Adopted as Rule: September 30, 2013

Toxicological Summary Sheet for Carbamazepine:
CAS: 298-46-4

Synonyms: 5H-Dibenz(b,f)azepine-5-carboxamide**;** Tegretol®; Equetro®; Carbatrol®, Mazepine, CBZ

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = 40 µg/L

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 36 rounded to **40**

* MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for those who have no other route of exposure besides drinking water because of the unlikelihood of exposure from any other sources. However, without additional information a specific value can not be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. For those who take carbamazepine according to prescription, the additional drinking water exposure will be negligible.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on the human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011), equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300
UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental endpoints have not been adequately evaluated in available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Nervous system effects reported in various human studies (drowsiness, vision disturbances, and equilibrium disturbances).
Co-critical effect(s):	Reduced body weight gain in offspring in laboratory animals during lactation. Developmental effects in humans including spinal bifida, head and facial deformities and heart defects;
Additivity endpoint(s):	Developmental, Nervous system

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 40 µg/L

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 36, rounded to **40 µg/L**

*Refer to RSC explanation provided for the acute non-cancer health risk limit.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011), equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)]
.Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300
UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental and immunotoxicity endpoints have not been adequately evaluated in available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Critical effects reported in various human studies include hematological effects (porphyria, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); immune reactions (hypersensitivity); nervous system effects (central nervous system depression, double-vision, blurred vision, disturbance of equilibrium, paresthesae, and suicide ideation); reproductive endocrine effects (male/female sex hormone disturbances) and thyroid hormone disturbances.
Co-critical effect(s):	Reduced body weight gain in offspring during lactation reported in laboratory animals; and developmental effects in humans (spinal bifida, head and facial deformities and heart defects).
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E), Thyroid (E).

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = Short-term nHRL = 40 µg/L

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 135 rounded to 100 µg/L

* Refer to RSC explanation provided for the acute non-cancer health risk limit.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011), equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300
UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental and immunotoxicity endpoints have not been adequately evaluated in available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Critical effects reported in various human studies include hematological effects (porphyria, decreased white blood cell counts, eosinophilia, thrombocytopenia, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); immune reactions (hypersensitivity); nervous system effects (suicide ideation); kidney effects (antidiuresis or hyponatremia, elevated BUN); reproductive endocrine effects (male/female sex hormone disturbances); skeletal effects (elevated serum markers for bone resorption, decreased bone density in children, decreased vitamin D levels); and thyroid hormone disturbances.
Co-critical effect(s):	Reduced body weight gain in offspring during lactation observed in laboratory animals. Developmental effects in humans including spinal bifida, head and facial deformities and heart defects.
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system, Male reproductive system (E), Female reproductive system (E), Skeletal system, Thyroid (E).

The Subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 40 µg/L. Additivity endpoints: Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E),Thyroid (E).

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = Short-term nHRL = 40 µg/L

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

$$= \frac{\text{(0.0057 mg/kg/d) x (0.8*) x (1000 µg/mg)}}{}$$

(0.043 L/kg-d)

= 106, rounded to 100 µg/L

* Refer to RSC explanation provided for the acute non-cancer health risk limit.

Reference Dose / Concentration:	0.0057 (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	5.7 mg/kg-d [LOAEL based on human minimum therapeutic dose for adults at 400 mg/day (200 mg - 2x/day)(Novartis 2011), equivalent to 5.7 mg/kg bw-d based on an average 70 kg adult].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	1,000
UF allocation:	10 for intraspecies extrapolation; 3 for database insufficiencies (neurobehavioral developmental, immunotoxicity, and endocrine endpoints have not been adequately evaluated in available studies), and 10 for use of a LOAEL, 3 for subchronic to chronic duration (because most of the human studies were conducted based on subchronic human exposure durations and a chronic animal study found progression of liver, kidney, spleen and testes effects from the 1-yr interim sacrifice period to the end of the 2-yr study.
Critical effect(s):	In various human studies, effects include hematological effects (porphyria, decreased white blood cell counts, eosinophilia, thrombocytopenia, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); kidney effects (antidiuresis or hyponatremia, elevated BUN); reproductive endocrine effects (male/female sex hormone disturbances); skeletal effects (decreased blood calcium and altered vitamin D leading to effects on bone density, and increased risk of bone fractures); and thyroid hormone disturbances.
Co-critical effect(s):	Developmental effects in humans including spinal bifida, head and facial deformities and heart defects. In animal studies, co-critical effects including development effects such as reduced body weight gain in offspring during lactation, increased number of unossified phalangeal nuclei of forelimbs in fetuses, considered indicative of slight fetal growth retardation and enlarged cerebral ventricles and cleft palate. Liver effects in animals including liver tumors, hepatic macules, hepatocytic vacuolar degeneration and hyperplasia and centrilobular liver hypertrophy. Kidney histopathologic lesions in animals including crater/granular/rough, cysts and ischemic lesions. In animal studies: Benign interstitial cell adenomas in testes, dose-related incidence of testicular atrophy and decreases sperm production.
Additivity endpoint(s):	Developmental system, Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system, Male reproductive system (E), Female reproductive system (E), Skeletal (bone) system, Thyroid (E).

