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September 12, 2003

Oscar Hernandez, Director – OPPT Risk Assessment Division
Environmental Protection Agency

Richard Hefter, Chief – HPV Chemicals Branch
Environmental Protection Agency

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Chemical Right-to-Know – HPV Challenge Program

Thank you for the comments provided on the HPV Test Plan and Robust Summaries for 2,3,4,5,6-Pentachloropyridine (PCP). Provided below is the response of Dow AgroSciences (DAS) to the Agency's comments. As requested and referenced in our comments, we have updated the relevant robust summaries. The revised IUCLID document is included as an attachment in this email.

DAS Response to EPA Conclusions (noted in *italics*):

1. Physicochemical Properties. The data provided by the submitter for melting point, boiling point, and partition coefficient are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured vapor pressure and water solubility data following OECD guidelines.

Response: The sponsors appreciate the Agency's confirmation that the data for melting point, boiling point, and partition coefficient are adequate. While we understand that OECD tests for vapor pressure and water solubility are available, we maintain that the measured values for these parameters, as conducted in 1967 prior to the publication of OECD guidelines, using scientifically valid methods, are adequate to fulfill data requirements for the purposes of the HPV program.

2. Environmental Fate. 1) The data provided by the submitter for photodegradation are adequate for the purposes of the HPV Challenge Program. 2) The submitter needs to provide a technical discussion in the stability in water robust summary. 3) The biodegradation data provided by the submitter are inadequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured ready biodegradation data. 4) EPA recommends using the Level III EQC model to estimate distribution in the environment.

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Response: 1) *The sponsors appreciate the Agency's confirmation that the data for photodegradation are adequate.* 2) *A brief technical discussion has been included in the updated robust summaries attached.* 3) *The sponsors believe that adequate biodegradation data exists for PCP. The robust summary for the ThOD study submitted has been enhanced to include more details of the methodology used. While we understand that "Ready Biodegradation" studies are commonly conducted today, we maintain, for purposes of the HPV program, the study summarized should be acceptable.* 4) *The sponsors agree with the agency's recommendations for using the Level III model where the nature of the chemical renders the analysis viable. Since environmental chemistry experts within our organization concur that Level III analysis is possible for this chemical, we will provide data derived from this model in subsequent robust summaries.*

3. Health Effects. EPA agrees with the submitter's test plan, except that EPA recommends the submitter conduct a combined reproductive and developmental toxicity screening study instead of the proposed developmental toxicity study.

Response: *The sponsors appreciate the confirmation that the summarized health effects data are adequate to meet the SIDS-level endpoints. However, the reasons the sponsors elected to submit a plan for a teratology study conducted according to OECD guideline No. 414 are as follows:*

Guidance from the OECD SIDS Manual, Section 3.4, Subsection 5.7, indicates that, "for the reproduction toxicity endpoint, when a 90-day repeated dose study is available and is sufficiently documented with respect to studying effects on the reproductive organs and a developmental study is available, the requirements for the reproduction toxicity endpoint are satisfied."

In the 90-day study described in the Robust Summaries, the EPA indicates that effects on the reproductive organs, in particular testes, were observed. The sponsors' summary indicates that the effect observed was judged not to be treatment-related. The sponsors further conducted a peer review of the data, as follows:

In the first study, ten adult rats per sex per dose level were provided dose concentrations of 0 (controls), 0.3, 1, 3, 10 or 30 mg pentachloropyridine (PCP) per kilogram body weight per day in the feed for 90 days. The histopathologic peer review of this study consisted of microscopic evaluation of both testes from all male rats at all dose levels. The peer review was conducted by a Diplomate of the American College of Veterinary Pathologists. Results of the peer review histopathologic evaluation showed that there were no treatment-related testicular effects. This was in agreement with the final conclusions of the original pathologist. There were comparable numbers of rats at all dose levels, including the control group, with very slight or slight degeneration of testicular seminiferous tubules. The quality of the microscopic slides from this study was less than optimal, with artifacts of suboptimal fixation or processing methods, and evidence of compression artifacts that occurred during the postmortem examination and sample collection. Some of the histopathologic diagnoses made by the original pathologist were determined to be reflective of artifactual changes, based on examination by the peer review pathologist. The diagnoses that were attributed to less than optimal fixation of tissues following the postmortem examination consisted of the accumulation of fluid in interstitial spaces between seminiferous tubules, and vacuoles in seminiferous tubules. These observations were consistent

