



74I-0794-001172

Texaco Chemical Company PO Box 430  
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March 1, 1989



FYI-94-001172  
INIT 07/14/94

Contains No. 001

Ms. Roberta Wedge  
Dynamac Corporation  
11140 Rockville Pike  
Rockville, MD 20852



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Dear Ms. Wedge:

Thank you for your letter of February 23, 1989 and the accompanying information on morpholine.

Texaco has not conducted reproductive or developmental toxicity studies on morpholine. Rather, our emphasis has been on carcinogenesis since this was the basis of the concern by the Food & Drug Administration several years ago. Our study is described in the Dynamac "Information Review-Morpholine" (October 14, 1988) under Section F. CHRONIC (LONG TERM) EFFECTS, p.34.

Your 2/23/89 letter stated that Texaco "will be submitting the data to EPA as an 8(e) submission." Actually, this has already been done and is referenced in your list of references under "Texaco".

Although I do not yet have a copy of the journal publication of our two-year study, it should be available almost any day. It was accepted for publication back in the fall of 1988 by Fundamental and Applied Toxicology. I am enclosing a copy of an "Executive Summary" of this study which we have used as an interim summary of this work.

I am also enclosing a copy of a document which Texaco contributed to the deliberative process of the IARC Working Group Meetings in October 1988. The emphasis here was also on carcinogenesis and there may be some references not included in the Dynamac document. The conclusions by IARC were that there is "inadequate evidence" for carcinogenesis in animals and humans and that morpholine is "not classifiable as to its carcinogenicity to humans (Group 3)."

One last point which I would like to make is with reference to the statement in the Dynamac Information Review on page 30 concerning Texaco's recommendation that morpholine not be used in food-related

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applications. This recommendation was made in July 1980 prior to the outcome of the two-year study. In a January 10, 1985 letter (copy enclosed), Texaco lifted this voluntary moratorium as a result of the favorable outcome of our chronic studies.

If you can pass any of this information on the ITC and you feel that it may assist in their evaluations, please do so. Thank you for your considerations.

Sincerely,



F. E. Bentley, Ph.D.  
Sr. Coordinator Product Safety

FEB:mc  
01/02

Encs.



Texaco Chemical Company PO Box 430  
Bellaire TX 77401  
713 666 8000

January 10, 1985

Dear Morpholine User:

In July, 1980 Texaco Chemical Company recommended that morpholine not be used in FDA-approved food contact applications including boiler water treatment pending the completion of chronic toxicological testing by Texaco. In May 1983 a status letter was issued which reported the encouraging nature of the 12-month interim data.

We are pleased to report that the study has been completed and the conclusion is that morpholine is not carcinogenic in laboratory animals and therefore not likely to be so in humans. This major two-year inhalation study, conducted for Texaco at a leading contract toxicological laboratory, provides a solid basis for assuring the safety of morpholine. Portions of the study have already been published in scientific journals and the final results will also be submitted for publication. Appropriate Federal agencies will be informed. Meanwhile, Texaco Chemical Company has concluded that the favorable outcome of this study justifies lifting the voluntary 1980 moratorium on food contact applications of morpholine.

We want to reemphasize our precaution against mixing amines, including morpholine, with nitrites. It is well recognized that such combinations can lead to the formation of cancer-causing nitrosamines. For example, the EPA has recently issued a chemical advisory on the potential risk of nitrosamines in metal working fluids. Texaco Chemical Company has warned for several years in its Material Safety Data Sheets and product labels on the hazards of formulating with amines and nitrites.

Should you require additional details on the test procedures and observations for the morpholine study please let us know. Thank you for your patience in this lengthy but successful investigation.

Sincerely,

F. E. Bentley  
Coordinator Product Safety

P.S. It is often difficult to reach all the proper people within an organization with information of this sort. We would appreciate your help in furnishing a copy of this letter to any others in your company who may be interested.



Texaco Inc

PO Box 509  
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August 10, 1988

Neil Krivanek, Ph.D.  
E. I. du Pont de Nemours & Co.  
Haskell Laboratory  
P. O. Box 50  
Elkton Road  
Newark, Delaware 19714

Dear Dr. Krivanek:

Enclosed is a short summary of relevant information pertaining to the potential carcinogenicity of Morpholine, with copies of cited references. I have also enclosed a copy of other references which may be of interest to you. This information has been compiled in an effort to assist you in preparing for the October 1988 IARC Working Group Meetings.

