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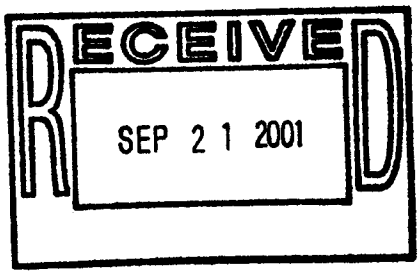

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Proposed Listing of Nitromethane in the 11th Annual Report on Carcinogens

Dear Dr. Jameson:

ANGUS Chemical Company, a subsidiary of The Dow Chemical Company, is the only North American producer of nitromethane. As such, ANGUS has a material interest in the proposed listing of nitromethane by the National Toxicology Program in the Eleventh Annual Report on Carcinogens (RoC)[1]. ANGUS is concerned that listing nitromethane as a substance "reasonably anticipated to cause cancer in humans" is misleading, and the subsequent mandatory labeling to inform users of this hypothetical risk will result in misdirecting users' attention from the very real fire and explosive hazards associated with this material. ANGUS further believes that the conditions of exposure identified in support of the proposed listing are incorrect and result in overestimating the numbers of persons potentially exposed to nitromethane. Therefore, ANGUS submits that the proposed listing is not justified based both on lack of exposure and lack of compelling toxicology information.

The NTP RoC mandates that the Secretary of the Department of Health and Human Services shall publish a biennial report which contains a list of all substances which are known to be carcinogens in humans or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed[2]. The RoC tends to largely reflect the findings from the animal bioassay program conducted by the US NTP, using inbred rats and mice as a screening mechanism. Nitromethane was thus nominated for inclusion in the RoC based on a result of studies in rats and mice, and not as the result of any observation of an increased risk of cancer in humans.

[1] Federal Register, Vol. 66, No. 142; Tuesday, July 24, 2001.
[2] National Toxicology Program, *About the RoC: What is the Report on Carcinogens?* http://ntp-server.niehs.gov/NewHomeRoC/WhatisRoC.html

Exposure

The circumstances of potential exposure provided by the NTP are not accurate and need to be revised to reflect current potential exposure scenarios. In the report of the NTP Bioassay results in rats and mice[3], NTP cites a 1990 NIOSH National Occupational Exposure Survey for a magnitude of the exposed worker population. The 135,000 males and 46,500 females potentially exposed during 1981 to 1983 would vastly overestimate the potential for exposure currently[4]. The opportunity for human exposure has been greatly reduced because of the change in the mix of markets in which nitromethane is used. ANGUS submits that the true number of workers currently exposed is closer to 10,000.

By far, the greatest use of nitromethane is in the synthesis of nitromethane derivatives, as well as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials. Eighty-five to ninety percent of the approximately 16 million domestic pounds of nitromethane sold by all producers go into these sophisticated industrial settings, in which nitromethane is used as a raw material. Additionally, each ANGUS customer must undergo a rigorous qualifying procedure to ensure that they will be capable of storing, handling, and using nitromethane safely because of the potential fire and explosion hazards associated with this material. These uses as closed system raw materials result in very low potential for exposure. OSHA regulation restricts the occupational exposure of nitromethane to less than 100 ppm (8 hr. TWA), while the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value of 20 ppm (8 hr. TWA). Occupational exposures at ANGUS' own manufacturing facility where nitromethane is produced, along with other nitroparaffin derivatives, suggest that exposures in the occupational setting can be kept quite low; our experience suggested exposures in the 1.0 ppm range (8 hr. TWA)[5].

The use of nitromethane as an additive in either halogenated solvents or as a stabilizer in aerosol propellants has diminished to virtually zero. At one point, nitromethane was included as an additive in 1,1,1-trichloroethane formulations. However, since the mandatory phase-out of 1,1,1-trichloroethane in 1995, based on concern regarding its potential effects on stratospheric ozone, nitromethane has not been used in this application nor in other dispersive solvent applications. As aerosols have transitioned to alternative propellant technologies and pump sprays, nitromethane exposure via this route is almost non-existent. Thus, exposure via these routes has decreased. Further, ANGUS no longer sells nitromethane into explosive applications. The decision to exit this application was made in 2000.

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[3] NTP TR 461. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Nitromethane (CAS No. 75-52-5) in F344/N Rats and $B_6C_3F_1$Mice (Inhalataion Studies). February 1997.

