in about 4.0 percent of the pens used in the United States, or 130 million pens (Ref. 3). However, a substantial percentage of these pens are for high performance industrial uses, such as high speed computer plotter pens, which would result in very little opportunity for human exposures (Ref. 4). It is difficult to characterize the uses of the remainder of pens containing formamide. Because of its characteristic quick absorption to paper, resistance to smearing, and added expense, EPA would expect that it is generally used in finer point pens, not the marker pens often used by children (Ref. 4).

Several factors tend to minimize the potential for exposure to persons writing with pens containing formamide.

Formamide's low vapor pressure and surface tension tend to reduce the possibility of inhalation. Thus, the only

significant potential route of exposure would be from skin contact with wet ink. Because formamide is rapidly absorbed in the fiber of the paper through a wicking action, smearing is prevented. As a result, once the ink is applied to paper, there would be no opportunity for dermal exposures. EPA recognizes that a person may from time to time get a small amount of ink on his hands from accidental contact with the tip of a pen. However, the amount of ink that would be applied to an entire written page would contain only 1 milligram of formamide (Ref. 5). EPA believes that the amount of ink which a person would generally place on the hands accidentally would be a very small percentage of that which would be applied to a page of writing. In addition, the construction of these porous-tip devices usually is such that the ink is held within the device and will emerge only through the porous tip. Thus, under reasonably foreseeable conditions, including abuse by children, the ink should stay in the device. Devices of similar construction and limited ink capacity are exempt from the special labeling requirements normally necessary for hazardous substances under the Federal Hazardous Substances Act as administered by the Consumer Product Safety Commission (40 CFR 1500.83).

Worst case exposure estimates using a child as a model were submitted to EPA by BASF (Ref. 5). Calculations for the ink application exposures were based on a total formulation loading of 1.5 gm for a pen; 6.0 gm for a marker; and an average formamide concentration of 20 percent. Oral exposure to a 20 kg child who ingested the entire ink contents from a porous-tip pen or marker would be 0.3 gm (.015 g/kg) and 1.2 gm (.06 g/kg), respectively. If a child painted the central surface of both hands with ink from a broad-tip marker, assuming 100 percent absorption of formamide, the dermal exposure would be about 0.1 mg/kg. Both the oral and dermal exposure values are well below the reported values for acute toxicity (Oral LD<sub>50</sub> Mouse 3.2 g/kg; Dermal LD<sub>50</sub> Rat 6.0 g/kg). Considering the physical-chemical properties of formamide and the construction of the porous-tip device, which acts to hold the ink in the pen, EPA believes the use of these products would not result in substantial exposure.

Based on the above information, EPA has concluded that although a large number of consumers may use writing instruments containing formamide, the levels of individual exposure are likely to be extremely low. EPA does not

believe that this exposure should be considered substantial or significant as those terms are used in section 4 of TSCA.

## B. Health Effects Data

Formamide and its vapors can cause moderate irritation to the skin, eyes, and mucous membranes (Ref. 7). The acute toxicity of formamide to laboratory animals is in the slight to moderate range. Oral LD<sub>50</sub> values range from 3.2 g/kg in the mouse to 7.5 g/kg in the rat (Refs. 32, 17). Dermal LD<sub>50</sub> values are reported to be as high as 17 g/kg in the rabbit; the lowest lethal dermal dose for this species is 6.0 g/kg (Refs. 16, 28).

