



N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

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8EHQ - 1198 - 14019

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November 23, 1998

PDEN: 88910000269

BY HAND

TSCA Non-Confidential Information Center (7407)
Attention: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
United States Environmental Protection Agency
401 M Street S.W.
Washington, D.C. 20460

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Re: Supplement to TSCA 8(e) Submission 8EHQ-97-14019; N-Methylpyrrolidone Oral Feeding 18-Month Carcinogenicity Study

The N-Methylpyrrolidone (NMP) Producers Group, Inc. submits this supplemental information pursuant to Section 8(e) of the Toxic Substances Control Act and the EPA's Statement of Interpretation and Enforcement Policy, 43 Fed. Reg. 11110 (March 16, 1978). This supplemental submission is made on behalf of the member companies of the NMP Producers Group: BASF Corporation, ISP Management Company, Inc., and Lyondell Chemical Company (formerly ARCO Chemical Company). We do not believe that the data discussed below demonstrate that NMP presents a significant risk to human health or to the environment. However, the NMP Producers are aware of the Agency's interest in receiving toxicological information as soon as possible and we are therefore submitting the following information.

The NMP Producers Group is sponsoring a series of health effects tests on N-Methylpyrrolidone, CAS Registry Number 872-50-4, pursuant to an Enforceable Consent Agreement under TSCA Section 4, 58 Fed. Reg. 61814 (Nov. 23, 1993). One of those tests is an oral (feeding) 18-month carcinogenicity study in B6C3F1 mice being carried out, pursuant to contract with the NMP Producers Group, in the laboratory of the Department of Toxicology of BASF Aktiengesellschaft (AG), Ludwigshafen, Germany. In this study, NMP was administered to 50 B6C3F1 mice per sex at dietary concentrations of 0; 600; 1,200; and 7,200 ppm for 18 months. These values correspond to a mean daily test substance intake of 0; 99; 192; and 1,210 mg/kg body weight in males and 0; 128; 249; and 1,584 mg/kg body weight in females, respectively.

The incidence of macroscopically observable liver masses following final sacrifice were reported to the Agency in a letter dated September 16, 1997 (8EHQ-1097). This letter supplements our earlier report and contains histopathological data.

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The incidence of histopathologically diagnosed tumors in the liver is given in the following table:

Sex	Male				Female			
	0	600	1,200	7,200	0	600	1,200	7,200
Dose level (ppm)	0	600	1,200	7,200	0	600	1,200	7,200
No. of animals/group	50	50	50	50	50	50	50	50
Hepatocellular adenoma	5 (10%)	2 (4%)	4 (8%)	12 (24%)	2 (4%)	2 (4%)	1 (2%)	7 (14%)
Hepatocellular carcinoma	4 (8%)	1 (2%)	3 (6%)	13 (26%)	0	0	0	3 (6%)

Hepatocellular adenomas and carcinomas were increased in high dose males and females. In high dose males, the incidence of hepatocellular adenomas (24%) and carcinomas (26%) is above the laboratory's control range for hepatocellular adenomas (0 - 14%) and carcinomas (4 - 22%). In high dose females, the incidence of hepatocellular adenomas (14%) is slightly above the historical control range for hepatocellular adenomas (0 - 10%), whereas the incidence of hepatocellular carcinomas (6%) is within the laboratory's historical control range (0 - 6%). The elevated liver tumor incidences at the highest dose level only are interpreted to be the consequence of enzyme induction, a non-genotoxic mechanism to which, as is known from literature, B6C3F1 mice respond in a highly sensitive manner.

Indications for this mechanism were also observed in a 90 day feeding study in B6C3F1 mice (BASF Project No. 60C0225/93053). NMP was administered to 10 B6C3F1 mice per sex at dietary concentrations of 0; 1,000; 2,500; and 7,500 ppm for 3 months. In this study, most of the high dose animals showed centrilobular hypertrophy of liver cells, resulting in elevated liver weights. The hypertrophy of liver cells was regarded as an adaptation process to the application of the test article. The hypertrophy is most likely related to proliferation of smooth endoplasmatic reticulum and is an indication of enzyme induction.

Thus, the occurrence of the liver tumors in high dose animals is most probably related to the centrilobular hypertrophy of liver cells and liver enlargement as a consequence of enzyme induction (e.g. cytochrome P-450). "Chemicals which induce cytochrome P-450 also produce proliferation of hepatocytes, which, if continued for a prolonged period, may lead to liver cancer." (Grasso and Hinton, Mutation Research 248, 261-290, 1991). These and other results will be fully detailed in a final report at the scheduled completion of the study in August, 1999.

N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

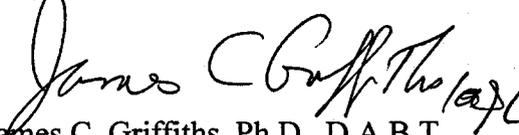
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Please do not hesitate to contact me at (973) 628-4087 if you have any questions about this submission.

Very truly yours,



James C. Griffiths, Ph.D., D.A.B.T.
Chair, Toxicology Committee

DCDOCS: 137452.1