MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY
WATER BUREAU

TOXICOLOGICAL ASSESSMENT FOR 4-CHLOROANILINE (CASRN 106-47-8) HUMAN CANCER VALUE (HCV)

Literature Review Date: March 20, 2008
Shannon Briggs

Chhabra et al. (1991) evaluated the carcinogenicity of p-chloroaniline (PCA) in Fischer 344 rats and B6C3F1 mice. In this study, PCA was administered as PCA hydrochloride in water by gavage 5 days per week to rats (0, 2, 6, or 18 mg/kg) and mice (0, 3, 10, 30 mg/kg) of each sex for 2 years (103 weeks). Carcinogenic effects included an increased incidence of sarcomas of the spleen and pheochromocytomas of the adrenal gland in male rats and a significant increase in hepatocellular adenomas/carcinomas in male mice.

In an NCI (1979) bioassay, male and female Fischer 344 rats and B6C3F1 mice were administered p-chloroaniline in the feed at either 250 or 500 ppm for rats and 2500 or 5000 ppm for mice for 78 weeks, followed by an observation period of 24 weeks for rats and 13 weeks for mice. Results showed a significant increase in mortality only in the high-dose group of male rats, but adequate numbers of animals survived to be at risk from late-developing tumors. The only neoplastic lesions found that might be related to administration of the compound were mesenchymal tumors in the spleens of male rats and hemangiomatous tumors in mice. While the incidence of these tumors are strongly suggestive of carcinogenicity, EPA concluded that, under the conditions of the bioassay, sufficient evidence was not found to establish the carcinogenicity of p-chloroaniline for Fischer 344 rats or B6C3F1 mice.

Differences in the incidence of neoplasms in the spleen reported by Chhabra et al (1991) and the NCI (1979) study could be related to the differences in dose and route of administration that were used in each study. It is possible that PCA administration in the NCI (1979) study was less than the targeted concentrations because of the instability of the chemical mixed in feed. The different routes of administration used could have affected the metabolism of PCA which could have resulted in quantitative differences observed in the two studies.

Data from the Chhabra et al. (1991) study were used to determine the HCV. The incidence of liver carcinomas reported for the B6C3F1 male mice were used over other groups because the carcinoma data showed a stronger dose-response relationship and produced a steeper slope (greater potency) in the Global 82 Linearized Multistage Model.

References:

Chhabra, R.S., et al. 1991. Carcinogenicity of p-chloroaniline in rats and mice. Fd. Chem. Toxic. 29(2):119-124.

National Cancer Institute (NCI). 1979. Bioassay of p-Chloroaniline for Possible Carcinogenicity. NCI TR 189.

HUMAN CANCER VALUE WORKSHEET

Chemical Name: 4-chloroaniline CAS No. 106-47-8
Developed By: S. Briggs
Reviewed By: D.Bush DB Verification Date: 9/26/2006

Key Study: Chhabra et al (1991) evaluated carcinogenicity of 4-chloroaniline in male and female F344/N rats and B6C3F$_1$ mice. 4-chloroaniline hydrochloride (PCA.HCL) was administered 5 days per week for 103 weeks by gavage at doses of 0, 2, 6, or 18 mg/kg to rats and 0, 3, 10, or 30 mg/kg to mice. Males were more sensitive to the effects of PCA.HCL than females in both species. The incidence of liver carcinomas reported for the male mice were used over other groups because the carcinoma data showed a stronger dose-response relationship and produced a steeper slope in the Global 82 model.

