CHEMICAL MANUFACTURERS ASSOCIATION

January 25, 1995

Brenda Boutin
Robert A Taft Laboratories
National Institute for Occupational
Safety & Health
DSDT/Mail Stop C-32
4676 Columbia Parkway
Cincinnati, Ohio 45226

Dear Ms. Boutin:

Enclosed are two position statements regarding triethanolamine and the recent NTP study. One position statement is from the CMA Alkanolamines Panel. The second position statement is from Dr. John Weisburger of the American Health Foundation. I have requested a clearer copy of Weisburger's document and will forward it to you when I receive it. The current version I have is a fax copy.

Please place these two position statements into the official NIOSH docket on metalworking fluids. Thank-you.

Please call me if you have any questions (202/887-1189).

Sincerely,

Jon Busch

Jon Busch,
Manager, Alkanolamines Panel

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

CHEMICAL MANUFACTURERS ASSOCIATION

FINAL

TRIETHANOLAMINE (TEA) CARCINOGENICITY STUDIES

POSITION STATEMENT OF THE ALKANOLAMINES PANEL, CHEMICAL MANUFACTURERS ASSOCIATION, USA

January 18, 1995

The National Toxicology Program (NTP) recently issued a summary of its findings based on its dermal cancer studies of triethanolamine (TEA) [Toxicology and Carcinogenesis Studies of Triethanolamine in F344/N Rats and B6C3F1 Mice; TR 449]. The Alkanolamines Panel of CMA has prepared this position statement to respond to questions regarding the potential carcinogenic risk of TEA. The Panel is comprised of the four United States producers of monoethanolamine (MEA), diethanolamine (DEA), and triethanolamine (TEA). Member companies include The Dow Chemical Company, Union Carbide Corporation, Huntsman Corporation, and Occidental Chemical Corporation. **For the reasons stated below, the CMA Alkanolamines Panel believes that the results of these studies do not indicate a potential carcinogenic risk of TEA for humans.**

Extensive data have been generated evaluating the potential of TEA to cause cancer in animals. No studies to date in cultured cells or in intact animals have shown that TEA causes damage to genetic material (*i.e.* DNA), a known cancer risk factor. TEA is clearly not a tumor initiator. A total of six cancer bioassays, including the two current NTP studies, have been conducted on TEA in rats or mice.[1/] None of the four previous bioassays showed a clear tumorigenic response. A single study conducted in mice and reported to be positive was severely flawed and of no use in risk assessment,[2/] a conclusion upheld by the TLV Committee of the American Conference of Governmental and Industrial Hygienists (ACGIH).[3/] The recent NTP studies report "some evidence" of carcinogenicity in mice, a designation used by NTP to signify a numerical change in total tumor count (benign and malignant), but in which "the strength of the response is less than that required for clear evidence" of a carcinogenic response.[4/] The value and relevance of these latter data for human risk assessment are also being questioned.

The current NTP studies report an increased incidence of benign liver tumors (adenomas) in female mice topically administered 1000 mg-TEA/kg body weight/day, 5 days/week, for a majority of their lifetime, up to 2 years. Twice this dosage did not cause tumors in

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male mice, nor did any lower dosages of TEA cause tumors in female mice. As part of these same studies, maximum tolerated dosages of TEA administered to male and female rats also failed to produce cancer. TEA was "painted" on the backs of rats and mice; however, a significant amount was likely to have been ingested during grooming resulting in a large portion of the dosing occurring via the oral, not dermal, route. This introduces ambiguity in the actual route of exposure. Significantly, female mice had a very high spontaneous incidence of liver tumors in controls, 44%, a situation attributed to their extreme obesity. Indeed, liver tumor incidence increases dramatically in these mice with increases in body weight, another known risk factor in cancer formation. In addition, the mouse colony utilized in the study is known to be infected with the bacterium *Helicobacter hepaticus*, which causes a chronic hepatitis in mice, yet another known risk factor in cancer formation.[5/] This latter condition was so prevalent in males that NTP considered any cancer assessment in the livers of these mice to be invalid. While classical signs of chronic hepatitis were absent in female mice, the potential impact of a latent or subclinical infection in these animals upon tumor formation, especially in mice chronically stressed with a high dosage of a chemical, cannot be discounted.

These factors taken together -- the lack of dose-response, tumors in one sex of one species and only at a single, relatively high, dosage, use of unusually obese, and, possibly, infected test animals -- greatly confound the interpretation of the NTP study results.

The CMA Alkanolamines Panel concludes that when all the data are examined, the recent findings of the NTP cancer studies of TEA do not suggest a potential human cancer risk. TEA is negative in sensitive tests measuring damage to genetic material and has repeatedly been negative in most animal cancer tests at dosages that are orders of magnitude higher than humans are ever exposed to or could ever tolerate. Thus, TEA lacks the ability to directly initiate (start) tumor formation in animals, putting TEA outside the scope of regulatory cancer risk assessment methods. TEA at extremely high dose levels may have only weak, if any, potential to facilitate the formation of benign tumors initiated by other, "spontaneous," factors. Like most substances, TEA has not been studied specifically for the latter activity.

Please direct any questions concerning these comments to Mr. Jonathon T. Busch, Manager of the CMA Alkanolamines Panel, at (202) 887-1189.

1/ The results of a number of these are discussed in more detail in CMA's Technical Data Summary - TEA Carcinogenicity Testing.

2/ Hoshino, H. and Tanooka, H. Carcinogenicity of triethanolamine in mice and its mutagenicity after reaction with sodium nitrite in bacteria. *Cancer Res.* 38 (1978) 2918-2921.

