ABSTRACT

Human exposures to simazine is a priority in California because of potential for public & occupational exposure (used in residential areas where children). Neuroendocrine effects are the main toxicological concern. The metabolites desmetrynol-sulfate and dihydroxydesmetrynol are of equal toxicity to simazine (common neuroendocrine toxicity mechanism) so for risk assessment purposes they were not evaluated separately. Hazard Identification (Haidit) involves evaluation of published literature and registrant-submitted data and the compilation of definitive studies inquiring target tissues and critical no-observed-effect levels (NOEL). Emphasis in selection of studies for Haidit is on quality of the study, relevance (e.g. route of exposure), FIFRA Guideline acceptability, duration and weight of evidence in cases where there is not a single definitive study. For simazine the focus is on oral exposure. Critical NOELs are significant for calculations for occupational, residential, bystander and dietary margins of exposure for Risk Characterization. Acute and short-term (<1 mo), subchronic (>3 mo) and chronic (>1 yr) exposure are more relevant to the simazine Haidit. An acute study was not available so the critical NOEL was obtained from a rabbit developmental germ failure study showing acute effects (NOEL = 5mg/kg) and a 90 day dietary rat study was selected for the subchronic duration (NOEL = 0.52 mg/kg) as well as a 2 year rat dietary study was used for the chronic duration (NOEL = 0.32 mg/kg) All definitive studies were FIFRA Guideline acceptable. While neuroendocrine effects are a priority, systemic effects at lower NOELs are selected as health protective endpoints. Mammary carcinogenesis is unique to Sprague-Dawley rats and is not a risk for humans. No useful studies were available for dental/implantation effects so oral NOELs were used. Views are not Cal/EPAs

MECHANISM OF NEUROENDOCRINE TOXICITY

SUBCHRONIC TOXICITY (Table 1)

a. Subchronic Oral and Dermal Inhalation NOEL for Simazine: Simazine administered in diet to Sprague-Dawley rats (CD-CDRSD) for 13 weeks showed: body weight, food consumption, 1 effect on histological and chemical chemistry parameters, liver organ weights and kidney pathology at 14 mg/kg which was also the lowest dose tested (LOEL, Tal et al., 1985a). The NOEL was estimated by a Benchmark Dose Lowess model (BMDE, 95% percentile) using body weight to achieve BMDEs of 2.28 mg/kg. (Table 1). The subchronic rat BMDEs is approximate to the LOEL with a 10% Uncertainty Factor (another method of estimating NOEL when a tested dose is not available for risk assessment). The subchronic oral NOEL was used for dental and implantation endpoints since acceptable studies were not available for those endpoints.

b. USEPA: NOEL = 1.8 mg/kg (LOEL = 3.67 mg/kg), for LH surge suppression and altered estrous cycle in a 6-mo. study using aracine in the female SD rat (Monsour, 1996).

ACUTE TOXICITY (Table 1)

a. Acute Oral, Dermal and Inhalation NOEL for Simazine: Acute studies are characterized to determine LD50 values, and as such, are relatively high dose levels in order to produce lethality and not to establish NOELs. Since an acute simazine NOEL was not established, a teratology study in rodent embryos with acute effects was used (Uamano and Arthur, 1984). Effects were: maternal toxicosis (<0.05%), body weight (0.01), body weight gain (0.01) and food consumption (0.01) at 75 mg/kg. Acute NOEL = 5 mg/kg. There were no studies that established dental or implantation NOELs for simazine. Therefore the NOEL (5 mg/kg) for oral acute exposure is used for these exposure routes.

b. USEPA: NOEL = 30 mg/kg/day, from a rat teratology study using simazine (LOEL = 100 mg/kg/day used by USEPA in the RED of 2006 for subchronic exposure (Rifkind, 1996).