

Dow AgroScience's Response to EPA's Preliminary Chlorpyrifos Human Health Assessment (submitted October 5, 2011)

Executive Summary

Chlorpyrifos remains one of the most important insect management products for U.S. agriculture and also is one of the most well studied products from the standpoint of human safety. EPA first reregistered chlorpyrifos following the evaluation period from 1984 to 2008, and the Agency has now embarked on an ambitious new round of re-evaluation as part of the Registration Review process to be completed during the period 2009 to 2015. We are glad to see that EPA has designed the Registration Review program to include a high level of transparency and to allow for public participation. Dow AgroSciences appreciates the opportunity to review and comment on the preliminary human health assessment for chlorpyrifos released by the Agency in a number of memos and supporting documents over the two-week period July 1 to 15, 2011. The willingness of the Agency, in response to stakeholder requests, to extend the comment period to a full 90 days, as originally envisioned upon introduction of the Registration Review program, is also most appreciated.

Detailed technical review comments by Dow AgroSciences scientists as well as invited comments and assessments by independent experts have been developed to assist the Agency in revising and refining this preliminary version of the human health assessment. Our primary points are briefly summarized below and are developed in full detail in this report and associated submission documents.

First, Dow AgroSciences would like to recognize the significant progress that the Agency has made in developing an updated human health assessment for chlorpyrifos based on the best available scientific data and employing appropriate methodologies and science policies. We understand that the EPA Health Effects Division (HED) team has worked tirelessly and under tight deadlines to develop this draft, and it is our opinion that some notable improvements have also been made in this version in comparison with the Agency's last human health evaluation of June 8, 2000. Specifically:

- *The Agency has concluded that cholinesterase inhibition remains the most suitable basis (and most sensitive indicator of biological effect) for establishing chlorpyrifos toxicological endpoints.* Dow AgroSciences agrees with EPA's reconfirmed assumption that cholinesterase inhibition is the most relevant and sensitive endpoint for assessment of potential health risk from exposure to chlorpyrifos.
- *The Agency issued a data call-in for a state-of-the-art study on comparative cholinesterase inhibition in the most sensitive lifestage and has now appropriately relied on results of this study to establish an updated point of departure concerning acute exposure assessment.* Dow AgroSciences supports the overall EPA approach for estimating benchmark doses (BMD) for cholinesterase inhibition.
- *The Agency has clearly demonstrated its commitment to science-based regulation in taking the appropriate step, based on the data, of proposing a reduction of the Food Quality Protection Act (FQPA) uncertainty factor from 10X to 1X for most assessment scenarios.* Dow AgroSciences supports EPA's evaluation of available data and notes that selection of the 1X FQPA UF is consistent with recent EPA policy actions, the completeness of the chlorpyrifos toxicology database, and reliance on toxicological points of departure based on testing with sensitive lifestages among other factors.
- *The Agency has relied on available food residue monitoring data to develop a refined dietary risk assessment for chlorpyrifos that identifies no acute or chronic intake concerns.* Dow AgroSciences acknowledges the conservative nature of EPA's dietary assessment in terms of the use of residue monitoring data, non-detects, and percent crop treated, and we agree with EPA's conclusions that food exposures to chlorpyrifos are below Agency levels of concern for all subpopulations.
- *The Agency has completed a bystander inhalation exposure assessment using available monitoring data and has concluded that off-target vapor drift from agricultural fields does not pose a substantial risk.* Dow AgroSciences supports EPA's preliminary assessment of bystander inhalation exposures resulting from agricultural uses.
- *The Agency has appropriately recognized the value of advanced human exposure and effects modeling in helping to inform risk assessment conclusions and*

assumptions. Dow AgroSciences strongly supports EPA's pursuit of advanced human exposure/effects *modeling* efforts. We also note that the conclusions of EPA's preliminary human health assessment in this regard are supported by the model favorably evaluated by the Scientific Advisory Panel (i.e., human infants have same range of sensitivity as adults, and current dietary exposures are far below levels that would affect cholinesterase levels in adults and children).

Second, however, Dow AgroSciences would like to point out areas of the preliminary human health assessment that are not yet complete or that require substantial refinement. In several instances we are submitting additional information or offering specific recommendations for the Agency to consider.

- *In some cases, the Agency has relied on non-representative and unrealistic use pattern assumptions for exposure and risk assessment scenarios which have resulted in exaggerated estimates.* Grape growers do not apply 33 lb ai/acre. Sod farm managers do not make 26 annual applications. Dow AgroSciences has reviewed EPA assumptions about product use and has offered a number of corrections and updates to help better characterize actual product use, including typical application practices. **Dow AgroSciences recommends** that EPA review use pattern scenarios employed for risk assessment purposes and select more realistic ones that better represent how and where the product is used in U.S. agriculture. To that end, **Dow AgroSciences also recommends** that EPA find more active and focused ways to engage the agricultural community and USDA in obtaining information on actual use patterns.
- *The Agency has inappropriately relied on gross overestimates of potential drinking water contamination generated by computer modeling while ignoring the available drinking water monitoring studies that have consistently shown no detection of chlorpyrifos or degradates.* Use of such crude *modeling* estimates is inconsistent with the Agency's sophisticated approach to food residue assessment and leads to unwarranted predictions of public health concerns from drinking water exposures. Robust monitoring data supplemented by appropriate statistical analyses provide realistic yet conservative estimates of the potential distribution of residues in drinking

water. Dow AgroSciences is submitting to EPA a refined drinking water assessment relying on best available monitoring data and which demonstrates that exposures are acceptable and well below Agency levels of concern. **Dow AgroSciences recommends** that EPA move from its reliance on overestimates of drinking water exposures generated by screening level modeling and adopt an approach using the best available monitoring data.