3/ ACGIH, "Draft Documentation: Triethanolamine." (Sept. 10, 1992).

4/ Explanation of Levels of Evidence of Carcinogenic Activity. NTP TR 449, pg. 14.

5/ J.M. Ward et al. (1994). Chronic active hepatitis and associated liver tumors in mice caused by a persistent bacterial infection with a novel Helicobacter species. *JNCI* 86, 1222-1227.

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SON COPY

January 10, 1995

Dr. Jonathon T. Busch
CMA
Fax: 202-887-5427

Dear Dr. Busch:

Attached please find my preliminary views on the NTP bioassay of triethanolamine in their 1994 report. This study extends earlier *in vitro* and *in vivo* bioassays, that I reviewed in 1991.

A more detailed report will be produced in February.

With all good wishes,

Sincerely yours,

JOHN H. WEISBURGER, Ph.D., M.D.(hon),FACN
Senior Member and Director Emeritus

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PS - If desired, we could do fairly rapidly a study on likely absence of DNA adducts in liver of mice with ³²P-postlabeling techniques.

Comments on 1994 NTP Bioassay of Triethanolamine in Mice and Rats

John H. Weisburger
American Health Foundation
Valhalla, NY 10595

First, it is important to note that studies of triethanolamine for genotoxicity were negative in all experiments performed.

The structure of triethanolamine is closely related to that of the natural product, choline. It is a fairly polar, basic amine and certain of the lesions on cutaneous application are associated with damage to the skin because of the basic nature of this chemical. In addition, upon absorption of high dose levels, this chemical may affect the pH and ionic balance of the body and organs involved in its excretion, such as liver and kidneys.

The chemical appeared to be much more toxic in male and female F344 rats. The MTD in female rats was 250 mg/kg and in males 125 mg/kg. In contrast, in mice the MTD in females was 1000 mg/kg and in males 2000 mg/kg.

There was severe skin irritation with high dose levels applied to mice and there was a dose response effect of cutaneous damage. With the lower dosages used in rats, there was somewhat less damage but nonetheless, there was evidence of acanthosis, inflammation and some ulceration.

Specific Comments on 2-Year Bioassay Results

As is usually found, in many rats held for two years there was chronic nephropathy. In male rats, it was discovered during detailed pathology, utilizing step sections, that some of the rats displayed adenomas in a bed of renal hyperplasia. However, only small numbers of rats had an adenoma in males, and there was no dose-response. In the females there was no evidence of chemically induced adenoma in the kidneys.

Studies in mice involved doses as high as 4000 mg/kg. No doubt because of the severe damage due to the alkalinity of the chemical, acanthosis was found at all dose levels utilized. In the two year study the cutaneous lesions were more pronounced in males, and there was a dose response effect.

The strain of mouse used in the bioassays have hepatocellular tumors in the control groups, a continuing finding in the NCI/NTP bioassay program. In the males and females, the groups of animals treated with the two lower dose levels 100 and 300 mg/kg of triethanolamine had an incidence of adenomas or carcinomas in the liver identical to that of control mice. However, at the highest dose level used, 2000 mg/kg in the group of males and 1000 mg/kg in the females, there was an increased incidence of hepatocellular adenoma and hepatoblastoma, but not of hepatocellular carcinoma. In the female mice, there was also a slightly higher non-significant incidence of

hepatocellular carcinoma at doses of 300 and 1000 mg/kg. Thus, there was no evidence of dose-response. Moreover, the latent period to the first tumor was basically similar in all of the treated groups compared to the controls in males and females for the adenomas and the carcinomas.

The mice at the highest dose rate in both sexes had a higher level of multiple hepatocellular adenomas, but not of the carcinomas.

A substantial number of the male and female mice displayed infection with *Helicobacter hepaticus*. Analysis of this infestation showed that most of the mice with liver tumors also had *Helicobacter* infiltration. Also, 61% of the mice with liver tumors were free of *Helicobacter* but there was no dose-response.

In the 13 week as well as in a 15 month period of the two year study, both rats and mice at the highest dose level had increased kidney weights. In the group of rats, the females had increased liver weights. In the group of mice, the liver weights were increased in males and females at the highest dose level.

As noted above, the MTD in rats was much lower than mice. In mice, the males were more sensitive than the females.

Conclusions

Considering the high dose levels tolerated by mice it is clear that this chemical is not very toxic in mice. Rats seem to be somewhat less tolerant, by a factor of almost 10.

Tumors in the kidneys in rats were found mainly as a result of careful pathologic workup, including step sections. Even then the diagnosis was adenomas and may be the result of overloading of the excretory system particularly in males that with other chemicals lead to the α-globinemia, associated with tumorigenesis in that organ. There is no equivalent human condition.

In mice, the finding was mainly of adenomas, discovered chiefly during the terminal autopsy procedures in the group at the highest dose level.

Considering that this chemical is not all genotoxic in a number of appropriate tests, and that the main finding in this set of studies was adenoma, not carcinoma without change in latent period, the opinion is clearly warranted that the data obtained cannot be interpreted as signifying a human disease risk. The previous reports dealing with the chronic toxicity of triethanolamine lead to the same conclusion. Doses used were 1 and 2% drinking water, also indicating low toxicity.

Studies of this type should not be considered by themselves but in the context of the overall knowledge currently available on what kind of data would lead to the interpretation that a given bioassay result signifies a human cancer risk. Human