Adopted as Rule: September 30, 2013

Toxicological Summary for Metribuzin:
CAS: 21087-64-9

Synonyms: 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one; Sencor, Lexone, Preview

Acute Non-Cancer Health Based Value ($nHRL_{acute}$) = 30 µg/L

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

$$= \frac{\text{(0.016 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 27.7 rounded to **30 µg/L**

Reference Dose / Concentration:	0.016 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.2 mg/kg-d (NOAEL, LOAEL = 7.9 mg/kg-day based on parental and developmental effects seen by Porter et al, 1988 as cited in the 1998 US EPA RED and 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.48 mg/kg-d (2.2 x 0.22) (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability
Critical effect(s):	Higher pup mortality, decreased body weight gain (maternal).
Co-critical effect(s):	Decreased motor and locomotor activity, drooping eyelids (ptosis), oral staining, and decreased body temperature.
Additivity endpoint(s):	Developmental, Nervous system

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 10 µg/L

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

$$= \frac{\text{(0.006 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 10.4 rounded to **10 µg/L**

Reference Dose / Concentration:	0.006 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.4 mg/kg-d (LOAEL, based on thyroid effects reported by Krotlinger and Vogel, 1982 as cited in the 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.58 mg/kg-d (2.4 x 0.24) (MDH, 2011)
Total uncertainty factor:	100

Reference Dose / Concentration:	0.006 mg/kg-d (rats)
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 for LOAEL-to-NOAEL (statistically significant thyroid hormone level changes along with thyroid histopathological changes reported at the lowest dose tested. A value of 3 rather than 10 was utilized because the changes to T4 and T3 levels were similar in magnitude and no histopathological thyroid changes were observed at 1.3 mg/kg-d following a 2-year exposure.
Critical effect(s):	Changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), and histopathological changes to the thyroid gland.
Co-critical effect(s):	None.
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = $nHRL_{short\text{-}term}$ = 10 µg/L

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

$$= \frac{\text{(0.006 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 16 rounded to 20 µg/L

Reference Dose / Concentration:	0.006 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.4 mg/kg-d (LOAEL, based on thyroid effects reported by Krotlinger and Vogel, 1982 as cited in the 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.58 mg/kg-d (2.4 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 for LOAEL-to-NOAEL (statistically significant thyroid hormone level changes along with thyroid histopathological changes reported at the lowest dose tested. A value of 3 rather than 10 was utilized because the changes to T4 and T3 levels were similar in magnitude and no histopathological thyroid changes were observed at 1.3 mg/kg-d following a 2-year exposure.
Critical effect(s):	Changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), and histopatholigical changes to the thyroid gland.
Co-critical effect(s):	None.
Additivity endpoint(s):	Thyroid (E)

The Subchronic HRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic HRL is set equal to the Short-term HRL of 10 µg/L. The Additivity endpoints are: Thyroid (E)

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = $nHRL_{short\text{-}term}$ = 10 µg/L

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

$$= \frac{\text{(0.0035 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 16 rounded to 20 µg/L

Reference Dose / Concentration:	0.0035 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	1.3 mg/kg-d (LOAEL based on decreased body weight gain and thyroid effects reported by Christenson & Wahle, 1993 as cited in the 1998 US EPA RED and 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.35 mg/kg-d (1.3 x 0.27) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 LOAEL to NOAEL (statistically significant thyroid hormone level changes with histopathological changes at higher doses)
Critical effect(s):	Decreased body weight gain, changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), (and histopathological changes to the thyroid gland at higher doses).
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid (E)

The Chronic HRL must be protective of the acute, short-term or subchronic exposures that occur within the chronic period and therefore, the Chronic HRL is set equal to the Short-term HRL of 10 µg/L. The Additivity endpoints are: Thyroid (E)

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

Cancer classification:	D, not classifiable as to human carcinogenicity. No human data and inadequate evidence from animal bioassays.
Slope factor:	Not applicable
Source of slope factor:	None.
Tumor site(s):	None.

Volatile: No (low volatility)

Summary of changes since 1993/1994 HRL promulgation:
A non-cancer Chronic HRL of 200 µg/L was promulgated in 1993. In 2010 Acute, Short-term, Subchronic, and Chronic Health-Based Values (HBVs) of 40, 10, 10, and 10 were derived. These values were 5 to 20-fold lower than the 1993 HRL as a result of incorporating: 1) a more recent evaluation of the toxicity

information, 2) updated intake rates that include higher intake rates in children, and 3) rounding to one significant digit. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. The resulting Acute HBV (30 µg/L) was 1.5 fold lower than the 2010 value. The Short-term, Subchronic and Chronic HBVs (10 µg/L) were unchanged. The HBVs were adopted as HRLs in 2013.

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

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

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.

Comments on extent of testing or effects:

[1]The critical study selected as the basis of the short-term HRL is a nine-week thyroid mechanism of toxicity study in rats. Additional repeated dose oral toxicity studies have also observed thyroid effects. (Note: the unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

[2,3]Several animal studies are available on metribuzin treatment and developmental effects. In general, the maternal toxic effects are accompanied by toxic effects to the fetus. The effects include a reduction in maternal body weight gain and food consumption as well as fetal mortality. These effects formed the basis of the acute HRL and were observed at dose levels >10-fold higher than the short-term point of departure. (Note: all unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

[4]Neurological effects were listed as co-critical effects and the additivity endpoint for the acute duration based on motor and locomotor activity in females given a single bolus dose at levels similar to the acute point of departure. In a 90-day dietary neurotoxicity study in Fisher F-344 rats, there were no reported treatment-related findings at 62.3 in the functional observational battery (FOB), motor and locomotor activity measures, or observed clinical signs. (Note: the unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

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