Animal Weight	Adj. Ave. Dose	Tumors	Animals at Risk
0.0429 kg	0	3	50
	2.1428	7	49
	7.1428	11	50
	21.428	17	50

Global 82

$$q = \frac{0.00001550721}{0.000581904498}$$

$q = 0.02664906363$ Species scaling factor = $(70 \text{ kg}/ 0.0429 \text{ kg})^{1/4} = 6.36$

$q^* = (q)(\text{species scaling factor})$
$q^* = (0.02664906363)(6.369)$

$q^* = 0.169372205 \quad (\text{mg/kg/d})^{-1}$

$$RAD = \frac{0.00001}{0.169372205} = 0.00005904156 \text{ mg/kg/d}$$

$$HCV_{dw} = \frac{(0.00005904156 \text{ mg/kg/d}) (70 \text{ kg})}{2.0 \text{ l/d} + [(.0036 \text{ kg/d} \times 2.4 \text{ l/kg}) + (.0114 \text{ kg/d} \times 3.4 \text{ l/kg})]} = \mathbf{2 \text{ ug/l}}$$

$$HCV_{non\text{-}dw} = \frac{(0.00005904156 \text{ mg/kg/d}) (70 \text{ kg})}{0.01 \text{ l/d} + [(.0036 \text{ kg/d} \times 2.4 \text{ l/kg}) + (.0114 \text{ kg/d} \times 3.4 \text{ l/kg})]} = \mathbf{72 \text{ ug/l}}$$

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TOXICOLOGICAL ASSESSMENT FOR 4-CHLOROANILINE (CASRN 106-47-8) HUMAN NONCANCER VALUE (HNV)

Literature Review Date: March 20, 2008
Shannon Briggs

Chhabra et al. (1991) evaluated the chronic toxicity of p-chloroaniline (PCA) in Fischer 344 rats and B6C3F1 mice. In this study, PCA hydrochloride was administered by gavage 5 days per week resulting in 0, 2, 6, or 18 mg PCA/kg in rats and 0, 3, 10, or 30 mg PCA/kg in mice of each sex for 2 years. Neither body weights nor survival of rats and mice were affected by PCA administration. No compound-related clinical signs of toxicity were noticed in mice. A NOEL of 30 mg PCA/kg was reported in mice. However, rats that received 18 mg PCA/kg had mild hemolytic anemia and slight increases in methemoglobin. Fibrosis of the spleen and bone marrow hyperplasia was significantly increased in all treated groups of male rats and only female rats treated at the high dose. A LOEL of 2 mg PCA/kg was reported for male rats based on adverse effects observed in the spleen and bone marrow. Carcinogenic effects were reported in the study and are summarized in the HCV Justification for PCA.

Chhabra et al. (1990) evaluated the toxicity of p-chloroaniline (PCA) in Fischer 344 rats and B6C3F1 mice. In this study, PCA was administered as PCA hydrochloride via gavage to rats and mice (10/sex/group) for 13 weeks. The doses, calculated as PCA, are 0, 5, 10, 20, 40, or 80 mg/kg/d for rats and 0, 7.5, 15, 30, 60, or 120 mg/kg/d for mice. No PCA-related mortality occurred in either rats or mice. Body weights of rats and mice that received PCA were similar to those of controls with the exception of the high-dose male and female rats that had a 16% and 4% decrease in body weight, respectively. Among organs observed at autopsy, only a dose-related increase in spleen weight was noted. PCA related lesions observed in rats and mice included pigmentation (hemosiderin) in the spleen (all doses), liver (3 higher doses), and kidney (all doses in rats and only the highest dose in mice). The proportion of hemoglobin in the form of methemoglobin was increased in all dosed groups in both species and resulted in a secondary anemia with dose related severity. An increased hematopoeisis in the liver, spleen, and bone marrow (in rats only) was reflective of the response to the hemolytic anemia and methemoglobinemia caused by PCA. Increased hematopoeisis in bone marrow of rats produced hyperplasia of the bone marrow with a dose-related severity. A LOEL of 5 mg PCA/kg/d in rats and 7.5 mg PCA/kg/d in mice was reported due to adverse effects which included increased methemoglobin proportions, femoral bone marrow hyperplasia, and histological lesions in the kidney and spleen (pigmentation and congestion).