Formamide has not demonstrated a mutagenic response in *in vitro* assays. Limited studies performed to date using bacterial, yeast, and cell culture systems show that formamide exhibits a slight degree of cellular toxicity but not a mutagenic response. When tested for use as a vehicle in the *Salmonella* mutagenicity test formamide was nontoxic and nonmutagenic in concentrations up to 200 micrograms per plate but was toxic to the bacteria at 500 micrograms per plate (Ref. 23). No indication of mutagenicity was seen using strains TA-68, TA-100, TA-1535, and TA-1537 (+S9) using the *Salmonella* assay (Ref. 30). Formamide's effect on cell survival was studied in yeast and mammalian cells (Ref. 1). Relatively low toxicity was reported in *Schizosaccharomyces pombe* and V79 lines of Chinese hamster cells; however, no data on the mutagenic activity of formamide was reported in this study (Ref. 1). Negative results were also observed in a dominant lethal assay on formamide, and on a series of structurally related amides (Refs. 9, 27). No mutagenic effects were demonstrated after single intraperitoneal applications ( $\frac{1}{2}$  LD<sub>50</sub>) to NMRI mice of formamide, acetamide and their mono- and dimethyl- derivatives.

Formamide was without effect in a cell transformation test of carcinogenic potential using rat embryo cells infected with Rausher leukemia virus (Ref. 19). Concentrations ranged from 0.001 to 100 mg/ml. In the same test, acetamide, a structural analogue, which is a weak hepatocarcinogen in rats, gave variable results with transformation induced in two out of five trials. The authors postulated that the variable results seen with acetamide in this test may be consistent with *in vivo* studies of this agent where large doses and extended periods were needed to induce a response (Ref. 19).

The teratogenic effects of formamide have been studied following administration by the dermal, oral, and intraperitoneal routes (Refs. 10 thru 15, 20). Dose-dependent embryotoxic and/or teratogenic effects have been observed in rats, mice, and rabbits (Refs. 10, 13, 14, 15, and 24). These studies indicate that formamide is embryotoxic and teratogenic in animals, but the effective doses appear to vary widely depending on the route of exposure, species, strain, time of application, and the methods used to identify teratogenic effects.

Very little is known about the chronic effects of formamide. The Agency received one study showing that repeated doses of formamide administered by gavage to rats 5 days per week for 4 weeks resulted in dose-dependent cumulative effects expressed as gastritis and erosion of the gastric mucosa, probably related to the release of formic acid (and ammonia) by stomach acid (Ref. 8). The no-observed-effect level reported in the study was 34 mg/kg. While this study cannot be used to predict the likely chronic effects of formamide, it does demonstrate the limitations of the oral route of exposure for testing formamide. The Agency could find no data to predict the potential chronic effects of formamide resulting from dermal exposure, the most common route of human exposure.

EPA is aware of no bioassays performed to assess the carcinogenic potential of formamide. However, there are no data which indicated any potential for oncogenic effects.

### III. Ongoing Testing

The National Toxicology Program is currently screening formamide for its potential genetic toxicity. Measurement of potential gene mutation in somatic cells (Ames test) and germinal cells (*Drosophila*) has been initiated. Testing commenced in August, 1982, with the Ames Test and is scheduled for completion in April, 1983. A program review of the data by the NTP staff will then be made before further testing is initiated. Cytogenetic testing on formamide is not planned at this time.

### IV. Planned Testing

BASF Wyandotte Corporation presented a testing proposal to EPA designed to characterize the potential subchronic effects of formamide. The BAPF proposal consists of a range-finding study followed by a 90-day subchronic study. Because dermal exposure is the most common route of human exposure the program is designed to clarify the doses at which formamide causes toxic effects after

repeated exposure to intact skin over a prolonged period (Ref. 6). The study will be conducted according to the Organization for Economic Cooperation and Development Subchronic Dermal Toxicity Guideline No. 411 (Ref. 28). The study will be performed in male and female Wistar rats, using dermal exposure for 6 hours/day and 5 days/week. The protocols for these studies have been reviewed by EPA scientists and appear to be acceptable. They are also available for examination in the public record of this proceeding.

Industry has agreed to begin the range-finding study on or about October 1, 1983. A program review by BASF and EPA personnel will occur after the range finding study is complete to review the data and select doses for the subchronic study. The subchronic phase of testing can be expected to be completed by early 1984. The subchronic testing, including histopathology, will be completed in 6-8 months, i.e., late 1984. An additional three months will be required for preparation of the study report and consultation among BASF and EPA scientists. The final report would be completed in early 1985.

