Adopted as Rule: August 2018

# Toxicological Summary for: Cyanazine

CAS: **21725-46-2**

Synonyms: Bladex, 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-s-triazine

**Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = 3 µg/L**

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0015 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 2.6 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

| | |
|---|---|
| Reference Dose/Concentration: | HED/Total UF = 0.46/300 = 0.0015 mg/kg-d (New Zealand White Rabbit) |
| Source of toxicity value: | Determined by MDH in 2016 |
| Point of Departure (POD): | 1.0 mg/kg-d (NOAEL, Shell Toxicology Lab [Turnstall] 1982 aci WHO, 2003 and USEPA 1988) |
| Dose Adjustment Factor (DAF): | 0.46 (Body weight scaling, subchronic female New Zealand White Rabbit) (USEPA, 2011) (MDH, 2017) |
| Human Equivalent Dose (HED): | POD x DAF = 1.0 mg/kg-d x 0.46 = 0.46 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed) |
| Critical effect(s): | Increased post-implantation loss |
| Co-critical effect(s): | None |
| Additivity endpoint(s): | Developmental, Female Reproductive System |

**Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 3 µg/L**

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0015 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 2.6 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

| | |
|---|---|
| Reference Dose/Concentration: | HED/Total UF = 0.46/300 = 0.0015 mg/kg-d (New Zealand White Rabbit) |
| Source of toxicity value: | Determined by MDH in 2016 |
| Point of Departure (POD): | 1.0 mg/kg-d (NOAEL; Shell Toxicology Lab [Turnstall] 1982 aci WHO, 2003 and USEPA 1988) |
| Dose Adjustment Factor (DAF): | 0.46 (Body weight scaling, subchronic female New Zealand White Rabbit) (USEPA, 2011) (MDH, 2017) |
| Human Equivalent Dose (HED): | POD x DAF = 1.0 mg/kg-d x 0.46 = 0.46 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed) |
| Critical effect(s): | Alterations in fetal skeletal ossification sites and decreased litter size |
| Co-critical effect(s): | Increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, decreased adult body weight gain and food intake |
| Additivity endpoint(s): | Developmental, Female Reproductive System |

**Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 3 µg/L**

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0012 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 3.4 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

| | |
|---|---|
| Reference Dose/Concentration: | HED/Total UF = 0.37/300 = 0.0012 mg/kg-d (Beagle Dog) |
| Source of toxicity value: | Determined by MDH in 2017 |
| Point of Departure (POD): | 0.625 mg/kg-d (NOAEL; Dickie 1986 aci WHO, 2003) |
| Dose Adjustment Factor (DAF): | 0.59 (Body weigh scaling, 1 year female dog) (USEPA, 2011) (MDH, 2017) |
| Human Equivalent Dose (HED): | POD x DAF = 0.625 mg/kg-d x 0.59 = 0.37 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed) |
| Critical effect(s): | Decreased adult body weight and body weight gain, increased relative liver and kidney weights in adults |
| Co-critical effect(s): | Increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, decreased adult body weight gain and food intake |
| Additivity endpoint(s): | Developmental, Female Reproductive System, Hepatic (liver) system, Renal (kidney) system |

**Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = 1 µg/L**

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00022 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 1.0 rounded to **1 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

| | |
|---|---|
| Reference Dose/Concentration: | HED/Total UF = 0.067/300 = 0.00022 mg/kg-d (Sprague Dawley Rat) |
| Source of toxicity value: | Determined by MDH in 2016 |
| Point of Departure (POD): | 0.259 mg/kg-d (NOAEL; Bogdanffy, 2000) |
| Dose Adjustment Factor (DAF): | 0.26 (Body weight scaling, Chronic Sprague Dawley female rat) (USEPA, 2011) (MDH, 2017) |
| Human Equivalent Dose (HED): | POD x DAF = 0.259 mg/kg-d x 0.26 = 0.067 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed) |
| Critical effect(s): | Significant decrease in adult mean body weight and body weight gain, decreased food consumption and food efficiency |
| Co-critical effect(s): | Decreased body weight gain in adults, reduced growth and food consumption |
| Additivity endpoint(s): | None |