In an NCI (1979) bioassay for the possible carcinogenicity of p-chloroaniline, male and female Fischer 344 rats and B6C3F1 mice were administered p-chloroaniline in the feed at either 250 or 500 ppm for rats and 2500 or 5000 ppm for mice for 78 weeks, followed by an observation period of 24 weeks for rats and 13 weeks for mice. Results showed a significant increase in mortality in high-dose male rats. Also, nonneoplastic proliferative lesions of the capsule of the spleen (focal fibrosis with subscapular mesenchymal proliferation) occurred in most of the treated rats. Fibrosis or fatty infiltration of the splenic parenchyma occurred in some of the high-dose males and one of the high-dose females. Splenic lesions did not occur in any of the control rats. This study did not report a NOEL, but a LOEL of 250 ppm (12.5 mg/kg/d) was reported in rats based on nonneoplastic lesions of the splenic capsule. EPA (1998) derived an RfD based on the LOEL of 12.5 mg/kg/d in this study.

Smith (1986) reported data that suggested humans may be more susceptible than rodents to the toxic effects of aniline and similar aromatic amines. Results from this study showed a ten-fold difference in the activity of NADH-dependent methemoglobin reductase in erythrocytes of mice or rats vs. humans.

The LOEL of 2 mg PCA/kg (1.43 mg/kg/d) from Chhabra et al. (1991) was used for the derivation of the HNV. The LOEL of 5 mg/kg/d reported by Chhabra et al. (1990) and the LOEL of 250 ppm (12.5 mg/kg/d) reported by NCI (1979) support the use of the LOEL of 1.43 mg/kg/d. An uncertainty factor of 1,000 was applied for intraspecies (10x), interspecies (10x), and LOEL to NOEL (10x) extrapolation.

References:

Chhabra, R.S., et al. 1990. Toxicity of p-chloroaniline in rats and mice. Fd. Chem. Toxic. 28(10):717-722.

Chhabra, R.S., et al. 1991. Carcinogenicity of p-chloroaniline in rats and mice. Fd. Chem. Toxic. 29(2):119-124.

National Cancer Institute (NCI). 1979. Bioassay of p-chloroaniline for possible carcinogenicity. NCI TR 189.

Smith, R.P. 1986. *Toxic responses of the blood. In Casarett and Doull's Toxicology. The Basic Science of Poisons.* 3rd Ed. Edited by S.C. Klaassen, M. O. Amdur and J. Doull. P.223. Macmillan, New York.

US E.P.A. 1998. Integrated Risk Information System (IRIS) for p-chloroaniline (106-47-8).

HUMAN NONCANCER VALUE WORKSHEET

Chemical Name: 4-chloroaniline CAS No. 106-47-8
Developed By: S. Briggs
Reviewed By: D. Bush DB Verification Date: 5/22/2008

Key Study: Chhabra et al. (1991) administered 4-chloroaniline.hcl by gavage 5 days per week for 103 weeks to male and female F344/N rats. Administration of 4-chloroaniline.hcl resulted in a dose of 0, 2, 6, or 18 mg/kg of 4-chloroaniline (PCA). A LOEL of 2 mg PCA/kg was reported based on bone marrow hyperplasia and fibrosis of the spleen in male rats.
Dose Adjustment: 2 mg PCA/kg x 5 days/ 7 days = 1.42857 mg/kg/d = **1.43 mg/kg/d**

ADE = 0.00143 mg/kg/d

$$ADE = \frac{1.43\ mg/kg/d}{1{,}000}$$

Where UF = 10x is applied to account for each intraspecies & interspecies extrapolation and 10x for LOEL to NOEL extrapolation.

drinking water

$$HNV = \frac{(0.00143\ mg/kg/d)\ (70\ kg)\ (0.8)}{(2\ L/d) + (0.0036\ kg/d \times 2.4\ L/kg) + (0.0114\ kg/d \times 3.4\ L/kg)} = 39.11\ ug/L$$

HNV for drinking water = 39 ug/L

non-drinking water

$$HNV = \frac{(0.00143\ mg/kg/d)\ (70\ kg)\ (0.8)}{(0.01\ L/d) + (0.0036\ kg/d \times 2.4\ L/kg) + (0.0114\ kg/d \times 3.4\ L/kg)} = 1{,}395.1220\ ug/L$$

HNV for non-drinking water = 1,400 ug/L