Peer Review Charge for

2, 4-D Toxicological Profile – Post-Public Draft

This version of Toxicological profile for 2, 4-D has been reviewed by external peer reviewrs, cleared by the Agency Office of Science, and offered for public comments. All comments from previous reviewers, clearing review and public comments were responded to and incorporated accordingly. However, public comments focused on the intermediate oral MRL resulted in the revision of this 2, 4-D MRL.

Additionally, ATSDR review the literatures again and derived a new chronic oral MRL.

Thus, we would like for you to focus on the new intermediate oral and chronic oral MRLs issue presented below.

New provisional MRL of 0.2 mg/kg/day has been derived for intermediate-duration oral exposure to 2, 4-D based on a NOAEL of 16.6 mg/kg/day and a LOAEL of 45.3 mg/kg/day for slight proximal tubule degeneration in the kidney of male Sprague-Dawley rats receiving 2, 4-D from the food for up to 11 weeks (Marty et al. 2013).

The previous intermediate oral MRL was 0.009 mg/kg/day and was derived based on dose-related decreased offspring body weight on postnatal day 16 using BMD software for analyses. Two BMD models (Exponential model 4 and Hill model) provided an adequate fit by the various statistical criteria. Because the $BMDL_{RD05}$ estimates are sufficiently close, the model with the lowest AIC (Exponential model 4) was selected. The Exponential model calculated BMD_{RD05} and $BMDL_{RD05}$ values of 1.27 and 0.93 mg/kg/day, respectively, for decreased pup body weight on PND 16. Dividing the $BMDL_{RD05}$ of 0.93 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) yields an intermediate-duration oral MRL of 0.009 mg/kg/day for 2, 4-D.

Based on public comments and EPA's critique of the studies conducted by Stürtz and associates, ATSDR has re-evaluated the basis of the intermediate oral MRL. In a Federal Register entry (Volume 77, No. 75, Wednesday, April 18, 2012), EPA (2012) compared results from Stürtz et al. (2006) with results from a 2-generation reproduction study (a DER cited as EPA 1986 in the profile), an extended 1-generation reproduction study (cited as Marty et al. 2013 in the profile), and a range-finding study (Saghir et al. 2013a). EPA (2012) noted the following:

- *The Stürtz et al. (2006) study did not make clear whether it was reporting decrements in body weight gain (the amount of weight gained between designated time periods) or absolute body weight. EPA noted that body weight is generally regarded as the more important measure because decrements in body weight gain, which is a calculated value and may be misleading, may occur even though the pup is otherwise within normal body weight levels.*
- *The pup body weight results were not consistent with a prior 2-generation reproduction study and were not replicated by either a range-finding study for the extended 1-generation reproduction study or the extended 1-generation study itself.*
- *The extended 1- and 2-generation studies were conducted under EPA's Good Laboratory Practice Standards regulations and all underlying data for these studies are available for review.*
- *The extended 1-generation study is considered state-of-the-science because it considered the toxicokinetic profile of 2, 4-D as it makes its way from the mother to the offspring, as well as a variety of other endpoints that are considered more sensitive than body weight (e.g., hormones, hematology, clinical chemistry, etc.). The toxicokinetic aspect is particularly important because, based on the toxicokinetic profile, the doses in the extended 1-generation reproduction study were adjusted during the lactational period to prevent excessive dosing both to the maternal rat and to the pups during early lactation and due to a "double exposure" when pups are both nursing and starting to consume diet (as in the case on postnatal day 16).*

- *Although adjustments to the diet were also performed in the Stürtz et al. (2006) study, the procedures used were different and may, to some extent, explain the results in the Stürtz et al. (2006) study compared to the extended 1-generation reproduction study.*
- *The Stürtz et al. (2006) study does not show a clear dose-response effect. Although there is a greater effect on body weight comparing the lowest and highest doses, the body weight effects are essentially the same in the lowest two doses despite significant differences in the doses, and that same phenomenon is observed for the highest two doses.*
- *The extended 1-generation reproduction study examined a much larger sample of pups. Roughly 4 times as many pups were evaluated in the extended 1-generation reproduction study from postnatal day 1 to 21 compared to the Stürtz et al. (2006) study, and the Stürtz et al. (2006) study evaluated no pups after postnatal day 16.*
- *Changes in the composition in maternal milk may provide an explanation for effects seen in the pups, but do not constitute an adverse effect independent of effects in the pups.*

-- Please comment on any aspect of our MRL database assessment that you feel should be addressed.

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New chronic-Duration Oral MRL was derived after postpublic comments period. A provisional MRL of 0.2 mg/kg/day has been derived for chronic-duration oral exposure to 2,4-D based on a $BMDL_{10}$ of 16.66 mg/kg/day for proximal tubule degeneration/regeneration in the kidney of male B6C3F1 mice receiving 2,4-D from the food for up to 2 years (Charles et al. 1996a; EPA 1996b). The incidence data for degeneration with regeneration of the descending portion of the proximal tubules in the male mice were analyzed using all available dichotomous models in the EPA Benchmark Dose Software (BMDS, version 3.1) using the extra risk option and a benchmark response (BMR) of 10% change from controls. The $BMDL_{10}$ of 16.66 mg/kg/day is divided by uncertainty facor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to calculate MRL of 0.166 mg/kg/day, then rounded to 0.2 mg/kg/day.

-- Please comment on any aspect of our MRL database assessment that you feel should be addressed.

APPENDIX A:

Please address the MRL worksheets based upon the questions provided above about the MRLs.