[4] There appears to be some dispute over the size of the population potentially exposed to nitromethane. NTP (1994) cites NIOSH unpublished provisional data as of July 1990 for their total of 181,500. The ACGIH in their documentation to the TLV for nitromethane cite NIOSH provisional data from 1989 for their reference to 70,500 potentially exposed workers. ACGIH, in their 6th edition supplement reference the NIOSH technical publication from 1988 and indicate that 27,530 workers were potentially exposed to nitromethane. All three of these reports represent the workforce from the same time frame, 1981-1983. With all the changes in the market, Angus believes the true current number is closer to 10,000 workers.

[5] ANGUS Chemical Company, Internal Report, 1994.

Nitromethane is still used in specialty fuel blends with methanol for drag racing and hobby fuel. This represents less than 20 percent of the market for nitromethane. Moreover, these are outdoor events, thus minimizing the potential for significant human exposure, and they involve only a limited number of participants. Additionally, the presence of methanol, another component of these blended fuels, already causes them to be labeled in a manner that will ensure awareness of proper safe handling of the fuels.

Thus, workplace and consumer exposure scenarios for nitromethane have been altered dramatically by other regulatory and market pressures. As a result, ANGUS believes that it is incorrect to characterize nitromethane as a chemical "to which a significant number of persons residing in the United States are exposed."[6]

Results of Animal Studies Are Not Relevant to Humans

ANGUS questions the relevance of the animal results to humans and suggests that classifying nitromethane as a chemical "reasonably anticipated to be a human carcinogen" is misleading and inaccurate. The basis for this proposal is exclusively related to the results in the highly sensitive rats and mice used in the NTP bioassay, and does not consider the negative mutagenicity studies conducted on nitromethane nor the results of another study conducted in another strain of rats.

Nitromethane was shown not to cause an increased incidence in tumors in Long Evans rats exposed by inhalation to up to 200 ppm nitromethane for 2 years. This study was conducted at a more reasonable multiple of potential human exposure levels to nitromethane than the NTP bioassay. Nitromethane appeared to slightly reduce body weight gain in female, but not male rats in both exposure groups. Survival of exposed animals was similar to those of the controls. There was no increased incidence of tumors in rats of either sex exposed to nitromethane relative to the concurrent control group.[7]

Nitromethane was not mutagenic according to the NTP test battery. Results of other published studies were also negative, as reflected in the NTP report. Nitromethane did not induce mutations in Salmonella typhimurium strains TA98, TA 100, TA1535, and TA1537, with or without metabolic activation. It was negative in a test for detecting sex-linked recessive lethal mutations and in a mouse micronucleus test for detecting chromosomal aberrations.[8]

Nitromethane did contribute to an increase in tumors with an historically high and variable background rate in mice and rats in the NTP study: Fisher 344/N female rat mammary fibroadenomas, adenomas and carcinomas, hepatocellular adenomas in male and female $B6C3F_1$ mice, and Harderian gland adenomas in male and female mice. Historical rates of mammary

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[6] NTP, *About the RoC.*
[7] Griffin TB, Coulston F and AA Stein. 1996, Chronic inhalation exposure of rats to nitromethane. Ecotoxicology and Environmental Safety (34): 109-117.
[8] Dow TIME summary.

carcinomas and adenomas in F344 female rats range from 22% to 54%[9]. The concurrent control group in the NTP bioassay had a combined rate of these tumor types of 42%, the majority being fibroadenomas in which the unexposed female rats had an incidence rate of 38%.[10]

Hepatocellular adenomas and carcinomas in the $B6C3F_1$ mouse have been shown to range as high as 58% in males[11], as they were in the nitromethane bioassay. The exposed groups actually had slightly lower incidence of tumors than the concurrent controls among the males. Female $B6C3F_1$ mice have experienced an historical control incidence of 56% for hepatocellular adenomas and carcinomas[12]. The concurrent control rate in the NTP nitromethane bioassay was 38%, with rates in the highest dose group reaching 80%. However, the high background rate in this strain of mouse calls into question the relevance of these findings for human cancer risk assessment.