BASF Wyandotte has furnished EPA with the name and address of the laboratory conducting the tests under this agreement. BASF has also agreed to adhere to the Good Laboratory Practice Standards issued by the U.S. Food and Drug Administration as published in the Federal Register of December 22, 1978 (43 FR 59986). BASF has agreed to permit laboratory inspections and study audits in accordance with the provisions outlined in TSCA section 11 at the request of authorized representatives of the EPA for the purpose of determining compliance with this agreement. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations and evaluations thereof, and that the studies are being conducted according to Good Laboratory Practice provisions.

BASF has further agreed that all raw data, documentation, records, protocols, specimens, and reports generated as a result of each study will be retained for at least 10 years from the date of publication of the acceptance of any protocols by EPA and made available during an inspection or submitted to EPA if requested by EPA or its designated representative. BASF understands that the Agency plans to publish quarterly in the Federal Register a notice of the receipt of any test data submitted under this agreement. Subject to TSCA section 14, the notice will

provide information similar to that described in TSCA section 4(d). Except as otherwise provided in TSCA section 14, any data submitted will be made available by EPA for examination by any person.

Finally, BASF understands that failure to conduct the testing according to the specified protocols and failure to follow Good Laboratory Practices procedures may invalidate the tests. In such cases, a data-gap may still exist, and the Agency may decide to require further testing.

### V. Decision Not To Initiate Rulemaking

EPA believes that the testing program proposed by BASF Wyandotte will provide sufficient data to reasonably predict the potential chronic effects of formamide. EPA has concluded that there is not a sufficient basis to require carcinogenicity testing of formamide under section 4 of TSCA at this time or to require additional genotoxicity testing of formamide beyond that being conducted by the NTP. For these reasons, EPA has decided not to initiate rulemaking under section 4(a) of TSCA to require testing of formamide. EPA's specific responses to the recommendations of the ITC are discussed below.

1. *Genotoxicity.* EPA has concluded not to propose to require any further genotoxicity testing for formamide. This decision is based on the fact that the testing being conducted by the NTP, in conjunction with existing genotoxic data, is expected to provide sufficient data to reasonably predict the genotoxic potential of formamide.

EPA recognizes that gene mutation is only one aspect of mutagenicity, and that the existing data and data from tests currently underway will not provide sufficient data to predict formamide's potential to induce chromosomal damage. However, EPA has concluded that there is not a sufficient basis to require such testing under section 4 of TSCA. The number of workers exposed to formamide is not substantial, and EPA has no reason to believe that the levels of exposure are significant. Although a large number of consumers may be potentially exposed to formamide in ink pens, EPA has concluded that this does not constitute "substantial human exposure" as those terms are used in section 4, because information about the use and design of the products indicates that even when exposure occurs, levels are extremely low. In addition, there are no data indicating that formamide is likely to cause chromosomal damage or any other mutagenic effect, and thus there is no basis for EPA to find that formamide

may present a risk from mutagenic effects.

2. **Carcinogenicity.** EPA has concluded that there is no basis for proposing testing for carcinogenicity at this time. As discussed above, the evidence indicates that there is neither significant nor substantial human exposure to formamide as those terms are used in section 4. EPA has also concluded that the existing data do not support a finding that formamide "may present an unreasonable risk" of carcinogenicity. Formamide has given consistently negative results in *in vitro* tests used to predict mutagenicity and carcinogenicity. Additionally, there were not other data indicating that formamide has potential carcinogenic activity.

EPA recognizes that acetamide, a structural analogue of formamide, is a carcinogen. In some cases this may be sufficient basis to require that a bioassay be conducted. However, as discussed below, EPA believes that based on the negative mutagenicity data for formamide and the uniqueness of acetamide's carcinogenic response in animals, a risk finding for the carcinogenicity of formamide cannot be made at this time.