Morpholine was recently tested by inhalation in male and female rats. Exposure to up to 150 ppm failed to produce any evidence of tumorigenicity or chronic toxicity. The only effects noted were those related to the known irritating properties of morpholine. A chronic morpholine feeding study was inconclusive in assessing the significance of tumors observed in rats and similarly treated hamsters failed to produce any evidence of carcinogenicity.

Mutagenicity experiments have produced inconsistent results. Morpholine has produced negative results in the following assays: Ames mutagenicity, host-mediated mutagenicity, unscheduled DNA synthesis, and sister chromatid exchange. On the other hand, positive results have been obtained in the Balb/C3T3 transformation assay and the L5178Y mouse lymphoma assay. Morpholine does not induce transplacental genotoxic effects.

Morpholine is readily converted to N-nitrosomorpholine in the presence of nitrite in an acidic environment. Animals exposed to dietary morpholine and nitrogen dioxide by inhalation also form the N-nitroso derivative. N-nitrosomorpholine is considered an animal carcinogen and has been placed in category 2B by IARC.

At this time, there does not appear to be any conclusive evidence for the carcinogenicity of morpholine. One feeding study suggested an increased incidence in rats; however, the authors suggested that the response may have been due to nitrites from an unknown source, especially since no tumors were observed in hamsters. Morpholine is not carcinogenic to rats by inhalation.

Genotoxicity studies are equivocal. It is probable then, that the evidence will be placed in the Limited Evidence of Carcinogenicity category. Morpholine should be placed in the overall category of Group 3.

Two Ccnaway references (Mutation Research 136: 153-157 and Proceedings, 13 Annual Meeting, Environmental Mutagen Society Abstract DG-7) will be sent to you as soon as they are available.

I hope the enclosed information is helpful to you. Scientific contacts from 3M Company and Nalco Chemical Company are requested to review and critique the attached summary on morpholine. Please contact me if you require additional information or if you are aware of relevant studies which have been overlooked.

Very truly yours,

*Mary Jane Von Allmen*  
MARY JANE VON ALLMEN, Manager  
Product Safety Programs

CJM:als

Attachments

cc: Nancy G. Doerr (Summary and reprints)  
Associate Director  
Health, Safety and Chemical  
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F. E. Bentley (Summary only)  
Texaco Chemical Company  
P. O. Box 430  
Bellaire, TX 77401

**MORPHOLINE**

**PERTINENT STUDIES RELATED TO CARCINOGENIC POTENTIAL**

Abstract DC-77 will be sent to you as soon as it is available.

**Inhalation Studies**

Male and female Sprague-Dawley rats, in groups of 60 each, were exposed to 10, 50, and 150 ppm morpholine for 6 hours/day, 5 days/week, for 104 weeks. The incidences of palpable masses and confirmed neoplasia were similar to current and historical control groups. No treatment related changes in mortality, body weights, organ weights, or clinical pathology were observed. Histologic findings were limited to ocular and anterior nasal cavity effects, which is consistent with the known irritating properties of morpholine. There was no evidence of increased incidence of carcinogenicity or chronic toxicity due to chronic morpholine inhalation (Harbison, et al, 1988).

**Feeding Studies**

All morpholine feeding studies are concerned with the carcinogenic potential upon reacting with nitrite to form the carcinogen N-nitrosomorpholine. These studies involve feeding animals dietary morpholine and sodium nitrite.

A group of 7 female rats exposed to 0.5% dietary morpholine for 8 weeks and then observed for the remainder of their lifespan did not demonstrate an increase in tumors. Animals treated with morpholine and nitrite concurrently at concentrations of 0.5% each all developed hepatocellular adenoma (6/7) or hepato-cellular carcinoma (1/7); renal adenomas were found in one animal (Sandler, et al, 1972; IARC, 1977)

Greenblatt, et al (1971) used lung adenoma induction in Swiss mice to assess the carcinogenic potential of secondary amines administered in food and sodium nitrite added to drinking water. Mice were treated for 28 weeks and then observed for an additional 12 weeks. At 40 weeks all survivors were sacrificed and examined. Animals receiving morpholine (6.33 g/kg food) did not display an increased incidence of pulmonary adenomas. Mice treated with dietary morpholine and sodium nitrite (1.0 g/l drinking water) demonstrated a significant increase in lung tumors.

