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TOXICOLOGY ENDPOINT SELECTION DOCUMENT as of 9/14/94

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Chemical Name: **Terbuthylazine**

PC Code: **080814**

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments. **This document supersedes the previous less than lifetime document on terbuthylazine (4/26/94).**

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Marion Copley Date: ____

Branch Chief: Karl Baetcke Date: ____

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Dermal Absorption Data

MRID: none

% absorbed: The dermal absorption should be considered to be 100%.

In the absence of dermal absorption data and considering the observation that toxicologic effects are observed in both gavage and dermal rabbit studies at similar dose levels, the default of 100 % absorption should be used.

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Acute Dietary Endpoint (One Day)

Studies Selected - Guideline No.: none

Endpoint and dose for use in risk assessment: none

Comments about study and/or endpoint: none

This risk assessment is not required. There are no food uses for this chemical and no toxicity concerns for acute dietary exposure were identified.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Studies Selected - Guideline No.:

28-day dermal toxicity study in the rabbit (82-3); two studies

MRIDs: (1) 00151622 and (2) 40514802 and 42059804

Summary (enter standard Executive Summary or equivalent)

(1) In a 28-day dermal toxicity study (MRID 00151622), male and female New Zealand White rabbits were dermally exposed to terbuthylazine (technical, 99.8% a.i.) at 0, 5, 50 or 500 mg/kg/day (10 animals/sex at 500 mg/kg/day; (5 animals/sex at all other dose levels). Doses were administered in an aqueous vehicle of 0.1% polysorbate/0.5% carboxymethylcellulose. Animals were exposed for 6 hrs/day, 5 days/week. Five high dose animals/sex were sacrificed at 29 days and 5 after a 2-week recovery period.

At 5.0 mg/kg/day, several clinical signs classified as minimal were observed among males and females. During the first 7 days of the study, clinical signs were observed only in 1 - 2 males (dyspnea, piloerection, sedation) and 1 - 2 females (curved body position). Thereafter, all animals developed dyspnea, piloerection, sedation and curved body posture, a few developed tremors (1 male, 2 females) and 1 female had ataxia. Dermal irritation was also observed in treated animals. At 50 and 500 mg/kg/day, clinical signs occurred earlier and with greater severity (classified as moderate). At 500 mg/kg/day, body weight gain was decreased compared to controls (87% less, males and 73% less, females) and food consumption was decreased during weeks 1 and 2 (42% - 71% less than controls, males; 23% - 37%, females). **The LEL of 5.0 mg/kg/day is based on clinical signs in males and females. The**

NOEL is less than 5.0 mg/kg/day.

This study is classified as Core-supplementary data for repeated-dose dermal toxicity in rabbit (guideline 82-3) and is not considered acceptable for regulatory purposes due to the following study deficiencies: small number of animals (5) tested at each dose except high dose, a tissue inventory for microscopic evaluation was not included, NOEL not established. However, the study does provide adequate information to determine that toxicity was observed at the doses tested and the time of onset of toxicity (clinical signs).

(2) In a second 28-day dermal toxicity study (MRIDs 40514802 and 42059804), terbuthylazine (technical, 97.1% a.i.) was applied daily to the intact skin of 5 male and 5 female New Zealand White rabbits for 29 consecutive days. Test material was moistened with distilled water and 0 (distilled water), 0.05, 0.5 or 500 mg/kg/day were applied for 6 hrs/day under occlusive wrap.

At 500 mg/kg/day, reduced body weight gain was observed in males (-36% of controls at Day 28) and females (-39%). Food consumption was also decreased (-76% and -89% of controls during week 1 in males and females; between -11% to -54% of controls at other times). Reduced fecal output was observed sporadically among both sexes. Mortality occurred in one female, preceded by cachexia, hypothermia and muscle wasting. **The LEL of 500 mg/kg/day is based on decreased body weight gain and food consumption in males and females and, in one female, hypothermia, cachexia and mortality. The NOEL is 0.5 mg/kg/day.**

Endpoint and dose for use in risk assessment:

The endpoint for short term occupational or residential exposure is the LEL from the 28-day rabbit dermal toxicity study (5.0 mg/kg/day; LDT).

Comments about studies and/or endpoint:

The LEL of 5.0 mg/kg/day from the first rabbit 28-day dermal toxicity study is considered appropriate because (1) exposure was via the dermal route and (2) the summarized daily clinical observation data indicates that during days 1-7 of the study, only marginal toxicity was observed in 1 - 2 males and females. For short-term exposure, 5.0 mg/kg/day is therefore considered a threshold LEL and an appropriate endpoint for risk assessment. The NOEL of 0.5 mg/kg/day from the second rabbit 28-day toxicity study was considered artificially low, due to the dose selection and based on oral toxicity data from rabbit and rat (see Intermediate Occupational or Residential Exposure comments).

This risk assessment is required.

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Intermediate Term Occupational or Residential (1 Week to Several Months)

Studies Selected - Guideline Nos.:

1 and 2. 28-day dermal toxicity studies (2) in the rabbit (82-3) - see Short-Term Occupational or Residential Exposure section

3. Developmental toxicity study in the rabbit (83-3b)

MRIDs: (1) 00151622; (2) 40514802 and 42059804; (3) 00130744

Summary (enter standard Executive Summary or equivalent):

In a rabbit developmental toxicity study (MRID 00130744), female New Zealand White rabbits were dosed by gavage from days 7 through 19 of gestation with terbuthylazine (technical, 98.5% a.i.) in 1% methylcellulose at 0, 0.5, 1.5 or 4.5 mg/kg/day. Animals were sacrificed on day 29 of gestation.