**Cancer Health Risk Limit (cHRL) = Not Applicable**

| | |
|---|---|
| Cancer classification: | Group C (possible human carcinogen) ( USEPA, 1994b) |
| Slope factor (SF): | 1.0 $(mg/kg\text{-}d)^{-1}$ (Sprague-Dawley Rat) |
| Source of cancer slope factor (SF): | (USEPA, 1994b) |
| Tumor site(s): | Mammary gland tumors in female Sprague Dawley rats are induced via a neuroendocrine-mediated mechanism of action. The tumors produced via this mechanism of action are not relevant in humans, however, the neuroendocrine disruption is a noncancer endpoint of concern.[1] |

[1] As part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity of cyanazine per the 2005 EPA Final Guidelines for Carcinogenic Potential and concurred with EPA (USEPA 2002a) that based on the scientific evidence specific for cyanazine, and cholo-s-triazines in general (including atrazine), tumor production is not relevant to humans. The chronic nHBV is considered to be protective and no additional Group C uncertainty factor should be applied.

**Volatile:** No

**Summary of Guidance Value History:**

A cancer health based value (HBV) of 0.4 µg/L was derived in 1995. In 2005, a noncancer chronic HBV of 1 µg/L was derived. In 2009, acute, short-term, and subchronic health risk limits (HRL) of 2 µg/L, and a chronic HRL of 1 µg/L were derived. In 2016, MDH re-evaluated the HRLs, resulting in no changes to any value. The 2016 values were the same as the 2009 values, but the basis of the values changed as the result of: 1) use of MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. The 2016 guidance values were adopted into rule as HRLs in 2018.

**Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):**

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

| | Endocrine | Immunotoxicity | Development | Reproductive | Neurotoxicity |
|---|---|---|---|---|---|
| Tested for specific effect? | No[1] | No[2] | Yes | Yes | No |
| Effects observed? | - | - | Yes[3] | Yes[4] | Yes[5] |

**Comments on extent of testing or effects:**

[1] No studies on cyanazine. Studies on several chloro-s-triazines (e.g., atrazine, propazine, simazine) have shown endocrine effects. Suppression of the luteinizing hormone (LH) surge is thought to be the most sensitive effect of chloro-s-triazines. It is believed that cyanazine is similar to other triazines. Therefore, neuroendocrine effects could be a more sensitive endpoint than fetotoxity, which is the basis of the acute & short-term HBV. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

[2] No studies on cyanazine. Immunological studies have been conducted for atrazine. These studies found that the immune system was not more sensitive than the neuroendocrine endpoints.

[3] Alterations in skeletal ossification sites and decreased litter size are the basis of the short-term critical study LOAEL. Post implantation loss was observed in a teratology study and is the basis of the acute HBV. Additional developmental effects (malformations of eye, brain, and chest wall as well as altered relative organ weights, higher incidence of a 13th rib, and complete loss of the litter) were reported at doses at least 2 times above the short-term critical study LOAEL.

[4] Limited reproductive testing for cyanazine. Post implantation loss was observed in a teratology study and is the basis of the acute HBV. Neuroendocrine effects, i.e., suppression of LH and disruption of the estrous cycle (disrupted and lengthened cycles) are thought to be the most sensitive effect of chloros-triazines. It is believed that cyanazine is similar to other

triazines. Therefore, neuroendocrine effects could be a more sensitive endpoint than fetotoxity, which is the basis of the short-term HBV. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

[5] Increased relative brain weight was observed in offspring in a three-generation study at doses similar to the acute & short-term critical study LOAEL. This developmental effect is a co-critical effect for the short-term and subchronic durations. Neurotoxicity of cyanazine has not been studied. However, triazines disrupt the hypothalamic control of pituitaryovarian function providing evidence of associated central nervous system toxicity. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

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