Sulfolane
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ToxStrategies of Austin (August 18, 2010) and URS of Houston (January 31, 2011) submitted proposed RfDs and/or RfCs for the March 2011 TRRP toxicity factor update. The Toxicology Division (TD) reviewed that information and provided toxicity factors in a March 9, 2011 document. This document updates the March 9, 2011 toxicity factor documentation with a slightly revised benchmark dose (BMD) and an animal-to-human extrapolation procedure reflective of the June 2011 proposed *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors (RG-442)* by the Texas Commission on Environmental Quality (TCEQ). These changes increase the RfD by a factor of 3.5, primarily due to the updated animal-to-human extrapolation procedure which received favorable external expert peer review as part of the proposed RG-442 guidelines.

ToxStrategies initially proposed an RfD of 1.2E-02 mg/kg-day based on a $BMDL_{1SD}$ of 15.1 mg/kg-day for reduced white blood cells (WBCs) (females more sensitive) in a 3-month (subchronic) rat study (Huntingdon Life Sciences 2001), adjusted to a human equivalent dose point-of-departure (POD_{HED}) of 3.7 mg/kg-day using BW scaling, divided by a total UF of 300 (3 animal to human, 3 database uncertainty, 10 subchronic study, and 3 intrahuman). ToxStrategies further proposed an RfC of 1.9E-02 mg/m^3 based on a NOAEL of 20 mg/m^3 for a four species (rats, guinea pigs, dogs, squirrel monkeys) 90-day (subchronic) study (Andersen et al. 1977) for effects such as chronic lung inflammation, lung hemorrhage, motor disturbances, seizures, convulsion and death (LOAELs of 159-200 mg/m^3). After duration adjustment (20 mg/m^3 x 23 hours/24 hours x 7 day/7 day = 19.2 mg/m^3), a total UF of 1,000 was used (10 animal to human, 3 database uncertainty, 3 subchronic study, and 10 intrahuman).

However, documentation from August 31, 2011 indicates that ToxStrategies made a minor error in entering data for BMD modeling which resulted in a slightly lower $BMDL_{1SD}$ and POD_{HED} in the original documentation than would have been calculated had the error not occurred. More specifically, in the data entry for the high dose group WBC count, a standard deviation of 1.109 was entered instead of 1.019. The correct standard deviation (1.019) results in a slight increase in the $BMDL_{1SD}$ from 15.1 to 16.1 mg/kg-day, and a corresponding increase in the POD_{HED} from 3.7 to 3.9 mg/kg-day using BW scaling. As such, the POD_{HED} of 3.9 mg/kg-day for decreased WBCs is the correct one for TD consideration.

URS proposed an RfD of 2.5E-03 mg/kg-day based on a NOAEL of 0.25 mg/kg-day for reduced serum enzyme levels (AST/ALT, a.k.a. GOT/GPT) and decreased bone marrow cells in a 6-month (chronic) guinea pig study (Zhu et al. 1987), divided by a total UF of 100 (10 animal to human, 1 database uncertainty, 10 intrahuman). ToxStrategies indicated that without measures of variability and normal reference ranges that the biological significance of these findings in guinea pigs is unclear (also, statistical analyses independent of the study authors cannot be performed). However, in the absence of sufficiently convincing information to the contrary, a conservative assumption is often that statistically significant findings are relevant when an endpoint such as

reduced bone marrow cells are reported (e.g., the reduction was 33% from controls to the 2.5 mg/kg-day dose group), especially when consistent with other effects on cell counts (e.g., decreased WBCs). Therefore, TD believes the results as reported (e.g., significant decreases in bone marrow cells) should still be considered.

RfD Derivation

The proposed RfDs are less than a factor of 5 apart. However, TD believes female rats being more sensitive than males is not justification for ToxStrategies reducing the intrahuman UF to 3 primarily because it is unknown how female rat sensitivity for the species tested relates to intrahuman variability (i.e., it is unknown how inter-gender TK/TD differences conferring differences in gender sensitivity to sulfolane in one homogeneous rodent species relate to potential TK/TD differences affecting sensitivity to sulfolane in the heterogeneous human population, especially considering that individuals in the human population may exhibit different sensitivities not only based on gender, but also age, pre-existing health conditions, etc.). Additionally, typically the most sensitive effects in the most sensitive species (and even gender) are used (bone marrow cell reduction in guinea pigs) but may not have been for their proposed RfD as independent statistics could not be run (even if under a conservative assumption of adversity) and ToxStrategies has other endpoint-specific concerns. TD believes a full intrahuman UF of 10 is justified. Additionally, consistent with TCEQ's proposed *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors (RG-442)*, TD believes BW scaling adequately accounts for both TK and TD in animal-to-human extrapolation (i.e., without use of an additional UF of 3 for TD). Thus, the total UF used by TD with the POD_{HED} of 3.9 mg/kg-day is 300 (3 for database uncertainty, 10 for use of a subchronic study, and 10 for intrahuman variability), which would result in an RfD of 1.3E-02 mg/kg-day (3.9 mg/kg-day / total UF of 300 = 1.3E-02 mg/kg-day). The resulting RfD is considered protective by TD for the effect it is based on (i.e., reduced WBCs), and is also significantly below the NOAEL reported for bone marrow effects in the potentially more sensitive guinea pig (0.25 mg/kg-day). This puts the RfDs considered for adoption a factor of 5 apart.

As TD considers both RfDs under consideration as sufficiently similar to be adequately protective and ToxStrategies used a more robust and modern analysis (e.g., BMDLs, multiple PODs), the TD will adopt the POD proposed by ToxStrategies (POD_{HED} of 3.9 mg/kg-day) divided by a total UF of 300 (as discussed above) for a final RfD of 1.3E-02 mg/kg-day.

RfD = 1.3E-02 mg/kg-day

RfC Derivation

Regarding the RfC proposed by ToxStrategies (1.9E-02 mg/m^3), given the steepness of the dose-response curve based on the subchronic study (a factor of only 8-10 separates no effects from convulsions and death potentially), the TD believes a higher subchronic UF to be justified. Chronic studies could identify more subtle effects (a chronic critical effect) at a LOAEL/NOAEL more than three times lower than the subchronic study. The relatively small difference between very severe effect levels and no effect levels reported in the subchronic study is of concern.

Using a subchronic UF of 10 instead of 3 yields a total UF of 3,000 and a resulting RfC of 6.4E-03 mg/m^3 (19.2 mg/m^3 / total UF of 3,000 = 6.4E-03 mg/m^3).

RfC = 6.4E-03 mg/m^3

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