- *The Agency has calculated an overly-conservative potency factor for the oxon degradate of chlorpyrifos and has predicted exposure concerns related to residues in human drinking water.* In addition to the recently completed comparative cholinesterase assay (CCA), there are additional reports and literature that inform on oxon biological potency. Based on evaluation of brain cholinesterase inhibition data, no toxicity adjustment factor appears necessary for the oxon. Consideration of existing drinking water monitoring data, typical drinking water treatment processes, and the most recent environmental fate data enables more realistic estimates of oxon exposure. **Dow AgroSciences recommends** that EPA consider using a more comprehensive and biologically-based approach in assessing relative potency of the oxon degradate. **Dow AgroSciences also recommends** that EPA review and revise its assumptions related to predicted occurrence of oxon residues in drinking water supplies.
- *The Agency has developed conservative, deterministic worker exposure assessments that may not accurately predict exposures under actual use conditions or make best use of available data.* Dow AgroSciences has conducted and is now submitting to the Agency a worker practices survey to better characterize chlorpyrifos use by growers and custom applicators. In addition, Dow AgroSciences has developed a probabilistic worker exposure assessment providing a more realistic calculation of exposure and risks based on current agricultural practices and product labelling. **Dow AgroSciences recommends** that EPA use a probabilistic rather than a deterministic assessment approach for developing more realistic estimates of potential worker exposures.
- *The Agency continues to place emphasis on the findings of epidemiology studies and the possible correlation of chlorpyrifos exposures with human developmental effects,*

but has not completed a full “weight-of-evidence” evaluation upon which to base conclusions. Several cohorts of individuals have been followed by academic researchers at Columbia University and elsewhere and much publicity has been accorded their claims with respect to low-level chlorpyrifos exposures and human health effects. Based on Dow AgroSciences’ latest evaluation, the substantial inconsistency of findings across studies and the lack of a plausible mechanism of action severely limits the value of these studies for regulatory purposes. Based on the recommendation of the September 2008 EPA Scientific Advisory Panel, Dow AgroSciences commissioned an independent “weight of evidence” evaluation of the relevant studies which has concluded that, taken together, the epidemiology data are inconsistent with respect to linking chlorpyrifos exposures and neurodevelopmental toxicity. **Dow AgroSciences recommends** that EPA consider the recently completed weight-of-evidence determination as it evaluates the findings and claims of the epidemiology literature. **Dow AgroSciences also recommends** that EPA not characterize human epidemiology study reports as “incidents” to be lumped together with anecdotal information related to poison control center reports of adverse effects in the absence of any clear assessment methodology.

- *The Agency continues to express interest and potential concerns related to findings of laboratory animal studies regarding neurodevelopmental and neurobehavioral effects but has not completed an updated evaluation of the non-cholinergic literature with respect to both positive and negative findings.* The Agency has presented summary information related to findings of selected literature reports of non-cholinergic toxicity effects and indicated that a full evaluation is planned. Dow AgroSciences commissioned an independent evaluation of the research literature, both published and unpublished, with respect to relevant non-cholinergic effects. This evaluation has been peer reviewed and is being published in the scientific literature. **Dow AgroSciences recommends** that EPA consider the recently completed assessment as the Agency evaluates the findings and claims of the non-cholinergic effects literature.
- *The Agency continues to raise questions about morphometric measurements in the developmental neurotoxicity (DNT) study and the possible need for additional*

information, although there is no evidence that supplemental information already filed with EPA to address these concerns has yet been considered or evaluated. In addition to providing EPA with supplementary information, Dow AgroSciences commissioned an independent evaluation of the DNT study and the Agency request for additional data. **Dow AgroSciences recommends** that EPA thoroughly evaluate all supplemental information that it has on file regarding the DNT study and consider also conclusions of the independent DNT study evaluation in reaching a decision concerning adequacy of the study.

- *The Agency has not yet completed an aggregate exposure assessment for chlorpyrifos as required under FQPA.* EPA indicated in the draft assessment that an aggregate exposure assessment (food, water, residential exposures) was not completed since preliminary estimates for water alone exceeded the Agency's level of concern. As noted earlier, Dow AgroSciences believes that the *modeling* estimate of drinking water exposure relied on by EPA in the draft assessment is unrealistic and overly conservative. Dow AgroSciences has demonstrated that refined assessments of drinking water concentrations based on actual monitoring data predict far lower exposures and this should allow a refined aggregate exposure assessment to be completed. **Dow AgroSciences recommends** that EPA develop an aggregate exposure assessment based on refined estimates of dietary exposure (EPA has completed), drinking water exposure (Dow AgroSciences has completed), and residential exposure (EPA has completed). **Dow AgroSciences also recommends** that EPA publish a draft version of the aggregate exposure assessment for comment to ensure transparency and public participation in the Registration Review assessment process.

Finally, there are a number of areas in this preliminary, first draft human health assessment for chlorpyrifos which are either incomplete (e.g., toxicology chapter, evaluation of non-cholinergic literature, weight-of-evidence evaluation of epidemiology studies, aggregate exposure assessment) or require substantial refinement (e.g., drinking water exposure assessment, worker exposure assessment). Consequently, the appropriate time and effort should be devoted to preparing a revised, second draft assessment. This is not only the first

substantial human health assessment to be developed by EPA under the Registration Review program, but it may also be one of the more complex ones to be undertaken. In light of the large number of incomplete tasks and likely revisions, **Dow AgroSciences recommends** that EPA publish a revised, second draft of the preliminary chlorpyrifos human health assessment for an additional 90-day public comment period.