APC Holdings
KMG-Bernuth, Inc.
Luxembourg-Pamol, Inc.

March 8, 2005 Our Ref.: MAATF/050303-278

Information Quality Guidelines Staff
United States Environmental Protection Agency
1200 Pennsylvania Avenue (Mail Code 2811R)
Washington, DC 20460

Re: Request for Correction of the *PPRTV Derivation Support Document for Cacodylic Acid (CASRN 75-60-5)*

Dear Staff Member,

The MAA Research Task Force (Task Force) is writing to request correction of information included in the U.S. Environmental Protection Agency's (EPA) document entitled *PPRTV Derivation Support Document for Cacodylic Acid (CASRN 75-60-5)* (PPRTV Support Document),[1] pursuant to Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (the Information Quality Act), and the implementing guidelines issued by EPA (EPA Guidelines).[2] The information in the PPRTV Support Document fails to meet the requirements of the EPA Guidelines.

The Task Force seeks, pursuant to the EPA Guidelines, correction of information included in the PPRTV Support Document. As discussed in detail below, the Task Force requests correction of the calculation of the provisional oral chronic reference dose (RfD) for cacodylic acid, using a more appropriate basis.

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1 EPA, PPRTV Support Document (undated), Doc. No. SRC TR 02-029/09-16-2002.

2 EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (Oct. 2002) (EPA Guidelines), available at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf.

The EPA Guidelines require that a request for correction contain several substantive components. These include: (1) a description of the specific material that is proposed for correction, (2) the reasons why the disputed information does not comply with the EPA Guidelines and is in error, (3) suggested recommendations for what corrective action(s) should be taken , and (4) an explanation of how the petitioning party is affected by the error.

The Task Force is adversely affected by the errors described in the PPRTV Support Document, as the errors in the document lead to an overestimation of the risk posed by products manufactured by the Task Force members, of which cacodylic acid is a metabolite. The use of the RfD by other EPA offices, as well as by federal and state agencies will lead to characterizations regarding environmental risks from cacodylic acid that are incorrect and not supported by the science and, when used as the basis for regulatory determinations, result in adverse regulatory actions for users of Task Force products.. The inappropriately conservative RfD has been disseminated by EPA, and continues to be disseminated, thereby stigmatizing cacodylic acid and inviting enhanced regulatory and consumer scrutiny of cacodylic acid, products containing cacodylic acid, and products that are metabolized to cacodylic acid. Each of the remaining components of the required request for correction is discussed below.

(1) A description of the specific material that is proposed for correction

The PPRTV Support Document calculates a provisional oral chronic RfD of 0.0003 mg/kg day for cacodylic acid.[3] This calculation is flawed for the following reasons:

- The PPRTV Support Document uses a no observed adverse effect level (NOAEL) from a subchronic study with rats to derive the chronic RfD, although multiple chronic studies containing NOAEL values exist and are available to the agency.[4] The NOAEL used for deriving a chronic RfD should be corrected.

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3 PPRTV Support Document at 8.

4 PPRTV Support Document at 8.

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- The PPRTV Support Document uses a total uncertainty factor of 3,000 to adjust the NOAEL in computing a chronic RfD, which is specified to be based on the following component uncertainty factors multiplied together:
  - Subchronic to chronic extrapolation (factor of 10);
  - Interspecies variability [for rat study NOAEL] (factor of 10);
  - Intraspecies variability/individual sensitivity (factor of 10); and
  - Database deficiencies, specifying the lack of a multigeneration reproduction study (factor of 3).

This uncertainty factor is dependent upon the selection of the NOAEL and should be corrected in conjunction with correcting the NOAEL value used for chronic RfD derivation.