Based on the available data, EPA believes that acetamide is not a valid indicator of the potential carcinogenicity of formamide. Formamide belongs to a series of compounds which include the amides of simple carboxylic acids, their N,N-dialkyl derivatives, and related compounds. Weak carcinogenic activity of acetamide, one member of this series, has been reported in rodents in a number of studies (Refs. 18, 21, 31). However, a recent review of the literature on acetamide and structurally related amides indicates that acetamide is unique in this amide series (Ref. 2). Despite its well established hepatocarcinogenic activity, acetamide is not mutagenic *in vitro* in various test systems (Ref. 2). Furthermore, in a cell transformation assay using rat embryo cells, acetamide induced transformation in two out of five trials, whereas the results for formamide were clearly negative (Ref. 19). As noted in section II B, acetamide required high doses (2.5-5.0 percent of the diet) over most of the animals' life span to induce liver tumors in rodents (Refs. 18, 21, 31). This fact has led a number of investigators to postulate reasons for the unique effects seen in rodent liver from high doses of acetamide; including *in situ* liberation of ammonia, interaction with latent viruses or hormones, or the alteration of cell membranes (Refs. 2, 18, 31). EPA has no reason to believe that formamide, even

at the high doses used in the acetamide bioassays, would induce cancer. Other structurally related amides, such as dimethylformamide and dimethylacetamide, have also failed to demonstrate any carcinogenic activity in a variety of animal studies (Ref. 2). In another series of screening tests of structurally related amides conducted by the NCI, only acetamide induced significant compound-related tumors (Ref. 18). Therefore, EPA has concluded that the acetamide data are insufficient to predict that formamide may present an unreasonable risk from oncogenic effects. Accordingly, EPA finds no current basis to require oncogenicity testing.

3. **Chronic Effects.** EPA has decided not to initiate a rulemaking to require chronic effects testing of formamide at this time because the Agency believes that the 90-day subchronic study to be conducted by BASF is likely to provide sufficient data to reasonably predict the potential of formamide to cause chronic health effects. EPA generally will accept, for purposes of section 4, a well conducted 90-day subchronic study as providing sufficient data to reasonably predict the chronic risks of a chemical other than oncogenicity. The protocols submitted by BASF have been reviewed by the Agency and appear to be acceptable.

Because of the expectation that the data received from the testing already undertaken by the NTP and committed to by BASF Wyandotte will be provided more expeditiously than would be possible under a test rule, EPA has tentatively concluded not to initiate rulemaking to require testing at this time. EPA's conclusion that the test data to be provided will serve to reasonably determine or predict chronic effects is reinforced by the provision for inspection to verify that the testing is being properly conducted by BASF. In addition, the data developed by BASF will be available to the public on a similar basis as the results of a test rule.

EPA is soliciting comments on the BASF Wyandotte's program and the Agency's decision to accept it and the NTP program in lieu of section 4(a) rulemaking at this time. After considering these comments, EPA will either publish in the Federal Register a final notice of acceptance of a negotiated test program or will initiate rulemaking under section 4(a) of TSCA.

#### VI. References

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VII. Public Record

The EPA has established a public record of this testing decision (docket number OPTS-42032). This record includes:

- (1) Federal Register notice designating formamide to the priority list.
- (2) Communications before industry testing proposal consisting of letters, contact reports of telephone conversation, and meeting summaries.
- (3) Testing proposals and protocols.
- (4) Published and unpublished data.
- (5) Federal Register notice requesting comment on the negotiated testing proposal and comments received in response thereto.

The record, containing the basic information considered by the Agency in developing the decision, is available for inspection in the OPTS Reading Room from 8:00 a.m. to 4:00 p.m., Monday through Friday, except legal holidays, in Rm. E-107, 401 M St., SW., Washington, D.C. 20460. The Agency will supplement this record periodically with additional relevant information received.

(Sec. 4, 90 Stat. 2003; (15 U.S.C. 2601))

Dated: May 10, 1983.

Lee L. Verstandig,  
Acting Administrator.

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