The Chronic nHRL must be protective of the acute, short-term and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 40 µg/L. Additivity endpoints: Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E),Thyroid (E).

Cancer Health Risk Limit (cHRL) = Not Applicable

Carbamazepine has limited evidence for carcinogenicity based on a single rodent bioassay. The approved FDA drug labels contain mandatory cancer statements. MDH staff evaluated the available information and concluded that the noncancer nHRLs are adequately protective of potential carcinogenicity. MDH staff considered: 1) the limited amount of information available to be insufficient for quantitative dose-response assessment; 2) carbamazepine is generally considered to be non-genotoxic; 3) the absence of human epidemiology studies supporting carcinogenicity potential; and 4) the chronic RfD is 1100-fold lower than the lowest dose evaluated in the single rodent bioassay.

Cancer classification:	Not classified by EPA or IARC. Classified by FDA as carcinogenic in rats with unknown significance to humans.
Slope factor:	Not available
Source of slope factor:	Not applicable
Tumor site(s):	Hepatocellular tumors in females; Benign interstitial adenomas in testes in males.

Volatile: No

Summary of Guidance Value History:
Health-Based Values (HBVs) were first derived for carbamazepine in 2011. The HBVs were adopted as HRLs 2013.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[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.

Comments on extent of testing or effects:
[1.] Endocrine effects, including decreased thyroid hormones, in the absence of clinical hypothyroidism, have occurred in multiple human studies and in only a few animal studies. Thyroid effects in animal studies were noted at human equivalent doses over 10 times higher than the human LOAEL. Reduced serum sex hormone binding globulin (SHBG) which results in decreased serum free estrogen and testosterone has occurred in men and women receiving carbamazepine therapy for epilepsy. Sex hormone studies in mammalian animal studies were not available, but reported effects on testes and spermatogenesis in

animals occurred at human equivalent doses from 7.3 to 23 mg/kg-d (within the human therapeutic maintenance dose range) and decreased fertility was reported in animals at human equivalent doses of over 8 times higher than the human LOAEL and above the “not to exceed” dose level of approximately 17 mg/kg-d for human adults. The human equivalent doses for thyroid effects in animals are over 3,000 times higher than the RfD and the human equivalent dose for reproductive effects are over 400 times higher than the RfD. Carbamazepine may also affect the pituitary gland because adverse effects in humans include edema and hyponatremia which is believed to be related to a syndrome of inappropriate antidiuretic hormone secretion. MDH based the RfD, in part, on endocrine effects observed in humans at therapeutic dose levels.

[2.] Human immunotoxicity effects have been reported at therapeutic doses. Serious hypersensitivity reactions, including life-threatening Stevens-Johnson syndrome and toxic epidermal necrosis (SJS/TEN) have occurred in sensitive individuals and there has been some association with development of drug-induced autoimmune disorders. Populations sensitive to SJS/TEN include those who are genetically susceptible due to the presence of an inherited HLA-B*1502 gene allele. The SJS/TEN effects generally occur within the first several weeks after starting treatment. Sensitive populations with genetic sensitivity include many Asians. Caucasian, African-Americans, Native Americans and Hispanics largely do not have this allele.

Some clinical studies have shown immunosuppression including inhibition of lymphocytic protein synthesis, decreased CD4+/CD8+ ratio, decreased IgA, and induced changes in IgG and IgM plasma levels with unknown clinical significance (Basta-Kaim, Budziszewska et al. 2008). A single 7-day mouse study with some reporting and study design deficiencies found some indicators of potential immunosuppression related to CBZ at 5, 10, or 15 mg/kg-d [HED 0.65, 1.3 and 2.0]. Although these effects are at human equivalent doses that are 2-8 times lower than the human LOAEL, the study limitations and lack of replication to-date prevent using this data quantitatively. However, a database uncertainty factor of 3 is used to account, in part, for limitations in availability of adequate immunotoxicity data and an uncertainty factor of 10 is used to account of sensitive populations. The RfD based on the human LOAEL is 36 times lower than the lowest dose causing slight immunosuppression effects in mice and is considered to be protective for immunotoxicity.