(2) The reasons why the disputed information does not comply with the EPA Guidelines and is in error

- Agency guidelines specify that the results from chronic testing should be used preferentially, where available, over the results from subchronic testing for the derivation of chronic RfDs. By deriving the chronic RfD from a subchronic NOAEL when chronic NOAEL results are available, the agency failed to comply with relevant guidelines.
- Agency guidelines specify that the lowest appropriate toxicity test result should be used for the derivation of corresponding RfDs. Values from chronic tests are lower than the subchronic test result used, so by excluding chronic results the agency also failed to choose the lowest (i.e., most protective) NOAEL value and, thus, failed to comply with the corresponding guidelines.

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- The use of a NOAEL from a subchronic study for deriving a chronic RfD requires an additional uncertainty factor of 10. Use of a NOAEL value from one of the existing chronic studies would eliminate the uncertainty factor component for extrapolating chronic values from subchronic test results.
- An uncertainty factor for interspecies extrapolation is assigned to account for the potential that the test species may be more sensitive than humans for the corresponding effect. This component uncertainty factor should not be used in conjunction with a NOAEL for cacodylic acid from a rat study because rats have been demonstrated to be more sensitive than humans to effects from cacodylic acid and the underlying toxicological mode of action which explains rat susceptibility has been established and demonstrated not to be relevant for humans.[5]
- The use of an uncertainty factor for database deficiencies with cacodylic acid is also incorrect because the agency has a complete set of GLP studies that were performed according to EPA guidelines, including a multi-generation reproduction study. These studies were submitted in support of the product re-registration.

(3) Suggested recommendations for what corrective action(s) should be taken

Calculation of RfD in the PPRTV Support Document should be revised to include the NOAEL from Wei et al. (1999)[6] one of the available chronic studies in place of the current subchronic NOAEL. The uncertainty factor should incorporate only the component for individual sensitivity (intra-species variability) and, thus should be 10, reflecting the elimination of the components for subchronic to chronic extrapolation (no longer relevant with revised NOAEL), for interspecies sensitivity (due to use of species more sensitive than humans), and for inadequate database (based on submittal of complete set of studies in conjunction with product registration).

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5 PPRTV Support Document at 8.

6 Wei, M., H. Wanibuchi, S. Yamamoto et al. 1999. Urinary bladder carcinogenicity of dimethylarsinic acid in male F344 rats. Carcinogenesis. 20: 1873-1876.

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Because of the flaws in the calculation of the RfD, the PPRTV Support Document must be revised to meet the EPA Guidelines. The EPA Guidelines apply to "influential scientific, financial, or statistical information," which includes information for which EPA "can reasonably determine that dissemination of the information will have or does have a clear and substantial impact (*i.e.*, potential change or effect) on important public policies or private sector decisions."[7] Dissemination of an inappropriately conservative RfD will have a substantial impact on public policy decisions regarding cacodylic acid.

The EPA Guidelines state:

> EPA will ensure, to the extent practicable and consistent with Agency statutes and existing legislative regulations, the objectivity of [influential scientific risk assessment] information disseminated by the Agency by applying the following adaptation of the quality principles found in the Safe Drinking Water Act (SDWA) Amendments of 1996:
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> (A) The substance of the information is accurate, reliable and unbiased. This involves the use of:
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> (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies. . . .[8]

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7 EPA Guidelines at 19.

8 EPA Guidelines at 21-22 (citations omitted).

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Thus, under the EPA Guidelines, the PPRTV Support Document must present accurate and reliable information, involving the use of the best available science and supporting studies. EPA's use of a subchronic toxicity study to calculate a chronic RfD, instead of a chronic toxicity study, is prohibited under the EPA Guidelines. EPA should revise the PPRTV Support Document to reflect use of a chronic toxicity study to calculate the chronic RfD. EPA must also ensure that the uncertainty factor used for interspecies extrapolation reflects the fact that humans are not more sensitive than rats, and that the uncertainty factor for database deficiency is not used. This will result in a value that more accurately reflects the risks of cacodylic acid, thus ensuring that use of the RfD in other risk assessment contexts will result in appropriate protective measures.

If you have any questions about this request for correction or require further information, please contact me at (800) 890-3301 or meldan@luxpam.com. Thank you for your attention to this matter.

Sincerely,
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M. Eldan

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