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**ICH Topic Q3C (M)
Maintenance of Note for guidance on Impurities: Residual
solvents (CPMP/ICH/283/95)**

ICH Step 4

**MAINTENANCE OF NOTE FOR GUIDANCE ON IMPURITIES:
RESIDUAL SOLVENTS
*Permissible Daily Exposure (PDE) for Tetrahydrofuran and
N. Methylpyrrolidone***

TRANSMISSION TO CPMP	July 2000
RELEASE FOR CONSULTATION	July 2000
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PDE for tetrahydrofuran (THF)

The ICH Q3C guidance reached step 5 in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs and allowed for minor changes to the guidance that included the existing PDEs. It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

The EWG visited new toxicity data for the solvent tetrahydrofuran (THF) late last year and earlier this year. The data in review was the information published by the U. S. National Toxicology Program (NTP) that consisted of data from several mutagenicity studies and two carcinogenicity studies in rodents via the inhalational route of administration. Information was sent to the members of the EWG for their analysis.

Animal toxicity

Genetic toxicology studies were conducted in *Salmonella typhimurium*, Chinese hamster ovary cells, *Drosophila melanogaster*, mouse bone marrow cells and mouse peripheral blood cells. The *in vitro* studies were conducted with and without exogenous metabolic activation from induced S9 liver enzymes. With the exception of an equivocal small increase above baseline in male mouse erythrocytes, no positive findings were found in any of the genetic toxicology studies.

Groups of 50 male and 50 female rats were exposed to 0, 200, 600, or 1,800 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 105 weeks. Identical exposures were given to groups of 50 male and 50 female mice. Under the conditions of the studies, there was some evidence of carcinogenic activity of THF in male rats due to increased incidences of adenoma or carcinoma (combined) of the kidney. There was clear evidence of carcinogenic activity of THF in female mice due to increased incidences of hepatocellular adenomas and carcinomas. No evidence for carcinogenicity was found in female rats and male mice.

Using the lowest THF exposure in the most sensitive specie, the male rat at 200 ppm was used for the PDE calculation.

$$200 \text{ ppm} = \frac{200 \times 72.10}{24.45} = 589.8 \text{ mg/m}^3 = 0.59 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{0.59 \times 6 \times 5}{24 \times 7} = 0.105 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.105 \times 290}{0.425} = 71.65 \text{ mg/kg}$$

$$\text{PDE} = \frac{71.65 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 7.165 \text{ mg/day} = \mathbf{7.2 \text{ mg/day}}$$

$$\text{Limit} = \frac{7.2 \times 1000}{10} = \mathbf{720 \text{ ppm}}$$

Conclusion

The former PDE for this solvent was greater than 50 mg/day (121 mg/day) and THF was placed in Class 3. The newly calculated PDE for tetrahydrofuran based upon chronic toxicity/carcinogenicity data is 7.2 mg/day, therefore, **it is recommended that Tetrahydrofuran be placed into Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. This is also the appropriate Class for THF because this Class contains those solvents that are non-genotoxic carcinogens and THF has been demonstrated to be a non-genotoxic carcinogen in rodents.

PDE for N-methylpyrrolidone (NMP)

The ICH Q3C guidance reached step 5 in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs and allowed for minor changes to the guidance that included the existing PDEs. It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

The EWG received new toxicity data for the solvent N-methylpyrrolidone late last year. It had been provided to the FDA by the NMP Producers Group. It was a 2-year chronic feeding study in rats performed by E.I. Dupont de Nemours & Co (unpublished data). The data was sent to the members of the EWG for their analysis. At the time, that data appeared to be the best available upon which to make a recommendation to the Steering Committee regarding a change in the status of NMP. At the last ICH meeting, February 28 to March 2, 2000, I briefed the Steering Committee on the results of the EWG's analysis and its consensus decision. The consensus was to remove NMP from Class 2 (PDE of 48.4 mg/day) and place it into Class 3 with a new PDE of 207 mg/day. Shortly thereafter, members of the EWG provided additional comment and data from which lower PDEs could be determined. The following paragraphs contain an analysis of an appropriate and more sensitive study from which to calculate a new PDE.

Animal Toxicity

The following paper was used for the calculation of the PDE for NMP:

“Effects Of Prenatal Exposure To N-Methylpyrrolidone On Postnatal Development And Behaviour In Rats”, Hass U. et al., *Neurotoxicol. Teratol.*: 1994, 16, (3), 241-249.

Wistar rats were exposed by inhalation to 150ppm NMP for 6 hours/day, daily from days 7-20 of gestation and were then allowed to litter. No maternal toxicity was detected and litter size was unaffected by treatment. No physical abnormalities were described. The offspring were reduced in weight, the difference being statistically significant up to week 5 after birth. Pre-weaning development was impaired as was higher cognitive function related to solving of difficult tasks. Basal function of the CNS was normal and there were no effects on learning of low grade tasks. A NOEL was not established.

$$150 \text{ ppm} = \frac{150 \times 99.13}{24.45} = 608.16 \text{ mg/m}^3 = 0.608 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{0.608 \times 6}{24} = 0.152 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.152 \times 290}{0.33} = 133.58 \text{ mg/kg}$$

$$\text{PDE} = \frac{133.58 \times 50}{5 \times 10 \times 1 \times 5 \times 5} = \mathbf{5.3 \text{ mg/day}}$$

$$\text{Limit} = \frac{5.3 \times 1000}{10} = \mathbf{530 \text{ ppm}}$$

Conclusion

This study was chosen because of the toxicity endpoint that was seen, that is, the effect of the solvent on the function of the developing nervous system in utero. This is a potentially serious toxicity since we do not know if it is a permanent effect or if it is reversible. We are not sure if this delayed development could be due to the lower body weight of the pups. However, the EWG has decided to be cautious in its interpretation and in its safety decision.

The EWG members thus recommend that **N-methylpyrrolidone should be kept in Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. A new PDE and limit as described above should also be declared for this solvent. Class 2 contains those solvents that have significant toxicities such as neurotoxicity, non-genotoxic carcinogenicity, teratogenicity etc., and should be limited in their use up to the PDE limits listed in the table.