Female rats and hamsters were fed from conception a diet containing various concentrations of morpholine and nitrite. After weaning, offspring were continued on their respective diets for the remainder of their lifespan. Although there was some evidence of tumorigenicity in rats exposed to a dietary level of

1000 ppm, the authors indicated that it was not possible "to determine with certainty whether the tumors resulted from the high morpholine level or from a high morpholine level combined with the presence of nitrite (coming from an unknown source). . . ." No increases in tumor incidence were observed in similarly treated hamsters (Newberne and Shank, 1973; Shank and Newberne, 1976).

#### Mutagenicity Studies

Morpholine has been found to be without mutagenic activity in the Ames assay (Litton Bionetics, 1979a) and host mediated assays using *S. typhimurium* detector strains (Braun, et al, 1977; Edwards, et al, 1979)

Pregnant hamsters were exposed to 500 mg/kg morpholine on the 11th or 12th day of pregnancy. Cells from embryos exposed in utero were examined for evidence of induced transplacental genotoxic effects. Morpholine failed to increase the incidence of mutation, chromosomal aberrations, micronuclei, or morphological transformation. N-nitrosomorpholine displayed significant genotoxic activity (Inui, et al, 1979).

Rats exposed to 20 ppm morpholine for 4 hours/day, 5 days/week, for 4 months showed an increase in chromosomal aberrations due to fragmentation (Migukina, 1973).

Morpholine did not produce a significant increase in sister chromatid-exchanges (SCEs) in CHO cells (Litton Bionetics, 1980). It did not induce unscheduled DNA repair in primary hepatocytes (Conaway, et al, 1984). Morpholine was tested in the Balb/C3T3 Transformation Assay (Litton Bionetics, 1979b) and the L5178Y Mouse Lymphoma Assay (Litton Bionetics, 1979c). The L5178Y mutagenicity was considered very weakly positive. The transformation assay was reported as positive. In both assays, positive responses occurred at toxic concentrations (Conaway, et al, 1982).

#### Russian Studies

The addition of morpholine to aquarium water did not result in tumor development in exposed pearly mussels, grass frogs, and fish (Sirenko, 1979).

Animals exposed to 20 ppm morpholine for 4 hours/day, 5 days/week, and 4 months demonstrated a variety of effects including changes in nervous system excitability, atrophy of splenic lymphoid follicles, degenerative changes in the liver and kidneys, and neutrophilia. No male reproductive effects were observed (Migukina, 1973).

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Non-Cited References (included as background information)

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**Texaco Chemical Company**  
Subsidiary of Texaco Inc.

## **EXECUTIVE SUMMARY**

### **Chronic Inhalation Study of Morpholine in Rats**

A chronic inhalation study of morpholine was conducted in 60 Sprague-Dawley rats/sex/group at exposure concentrations of 0, 10, 50, and 150 ppm for 6 hours per day, 5 days per week for 104 weeks.

Body weight gains, organ weights, and hematology and clinical chemistries were normal in the exposed groups and comparable to the control animals. There were no exposure-related adverse changes observed in the liver, kidney, brain, intestine, lung, or any other internal organ or tissue. The incidences of neoplasia were comparable among all groups, including the control group, and were typical of the strain and age of the rats. Thus, there was no increase in cancer among the exposed animals.

The only adverse effects observed during the study were irritation of eyes, nose, and skin. Chronic irritation of the eyes produces corneal changes (keratitis) at the highest exposure concentration of 150 ppm. Near the end of the study, corneal opacities were observed. Cataracts were noted in a few rats, but these findings were not believed to be significant. A sex-related increased incidence of retinal degeneration was seen in the high exposure females, but the significance of the finding is unclear. These effects are consistent with the irritating properties reported for morpholine.

In conclusion, the study demonstrated that morpholine is not carcinogenic and produces only ophthalmic and nasal lesions consistent with its irritating properties.