Office of Environmental Health Hazard Assessment

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DATE: September 30, 2005

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT IMIDACLOPRID

Thank you for the opportunity to review the draft risk characterization (RCD) document for imidacloprid dated May 5, 2005, prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of California Health and Safety Code (HSC) Section 59004, and also under Food and Agricultural Code (FAC) Section 13129, in which OEHHA provides advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

This draft RCD evaluates solely dietary exposure to imidacloprid. As stated in the cover letter, the risks from occupational and residential exposures will be included as an addendum to this RCD once the exposure assessment document (EAD) is completed. Additionally, since it is stated in the text of the document that exposures from imidacloprid in ambient air will also subsequently be evaluated, we are assuming that this active ingredient is also a candidate TAC.Overall, we find the document thorough and well written. Generally, we find the assumptions, considerations and conclusions contained in the RCD appropriate, scientifically defensible and sufficiently supported. OEHHA does have a major concern, however, that the acute regulatory level used to evaluate dietary risks from imidacloprid exposure may not be sufficiently health-protective. This concern and other suggestions and recommendations are outlined below. We hope that you find our comments and recommendations supportive and useful.

Imidacloprid is a neonicotinoid insecticide that is registered to control pests on agricultural and nursery crops, structural pests, and parasites on companion animals. The material is a nicotinic receptor agonist and is structurally and functionally related to nicotine. Imidacloprid is representative of the "new generation" of neurotoxic insecticides that are more selectively toxic to insects than to mammals, in comparison to the more classic neurotoxins.

Our comments on the draft RCD are as follows:

1. Acute oral exposure to imidacloprid is evaluated in the draft RCD using the results from an acute neurotoxicity study in rats (Sheets, 1994). From this study, a no-observed-adverse-effect-level (NOAEL) of 42 mg/kg is identified based on a decrease in motor and locomotor activity in females at the next higher dose of 151 mg/kg versus the controls. The effect on motor and locomotor activity was dose-related and was observed at all doses in the study (42, 151 and 307 mg/kg). Even though the decrease in motor and locomotor activity was not statistically significant versus the controls at the lowest dose tested, since a dose-related trend was observed, a benchmark dose (BMD) analysis of the dataset was conducted and a LED_{05} (lower bound on the 5% BMD response) of 9 mg/kg was derived and was used to evaluate risk in the RCD. OEHHA supports the use of BMD methodology in establishing an acute regulatory level from this dataset.

   An estimated NOAEL (NOAEL-est) of 5.5 mg/kg-day was derived from a LOAEL of 54.7 mg/kg in a rat developmental neurotoxicity (DNT) study (Sheets, 2001). The LOAEL was based on a statistically significant decrease in the widths of the caudate putamen and thickness of the corpus callosum in female offspring of dams exposed to the highest dose tested, 54.7 mg/kg-day, from gestation day zero (GD 0) to GD 20 versus that observed in the controls. BMD analysis of the dataset was not possible since brain

measurements were not made in the pups from the other two dose levels in the study (8 and 19 mg/kg-day).

The regulatory value of 9 mg/kg was selected for evaluating acute exposures to imidacloprid since it was based on a BMD analysis of a dataset that showed a clear dose-response and was from a high-quality study with comprehensive evaluations (clinical observations, functional observational battery, motor activity, neuropathology, etc.) of a relatively large number of animals (18) per dose level. In addition, the LED_{05} is supported by a NOAEL of 10 mg/kg observed in a mouse study that was based on apathy, decreased motility, labored breathing, staggering gait and trembling at the next higher dose of 71 mg/kg. In contrast, considerable uncertainty is associated with the NOAEL-est of 5.5 mg/kg-day from the rat developmental neurotoxicity study since it was an estimated NOAEL from only one data point, the LOAEL. Because of these considerations, the value of 9 mg/kg was selected as the regulatory value for acute oral exposures to imidacloprid.

While we agree that there is less uncertainty associated with the chosen regulatory value of 9 mg/kg versus the NOAEL-est of 5.5 mg/kg, we note that the latter study (Sheets, 2001) is well conducted, utilized sufficient numbers of animals (16 dose/sex) and is deficient only in the sense that brain measurements were not made on the animals at the intermediate doses. The results from this study are particularly and uniquely useful since this is the only study with imidacloprid where these measurements were taken and this effect observed. Indeed, it appears that the authors of the RCD deem the study to be useful and of acceptable quality since it is suggested in the RCD (page 58) that the estimated NOAEL may be applied to assessing imidacloprid risk to women of childbearing age, although the RCD stops short of officially doing so. OEHHA agrees with DPR that this study is of sufficient quality to use for regulatory purposes. Further, we are concerned that the chosen regulatory value is insufficiently protective against developmental effects and/or effects on adults possible at lower doses of imidacloprid. As pointed out in the RCD, there is at least a hypothetical mechanistic link between decreases in the widths of the caudate putamen and corpus callosum and decreases in motor/locomotor activity such as that observed in adult female rats exposed to imidacloprid, implying that the effect may not be limited to *in utero* exposure and that adult animals may be susceptible as well.

