MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 18
Species: Rat

Minimal Risk Level: 5 [X] mg/kg/day [ ] ppm


Experimental design: Groups of 17–20 pregnant Sprague-Dawley rats were treated with 0, 0.25, 0.5, or 1 mL 1,4-dioxane/kg/day (0, 258, 516, or 1,033 mg 1,4-dioxane/kg/day based on a specific gravity of 1.034) by gavage in water on Gds 6–15. Food consumption was determined daily and body weight was monitored every 3 days. Sacrifices were conducted on Gd 21 and the number of corpora lutea, implantations, resorptions, and liver fetuses was recorded. The fetuses were weighed and inspected for external malformations and half were examined for visceral abnormalities; the other half were examined for skeletal malformations.

Effects noted in study and corresponding doses: Rats treated with 1,033 mg 1,4-dioxane/kg/day gained 18% less weight than controls during treatment days, although the difference was not statistically significant. Food consumption was slightly (5%) but significantly (p<0.05) reduced in these rats during treatment. The average fetal weight in the high-dose group was slightly but significantly (p<0.01) lower than in controls. Also, a slight but significant (p<0.05) reduction in sternum ossification was seen in high-dose fetuses. There were no significant effects on the number of implantations and live fetuses, post-implantation loss, or incidence of malformations. Based on the reduced maternal and fetal body weight and reduced sternum ossification, a maternal and developmental LOAEL of 1,013 mg 1,4-dioxane/kg/day can be defined; the maternal and developmental NOAEL is 516 mg/kg/day. Attempts made to apply dose-response models to the data were unsuccessful, as no adequate fits of EPA BMDS models to the data were obtained; therefore, the NOAEL/LOAEL approach was used for MRL derivation.

Dose and end point used for MRL derivation: 516 mg/kg/day; NOAEL for developmental and maternal effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? A conversion was done from mL of 1,4-dioxane to mg of 1,4-dioxane using the specific gravity of 1,4-dioxane.
If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
Not applicable.

Other additional studies or pertinent information which lend support to this MRL: JRBC (1998) conducted a 2-week drinking water study in F344 rats and B6C3F1 mice and reported that the most sensitive effect was an increased incidence of nuclear enlargement of the olfactory epithelium in male and female rats receiving doses of approximately 1,010 and 1,040 mg 1,4-dioxane/kg/day, respectively; the corresponding NOAELs were 370 and 400 mg/kg/day. The use of the nasal lesions as the point of departure for MRL derivation was precluded by recent data strongly suggesting that these lesions in rats are due to direct contact of the drinking water containing 1,4-dioxane with nasal epithelium while the rats drink the water (Sweeney et al. 2008). Increased incidence of hepatocyte swelling and vacuolation and hydropic changes in the renal proximal tubule were also reported in male and female rats dosed with 2,960 and 2,750 mg 1,4-dioxane/kg/day, respectively; the corresponding NOAELs were 1,010 and 1,040 mg/kg/day. Although the NOAELs for liver and kidney changes could have been considered as points of departure for MRL derivation, several study limitations, including the lack of statistical analysis of the results due to the fact that only 2 or 3 animals (out of 10/group) were examined, and the fact that end points such as hematology, clinical chemistry, clinical signs, and gross examinations were not conducted or reported, severely compromise the interpretation of the results.

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