



Web Publication Date: May 2009
Expiration Date: May 2014

Chemical Name: Cyanazine
CAS: 21725-46-2
Synonyms: Bladex

Acute and Short-term Non-Cancer Health Risk Limit (nHRL_{acute & short-term}) = 2 ug/L

$$= \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Acute/Short-term intake rate, L/kg/d})}$$

$$= \frac{(0.001 \text{ mg/kg/d}) \times (0.5) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

$$= 1.73 \text{ rounded to } \mathbf{2 \text{ ug/L}}$$

Reference Dose:	0.001 mg/kg-d (laboratory animal)
Source of Reference Dose:	MDH, 2007
Point of Departure:	1.0 mg/kg-d (NOAEL, Shell Toxicology Lab [Tunstall] 1982 as cited by WHO 2003)
Human Equivalent Dose Adjustment:	None (inadequate information)
Total uncertainty factor:	1,000
UF allocation:	10 for interspecies, 10 for intraspecies, 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s):	alterations in skeletal ossification sites, decreased litter size, increased post-implantation loss, and slight increase in mean resorptions per pregnant animal
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental, Female Reproductive System
Secondary effect(s):	additional developmental effects (e.g., altered relative organ weights, malformations) and decreased body weight gain

Subchronic Non-Cancer Health Risk Limit (nHRL_{subchronic}) = 2 ug/L

$$= \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic intake rate, L/kg/d})}$$

$$= \frac{(0.00063 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

= 1.62 rounded to **2 ug/L**

Reference Dose: 0.00063 mg/kg-d (laboratory animal)
Source of Reference Dose: MDH, 2007
Point of Departure: 0.63 (NOAEL, Dickie 1986 as cited by EPA 1991 and WHO 2003)
Human Equivalent Dose Adjustment: None (inadequate information)
Total uncertainty factor: 1,000
UF allocation: 10 for interspecies, 10 for intraspecies, 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s): increased relative kidney and liver weights
Co-critical effect(s): None
Additivity endpoint(s): Hepatic (liver) system, Renal (kidney) system
Secondary effect(s): altered clinical chemistry (e.g., decreased protein and calcium)

Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = 1 ug/L

$$= \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic intake rate, L/kg/d})}$$

$$= \frac{(0.00026 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{ L/kg-d})}$$

= 1.20 rounded to **1 ug/L**

Reference Dose: 0.00026 mg/kg-d (laboratory animal)
Source of Reference Dose: MDH, 2007
Point of Departure: 0.26 (NOAEL, Bogdanffy et al 2000)
Human Equivalent Dose Adjustment: None (inadequate information)
Total uncertainty factor: 1,000
UF allocation: 10 for interspecies, 10 for intraspecies, 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s): decreased adult BW/BW gain and decreased food consumption /efficiency.
Co-critical effect(s): None
Additivity endpoint(s): No health endpoint (decreased adult body weight and body weight gain and decreased food consumption/efficiency are not utilized as additivity endpoints)
Secondary effect(s): increased incidence of extramedullary haematopoiesis of the spleen and granulocytic hyperplasia of the bone marrow, reduced serum protein, increased incidence of palpable masses, and reduced growth rate.

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: Group C (possible human carcinogen)
Slope factor: 1.0 (mg/kg/d)⁻¹ (laboratory animal)
Source of slope factor: EPA 1993 – as cited by EPA 1994
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 Risk Assessment. The committee determined that for cyanazine there is Suggestive Evidence of Carcinogenic Potential and concurred with EPA that based on the scientific evidence specific for cyanazine, and chloro-s-triazines in general (including atrazine), tumor production is not relevant to humans. The chronic nHRL is considered to be protective and no additional uncertainty factors should be applied.

Volatile: No

Summary of changes since 1993/1994 HRL promulgation:

No HRL exists for cyanazine. In 1995 MDH derived a cancer HBV of 0.4 ug/L. In 2005 MDH derived a revised HBV of 1 ug/L. The noncancer HRLs (acute – 2 ug/L; short-term - 2 ug/L, subchronic - 2 ug/L, and chronic - 1 ug/L) range from the same up to 2-fold higher than the 2005 HBV due to: 1) use of higher, duration specific intake rates; 2) use of non-cancer endpoints rather than a cancer potency value, which is no longer considered relevant to humans; and 3) rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No ¹	No ²	Yes	Yes	No
Effects?	--	--	Yes ³	No ⁴	Yes ⁵

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

-- indicates that no specific tests for that effect were conducted, and that effect was not observed as a secondary effect in any other study used in the HRL evaluation.

Comments on extent of testing or effects:

In 1994 EPA initiated a special review for cyanazine to evaluate potential carcinogenic activity and developmental effects. The manufacturer requested to voluntarily terminate production by the end of 1999. EPA subsequently terminated the special review.

- 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 fetotoxicity, which is the basis of the acute & short-term HRL. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HRLs 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, increased post implantation loss, and decreased litter size are the basis of the acute & short-term critical study LOAEL. 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 acute & short-term critical study LOAEL and are listed as secondary effects.
- ⁴ No reproductive testing for cyanazine. 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 chloro-s-triazines. It is believed that cyanazine is similar to other triazines. Therefore, neuroendocrine effects could be a more sensitive endpoint than fetotoxicity, which is the basis of the acute & short-term HRL. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HRLs for all durations.
- ⁵ Increased relative brain weight was observed in offspring in a three-generation study at doses approximately 2 times the acute & short-term critical study LOAEL. This effect is listed as secondary effects. Neurotoxicity of cyanazine has not been studied. However, triazines disrupt the hypothalamic control of pituitary-ovarian 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 HRLs for all durations.

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