Accordingly, OEHHA is concerned that a number of issues regarding the adoption of the acute regulatory level for imidacloprid are left unresolved in the RCD and recommends additional discussion be added to the document. First, are the effects of imidacloprid on the dimensions of specific brain structures solely a developmental effect or, as suggested in the RCD, are they more general and applicable to adults as well? If these effects are applicable to more mature animals, are they responsible for or related to the observed reduction in motor activity observed in female rats? Lastly, what regulatory level would

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likely protect against the effect of imidacloprid on brain dimensions? These issues should be resolved and or discussed in more detail in subsequent versions of the RCD. Suggested approaches to more satisfactorily address these issues are offered below:

Adopt the LED_{10} of 9 mg/kg for all population groups. In other words, keep the document essentially the same as it is. While we strongly support and encourage the application of BMD approaches to determining regulatory values where appropriate, in this case the LOAEL/NOAEL approach gives a slightly lower (more health-protective) value. This results in a quandary, pitting a lower number based on a legitimate toxic endpoint against a statistically superior approach. Both approaches have merit. However, it seems to us that a better rationale is needed to choose the less-health-protective approach. Therefore, if the RCD remains essentially unchanged, we recommend additional discussion be added to the document specifically addressing how adoption of this numerical value will protect adults if the effects of imidacloprid observed in the DNT study are applicable to this age-group.

Adopt the LED_{10} of 9 mg/kg for all population groups except women of childbearing age. Similar to the above, with the exception of officially adopting the estimated NOAEL of 5.5 mg/kg-day for this specific population sub-group and calculating margins of exposure instead of merely mentioning it in the text of the document. If this approach is taken, justification in addition to that recommended above should be added to the RCD, in support of use of the lower regulatory value for only this sex/age-group.

Adopt the estimated NOAEL of 5.5 mg/kg-day for all population groups. Again, although OEHHA strongly supports the use of BMD methodology, adopting the estimated NOAEL is the most health-protective option and is a reasonable approach considering the uncertainty discussed above. If this option is chosen, we recommend additional discussion be added to the document clarifying and strengthening the possible link between the effects of imidacloprid on brain dimensions with decreases in motor activity in adult animals.

Although the third option is preferred by OEHHA, all three of these potential options, assuming appropriate and sufficient justification, address the currently unresolved issues and, therefore, we could support any one of these approaches in the final version of the RCD.

2. If an acute regulatory value of 5.5 mg/kg were adopted, MOEs for acute exposures would be reduced by nearly 40%. MOEs for acute dietary exposures (99^{th} percentile point estimates, tier 2) would range from 71 for children 1-2 years of age to 239 for females 13 – 39 years of age. The MOE for children would, therefore, reflect an exposure level of concern for this population subgroup. OEHHA recommends that a more refined exposure analysis and risk evaluation be performed in order to determine if exposure mitigation measures are necessary. See also comment number 3, below.

3. Refined exposure analyses such as Monte Carlo analysis were not performed in this RCD because of a lack of residue data. In light of the low MOEs estimated in the RCD and even lower MOEs if the recommended acute regulatory value of 5.5 mg/kg is adopted, OEHHA recommends that additional residue data be generated and collected and a more refined exposure analysis be performed so that the actual risks from dietary exposure to imidacloprid may be better characterized.

4. Chronic dietary exposure to imidacloprid is evaluated in the RCD using a NOAEL of 5.7 mg/kg-day based on a statistically significant increased incidence and severity of mineralized particles in the thyroids of male rats at the next higher dose of 25 mg/kg versus the controls (Eiben and Kaliner, 1991). In the risk appraisal section of the document (page 88), it is stated that this value (5.7 mg/kg-day) "was sufficiently close to the estimated-no-effect-level of 5.5 mg/kg-day for developmental toxicity, and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system." Since chronic exposure is normalized over extended periods of time, typically years, it is expected that "spikes" of relatively high exposure exceeding the normalized daily dose occur during the chronic time frame, which would constitute a significant acute exposure. Accordingly, OEHHA is unsure how evaluating chronic exposures with a NOAEL that is essentially equivalent to an acute NOAEL would protect against the acute effects associated with that NOAEL. We recommend that additional discussion be added to the RCD to clarify this concept.

5. In the cover memorandum and in the body of the RCD it is stated, "this document pertains to the assessment of dietary and drinking water exposures." No drinking water exposure or risk assessment is found in the current version of the RCD. OEHHA recommends correcting this inconsistency.

6. A number of typographical and grammatical errors are found in the RCD. Most notable is the incorrect use of the word principle (should be principal). We recommend that the document be thoroughly proofread and spellchecked.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

cc: See next page

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