[3.] Human developmental effects have been reported at therapeutic doses in many prospective studies of epileptic women who have taken carbamazepine while pregnant. Most developmental effects in animal studies have occurred at doses near or above 200 mg/kg-d, with a human equivalent dose > 44 mg/kg-d which is over 8 times higher than the human LOAEL and over 2,000 times higher than the RfD. A smaller number of animal studies reported slight effects on skeletal and brain development and slight fetal and pup growth retardation of uncertain biological or statistical significance at human equivalent doses at or near the human LOAEL (HED ranging from 4.4 to 9.75 mg/kg-d) but are over 200 times higher than the RfD. Study limitations prevented use of the animal studies for quantitative evaluation. MDH based the RfD, in part, on developmental effects observed in humans at therapeutic dose levels.

[4.] Carbamazepine has produced decreased fertility in animal studies at human equivalent doses of 52 mg/kg-day or more (over 10 times higher than the human LOAEL and over 2500 times higher than the RfD). Effects on testes and spermatogenesis in animals occurred at human equivalent doses from 7.3 to 23 mg/kg-d (within the human therapeutic maintenance dose range) and decreased fertility was reported in animals at human equivalent doses of over 8 times higher than the human LOAEL and above the “not to exceed” dose level of approximately 17 mg/kg-d for human adults. MDH based the RfD, in part, on reproductive effects observed in humans at therapeutic dose levels.

[5.] The neurotoxicity dataset is limited by the absence of a multigenerational rodent study to evaluate neurobehavioral developmental toxicity and/or pending completion of ongoing human clinical trials to

measure various neurobehavioral developmental parameters in children who were exposed during gestation. A small number of animal studies reported slight effects on brain development at HEDs at or near the human LOAEL. Temporary, reversible neurotoxicity occurs in human during the first few weeks of therapeutic doses. Neurotoxicity can occur in 5-14% of patients and persons with prior brain injury and elderly may be more sensitive. Typical neurotoxicity symptoms include diplopia, drowsiness, blurred vision, disturbed equilibrium and paresthesae. Long-term or irreversible neurotoxic effects are not known to occur with carbamazepine therapy. Neurotoxicity reactions can be reduced or prevented by gradually building up the therapeutic dose from initial, smaller starting doses.

The FDA-approved drug labeling indicates a risk for suicidal behavior and ideation for persons taking antiepileptic drugs, in general. Pooled analyses of 199 clinical trials of 11 different antiepileptic drugs with a median treatment period of 12 weeks showed an estimated incidence of 0.43% compared to 0.24% among controls. The increase was observed as early as one week after starting treatment and the trials did not go longer than 24 weeks, so the risk beyond 24 weeks is uncertain (Novartis Pharmaceuticals Corporation 2011).

One limited mouse study of neurobehavioral effects of carbamazepine in adult offspring whose mothers were exposed during gestation reported effects on locomotor activity and startle response at a human equivalent dose of approximately 14 times higher than the human LOAEL and over 4,000 times higher than the RfD. Enlarged cerebral ventricles were reported in fetuses of mice exposed at a human equivalent dose of 5.2 mg/kg-day, similar to the human LOAEL, but this effect is of questionable biological and statistical significance and the study design is limited.

Carbamazepine may also be a neurodevelopmental toxicant in humans, causing effects in children (aged 9 mo to 5 yrs) exposed to carbamazepine *in utero* as measured by the Bayley Scales of Infant Development or the Griffiths Mental Development Scales (OR 7.7, 95% CI 1.4 to 43.1; $p<0.01$) (Cummings, Stewart et al. 2011). Newborn infants exposed *in utero* had no alterations in brainstem auditory evoked potentials. However, significant effects on latencies of brainwaves III and V and brainwaves I-V interwave intervals were correlated with third trimester exposure (Poblano, Belmont et al. 2002). Neurodevelopmental outcomes in 6-yr old children exposed *in utero* to carbamazepine are currently being studied a large multicenter study in the US and UK and the mean IQ in an interim study of 3-yr olds was not impacted (Meador, Baker et al. 2009). MDH based the RfD, in part, on neurotoxicity effects observed in humans at therapeutic dose levels.

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