No signs of maternal toxicity were observed at any dose tested (in a preliminary study, body weight loss was observed at 12.5 mg/kg/day but not at 5 mg/kg/day). **The maternal toxicity LEL is greater than 4.5 mg/kg/day. The maternal toxicity NOEL is equal to or greater than 4.5 mg/kg/day.**

No signs of developmental toxicity were observed at any dose tested. **The LEL for developmental toxicity is greater than 4.5 mg/kg/day. The NOEL for developmental toxicity is equal to or greater than 1.5 mg/kg/day.**

This study is classified as Core-minimum for developmental toxicity in rabbit (83-3b) and is considered acceptable for regulatory purposes. Although a LEL was not established, this study is considered adequate for regulatory purposes since (1) the data indicates that the rabbit is not more sensitive than the rat for developmental toxicity (rat NOEL = 5.0 mg/kg/day) and (2) the rabbit preliminary study indicated that maternal toxicity was observed at 12.5 mg/kg/day.

Endpoint and dose for use in risk assessment:

The endpoint for intermediate term occupational or residential risk assessment is the mid-dose from the rabbit developmental toxicity study (1.5 mg/kg/day) from the rabbit developmental study.

Comments about study and/or endpoint:

In the two 28-day dermal toxicity studies in rabbits (see Short-Term Toxicity Study Summaries), toxicity was observed at 5.0 mg/kg/day but not at 0.5 mg/kg/day. However, no intermediate dose levels were tested. Several studies on terbuthylazine, when evaluated together, suggest that doses between 2 and 5 mg/kg/day may be threshold effect levels for intermediate-term exposure. The mid-dose of 1.5 mg/kg/day (13-day administration by gavage) from the rabbit developmental toxicity study is considered the most appropriate endpoint since (1) although a NOEL of 4.5 mg/kg/day was identified in the rabbit developmental toxicity study, toxicity was observed at 5.0 mg/kg/day in the 28-day rabbit dermal study and (2) the NOEL of 0.5 mg/kg/day from the rabbit 28-day dermal study is considered artificially low, due to dose selection in that study; supported by lack of toxicity following oral administration to rabbit at 1.5 mg/kg/day. The endpoint selection is further supported by a rat 28-day gavage study (MRID 00161104; not summarized in this document), which showed marginal effects at 2.3 mg/kg/day, the lowest dose tested.

This risk assessment is required.

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Cancer Classification and Basis:

Terbuthylazine has been classified as a Group D carcinogen (insufficient information to determine carcinogenicity in humans) by the HED Cancer Peer Review Committee (Peer Review document dated 8-24-94). This decision was based on the finding of increased incidence of mammary gland carcinomas (but not combined benign/malignant tumors) and benign interstitial cell tumors of the testes only in the rat which were significantly increased only at a dose which the CPRC believed to be excessively toxic, but which are the same tumor types induced by closely related analogs.

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RfD and Basis: 0.00035 mg/kg/day based on a NOEL of 0.35 mg/kg/day. The LEL was 1.6 mg/kg/day based on decreased body weight and food consumption observed in males and females. The uncertainty factor (UF) was 1000 to account for inter-species extrapolation (10) and intra-species variability (10) with an additional UF of 10 to compensate for the lack of chronic toxicity data in a non-rodent species and data on reproductive toxicity.

NOEL for critical study: 0.35 mg/kg/day

Study Type - Guideline No.: Two chronic/onco feeding studies in the rat (83-5)

MRIDs: 00103090, 00157342, 92180009, 921800010; 00103089, 00156486, 92180009, 92180010

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Acute Toxicity Endpoints

The table below summarizes the results of acute toxicity studies on terbuthylazine and the toxicity categories for the different routes of administration:

ACUTE TOXICITY DATA FOR TERBUTHYLAZINE

TEST	RESULT	CATEGORY
Oral LD50 in rat (MRID 41907702)	LD_{50} 1000 - 1590 mg/kg (males); 1503 mg/kg (females)	III
4 hr inhalation LC50 in rat (MRID 41603305)	LC_{50} >5.3 mg/L	III
Dermal LD50 in rat (MRID 41907703)	LD_{50} >2000 mg/kg	III
Eye irritation in rabbit (MRID 41907704)	Mildly-to-moderately irritating	III
Dermal irritation in rabbit (MRID 41907705)	Slightly irritating	III
Dermal sensitization in Guinea pig (MRID 41907706)	Not a sensitizer	N/A

Treatment-related clinical signs reported following acute oral or inhalation exposure included piloerection, dyspnea, reduced locomotor activity and/or diarrhea.

Slightly different results were obtained in two other acute toxicity studies. In a second acute oral toxicity study (MRID 41603304) in rats, an LD_{50} of >2000 mg/kg was determined (Tox. Category III). In a second ocular irritation study in rabbits (MRID 41603306), terbuthylazine caused minimal eye irritation (Tox. Category IV). The more sensitive studies (listed in the above table) are used for regulatory purposes.