



MEMORANDUM

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VIA: Svetlana Koshlukova, PhD, Senior Toxicologist *[original signed by S. Koshlukova]*
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DATE: February 28, 2019

SUBJECT: Response to Reviewer Comments Made by the US EPA on the DPR Draft Propanil Risk Characterization Document (dated December 30, 2016)

I. Background

At the request of the Human Health Assessment (HHA) Branch of the California Department of Pesticide Regulation (DPR), the United States Environmental Protection Agency (USEPA), Office of Pesticide Programs (OPP), Health Effects Division (HED) reviewed the draft Risk Characterization Document (RCD) for Propanil (December 30, 2016) and provided comments in letter submitted to HHA on April 21, 2017.

DPR sincerely appreciates the efforts taken by the HED to review the draft Propanil RCD. We consider comments by regulatory agencies, such as the ones provided by the HED, to be helpful in the development of technically complex, science-based regulatory documents. As appropriate, HED's comments were incorporated into the final Propanil RCD and responses to specific comments are detailed below.

II. Response to Comments

A. Toxicology

HED Comment: As the registration review of propanil is still underway, updated endpoints for propanil have not been determined. EPA has requested that the registrant submit acute neurotoxicity and subchronic inhalation studies for propanil, and the results of these studies will be considered during the endpoint selection process.

DPR HHA Response: This current RCD is a comprehensive evaluation of all data available and reviewed up to June, 2016. HHA will re-consider its endpoint selection and points of departure if new data become available through the USEPA data call-in process.

HED Comment: EPA considers acute effects to be those caused by a single dose. DPR used effects that occurred after 5 days of treatment to select their acute endpoint. Although it was mentioned in the text that effects started occurring at day 1, data from day 1 were not modeled or presented. If the data from day 1 were not modeled because of lack of statistical significance, then this effect would not be considered acute in nature.

DPR HHA Response: HHA considered data that occurred up to 7 treatment days after the initial treatment for the development of acute points of departure (PODs). In this case, methemoglobin (metHb) levels increased on Day 1 in male and female rats. The Day 1 data was of marginal suitability for benchmark dose (BMD) analysis because neither males nor females had a continuous dose response. The latter is important for obtaining acceptable models that accurately reflect the data and are biologically plausible. As expected, corresponding BMD models for Day 1 metHb data did not result in any acceptable models based on goodness-of-fit test results or visual inspection for model plausibility.

HED Comment: EPA no longer considers changes in body weight gain to be toxicologically relevant. In Section IV; A; under sub-section entitled Acute Toxicity (page 92), DPR mentions that effects observed in the subchronic feeding study were statistically significant for both males and females. However modeling results are only presented for males without any explanation of whether the female data was taken into account. Similarly, for other endpoints, data from one sex or the other is chosen for modeling but no information is provided to explain why males or females were chosen.

DPR HHA Response: HHA currently regards decrements in both bodyweight and bodyweight gain from acute or short-term exposures as clinical signs related to general health and, in this case, as signs of acute, systemic toxicity when there is adequate support. The corresponding female data from the chronic carcinogenicity study in rats (Bellringer, 1994) did not yield any acceptable BMD models. Text was revised in the final Propanil RCD to reflect that when more than one set of BMD or BMDL values were generated for a given study, the lowest value for each endpoint will be reported and used for comparisons in the hazard identification process.

B. Dietary Risk

HED Comment: EPA intends to update its dietary risk assessment for propanil as part of the registration review.

DPR HHA Response: No response necessary.

HED Comment: EPA conducted a dietary risk assessment in 2003 for chronic dietary exposure only since no acute toxicity end point could be determined. In the DPR report, they have

conducted both acute and chronic risk assessments. However, EPA may conduct an acute assessment in addition to a chronic dietary risk assessment during registration review depending on the outcome of the review of the required toxicology studies: i.e., if an acute oral toxic endpoint is determined.

DPR HHA Response: No response necessary.

HED Comment: In 2003 EPA conducted a dietary assessment for propanil. The risk for food-only was below the level of concern for US general population and all population subgroups. At that time, exposure for water was considered separately using the Drinking Water Level of Comparison (DWLOC) approach. During registration review, EPA will estimate dietary exposure to propanil by combining food with drinking water. In the DPR dietary assessment, the results for both acute and chronic dietary exposure, (combined food and drinking water) are below the level of concern; however, DPR reported the results in terms of margin of exposure (MOE) rather than as a percent of the population adjusted dose (%PAD) as EPA typically does.

DPR HHA Response: No response necessary.

HED Comment: DPR used DPR surface water monitoring data in their dietary assessment. Generally, EPA uses modeled water residues.

DPR HHA Response: The USDA PDP program did not analyze drinking water samples for the metabolite of interest, 3,4-DCA. As such, PDP drinking water data were not included in this risk assessment. Instead, HHA used the department's own surface water sampling data to assess the risk from drinking water exposures. We acknowledge that DPR surface water residue data may overestimate exposure to pesticide active ingredients and we consider such data to be a very conservative surrogate for finished drinking water exposure estimates. In the future, HHA will use a combination of California-specific monitoring and modeling data to provide realistic worst-case estimates of drinking water exposures for its human health risk assessments.

References

Bellringer, M. E. (1994). Propanil Technical, Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Project No.: PTF 3/93931856) (DPR Vol. No. 274-0018, DPR Record No. 132825). Huntingdon, Cambridgeshire, England Huntingdon Research Centre Ltd.: 1-2354.