The relevance of the mouse Harderian gland adenomas to humans is not known[13]; however, even this site should be scrutinized due to the abnormally high rate observed in control animals in the nitromethane bioassay. For example, the historical control incidence of Harderian gland adenomas and carcinomas in female mice at that testing facility is 6.0%, while for all NTP studies, it was 3.4%. For the nitromethane study, the female mice unexposed to nitromethane had a 12% incidence of Harderian gland adenomas and carcinomas; twice the historical rate seen at the testing facility and more than three times that previously seen in NTP studies.[14]

The ACGIH has reviewed the data on nitromethane and classified it as an "A3" carcinogen, a "confirmed animal carcinogen with unknown relevance to humans." The ACGIH based its 20 ppm TLV not on the carcinogenicity data, but on adverse thyroid effects in rabbits exposed for 6 months to 98 ppm nitromethane, transient pulmonary hemorrhage and congestion, dose-related increases in thyroid weights, and the non-neoplastic effects in the nose and respiratory system of mice. The ACGIH indicates that, "Based on the results of the inhalation lifetime carcinogenicity bioassay in rats and mice, the A3 designation, Animal Carcinogen with Unknown Relevance to Humans, is appropriate."[15] This classification is used on the occasion that an "agent is carcinogenic in experimental animals at a **relatively high dose**, by route(s) of administration, **at site(s), of histologic type(s), or by mechanism(s) that may not be relevant** to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available evidence does not suggest that the agent is likely to cause cancer

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[9] NTP TR 486. NTP Technical Report on the Toxicology and Carcinogenicity Studies of Isoprene (CAS No. 78-79-5) in F344/N Rats. July 1999. (Chamber controls, Inhalation studies, Battelle Pacific Lab).
[10] NTP TR 461.
[11] Haseman, JK, et al. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344 Rats and $B6C3F_1$ Mice. JNCI (75): 975.
[12] NTP TR 504. NTP Technical Report on the Toxicology and Carcinogenicity Studies of o-Nitrotoluene (CAS No. 88-72-2) in Male $B6C3F_1$ Mice (Feed Studies). DRAFT.
[13] Monro A and J Mordenti. (1995) Expression of exposure in negative carcinogenicity studies: Dose/body weight, Dose/body surface area, or plasma concentration. Toxicologic Pathology (23): 187. The authors indicate that the Harderian gland is among the tissues present in rodents, but absent or rudimentary in humans, and suggest that it is "difficult to interpret tumors in organs that are present in one species and not the other."
[14] NTP TR 461.
[15] American Conference of Governmental Industrial Hygienists, 2000, 6th edition supplement.

in humans except under uncommon or unlikely routes or levels of exposure (emphasis added)."[16] The ACGIH did not use the more cautious classification of "A2-- Suspected Human Carcinogen," which appears to be the equivalent of that proposed by the NTP. This assessment by the ACGIH seems a more valid characterization of the available data on nitromethane.

Finally, absence of positive findings in mutagenicity studies and the absence of carcinogenicity in the earlier rat study at a more reasonable dosing regimen argue for a threshold below which nitromethane would not be expected to produce tumors. The highest exposure levels in the NTP study were far in excess of those permissible in occupational settings (top dose in rats was 375 ppm and top doses in mice were 375 and 750 ppm), and thus unreasonable for the purposes of drawing conclusions about potential human cancer risk. Potential consumer uses of nitromethane are limited and would not be expected to generate exposures at all similar to those used in the NTP study.

In conclusion, the NTP proposal overstates the applications and the numbers of people potentially exposed to nitromethane and should be revised to reflect the more recent changes in the markets for nitromethane. Further, the proposed listing of nitromethane as a chemical "reasonably anticipated to be a human carcinogen" overstates the evidence from the NTP study and fails to incorporate negative mutagenicity studies and a second rat study at more reasonable exposure levels. Therefore, ANGUS submits that the NTP has not met their criteria for listing nitromethane in the RoC: "significant" numbers of people are not exposed to levels of nitromethane sufficient to pose a risk of cancer, nor are the data on carcinogenicity of nitromethane, combined with the absence of positive genotoxicity, sufficiently compelling to qualify nitromethane as a candidate for the Annual Report on Carcinogens.

We appreciate the opportunity to comment. Questions regarding these comments should be directed to: Susan Hearn, EH&S Product Leader, The Dow Chemical Company, 1691 N. Swede Road, Midland, MI 48674. Telephone: 989-636-9192. Fax: 989-636-9899. E-mail: shearn@dow.com.

Sincerely,

Signature

Mark A. Henning
Global Business Director

khm

cc: Allen F. Bollmeier
Alan C. Eachus
Susan Hearn

[16] American Conference of Governmental Industrial Hygienists, TLVs and BEIs. 2001.