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with published literature on postmortem changes in the testes of rats (Seaman, 1987). The diagnosis of primary or secondary spermatocytes in the lumens of seminiferous tubules was attributed to postmortem compression artifacts, and not a degenerative alteration of the testes.

In the second study, groups of 30 male rats per dose level were provided dose concentrations of 0 (controls) 62.5, 125 or 250 mg PCP per kilogram body weight per day in the feed. Five rats per dose group were necropsied after 49, 119, 175 and 242 days on the diet. The histopathologic peer review of this study consisted of microscopic evaluation of both testes from all male rats at all dose levels. The peer review was conducted by a Diplomate of the American College of Veterinary Pathologists. Results of the peer review histopathologic evaluation showed that there were no treatment-related testicular effects. This was in agreement with the original pathologist. As with the previous 90-day study, there were comparable numbers of rats at all dose levels, including the control group, with very slight or slight degeneration of testicular seminiferous tubules. The quality of microscopic slides in the second study was optimal, with no significant artifacts related to fixation, processing, or tissue handling.

Reference:

Seaman, W. J. (1987). Reproductive System. In Postmortem Change in the Rat: A Histologic Characterization. pp. 60-61. Iowa State University Press, Ames, Iowa.

In a separate communication, the Physicians Committee for Responsible Medicine indicated that they had located a published work about developmental toxicity of PCP (Nehez et al., 1993). The sponsors appreciate the Committee's efforts in bringing this study to our attention, but review of this publication revealed several deficiencies which render the study unusable for satisfaction of SIDS testing requirements: a single dose level was tested, and no examination of fetuses for visceral or skeletal malformations was conducted. A summary of this publication has now been included with the Robust Summaries. The Committee has also requested consideration of an in vitro test as a surrogate for a developmental toxicity study, but no such tests have been validated for use in satisfying SIDS endpoints.

In view of these findings, the sponsors believe the repeated dose toxicity study partially satisfies the requirements for the reproduction toxicity endpoint. The other requirement, a developmental study, was included in the test plan.

The sponsors appreciate the confirmation that the test plan for genetic toxicity testing is adequate to meet SIDS-level endpoints. The Physicians Committee for Responsible Medicine, however, in their cited communication, indicates that the previously mentioned publication (Nehez et al., 1993) also provides genetic toxicity data. The sponsors appreciate the Committee's efforts in bringing this study to our attention, but review of this publication revealed a deficiency, which renders the study unusable for satisfaction of SIDS testing requirements: only 20 mitoses in metaphase per mouse were counted, as opposed to the 100 mitoses required under guidelines.

The sponsors understand the concern of the Committee about conducting further testing which would result in the death of 40 rats. Consistent with this, the in vitro assay chosen for the test

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plan would result in the use of the minimum number of animals necessary to conduct the study: four rats.

4. Ecological Effects. EPA reserves judgement on the adequacy of submitted fish studies pending submission of missing critical data elements. EPA recommends that the submitter conduct toxicity testing for daphnia in addition to the proposed algal test because the data submitted for aquatic invertebrates are inadequate to address this endpoint.

Response: The robust summaries for all studies have been revised to provide additional information on exposure conditions and test concentrations. The sponsors maintain that, although the sand shrimp is not the usual species upon which aquatic toxicity testing is conducted, it satisfies the requirements for SIDS-level endpoint testing.

We do appreciate the time that you spent in review of our Robust Summaries and Test Plan. We hope that you find that the further information provided in our response above and in the updated robust summaries adequately addressed the issues that were identified.

Regards,

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