632

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 1,4-dichlorobenzene: Review of Additional Toxicology Data Submitted by the Registrant.

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Registrant: Chlorobenzene Producers Association

Action Requested: Review of additional data submitted by the Chlorobenzene Producers Association to upgrade an existing metabolism study (MRID # 416978-01).

1

Summary:

The law offices of Paul, Hastings, Janofsky, and Walker, as agent for the Chlorobenzene Producers Association (Monsanto Co., PPG Industries, Inc., Standard Chlorine Chemical Company), submitted materials in support of a metabolism study conducted with 1,4-dichlorobenzene in rats and mice. Initial review of this study led to a classification of core supplementary, based on missing data and unexplained pharmacokinetic issues. The issues raised in the initial review, the registrant's response to these issues, and the conclusions of Toxicology Branch II are listed below:

Issue 1:

The registrant was asked to address the question as to whether the methyl sulfone and methyl sulfoxide metabolites of 2,5-dichlorophenol (the major oxidative product of 1,4-dichlorobenzene) could be involved in the mechanism of hepatic and/or renal tumorigenesis as observed from the 2-year NTP bioassay in mice and rats.

Response:

The registrant stated that all major metabolites as specified under § 85-1, including those representing more than 5% of the administered dose, were identified in this study. The methyl sulfoxide and methyl sulfone metabolites were not specifically identified in this study. Previous work by Kimura *et al.* identified these 2 metabolites in blood, and to a lesser extent in fat, kidney, and liver. The low levels in liver as compared to blood in this study do not support the view that these metabolites are accumulated or localized in the liver. Based upon the study results, the role of the methyl sulfoxide and/or sulfone in hepatic and renal carcinogenesis from 1,4-dichlorobenzene administration cannot be determined. However, it is the registrant's position that there is little evidence to support a role for the methyl sulfone and sulfoxide metabolites in a mechanism for hepatic and/or renal tumorigenesis.

Conclusion:

The registrant has adequately addressed this issue. It should be pointed, however, that metabolites do not have to be present in major quantity in order to exert a toxic and/or carcinogenic effect, as could be the case with the methyl sulfoxide and methyl sulfone metabolites of 2,5-dichlorophenol. These metabolites could possess substantial reactivity, and have the potential for toxicity. It is pointed out that in the study by Kimura *et al.*, highest levels of the methyl sulfoxide were found within the kidney, while blood contained the highest amount of methyl sulfone metabolite.

Issue 2:

Clarification of the kidney $t_{1/2}$ as defined for male rat kidney clearance after oral exposure was requested. The term "alpha" was used to describe kidney elimination kinetics in male rat kidney, and it was unclear whether this referred to distribution or elimination kinetics.

Response:

The registrant acknowledged that elimination kinetics in male rat kidney, unlike female kidney, were mono-exponential. Since the kidney data for males could only be appropriately resolved into one exponential term, it is appropriate to refer to this as the "alpha" phase. This component would presumably include both distributive and elimination processes in the male rat kidney.

Conclusion:

The registrant has adequately clarified this issue.

Issue 3:

Distribution and elimination curves for the tissues examined in this study were requested. As only 2 time points per tissue were used to estimate half lives in this study, the question was raised as to the goodness of fit for the experimental data.

Response:

The registrant recognizes that the number of data points limited the extent of kinetic analysis that was appropriate, and that the data reflects analysis of total radioactivity. The data were sufficient, however, to distinguish between a mono- and bi-exponential process. The data were sufficient to calculate tissue half lives, although this type of calculation is not possible under the current data requirements for § 85-1.

Conclusion:

The registrant has adequately addressed the issue. However, tissue half lives in this study can only be considered estimates, based on the use of only 2 time points for analysis. The registrant is correct in stating that such data are not routinely required under § 85-1, but this was not a routine study, based on the complexity of its design. Therefore, the registrant should be aware that additional time points should be used in future measurement of tissue half life.

Issue 4:

The registrant was asked to explain the apparent decrease in cumulative percent excretion for group 9 (multiple oral dose group) as listed in Table 20, page 105 of the report. Cumulative percent excretion implies an increasing amount with time, at least until all radioactivity is excreted by that route. It was unclear why a decrease would occur between 3 and 7 days post-dose.

Response:

The registrant stated that 3 animals per time point were used. As excretion was essentially complete by 3 days, the data between days 3 and 7 merely reflects the small variance between the 3 animals analyzed at the 3 and 7 day time point.

Conclusion:

The explanation given by the registrant makes clear the reason for the discrepancy in cumulative percent for 3 days vs 7 days in the repeat dose group of rats. It is apparent that there is a large standard error for the rats on day 7, which no doubt contributed in part to the apparent decrease in "cumulative" percent excreted. It is suggested that in future studies of this type, that a set of animals be monitored for all time points of collection, to avoid the kind of data generated in this table, which is not actually "cumulative."

Issue 5:

The registrant was asked to address the issue of radiolabel stability as it applied to the preparation and use of dosing solutions. Because radiolabel purity was observed to decline with time in this study, the dose solutions may have contained impurities which may have interfered with identification of urinary metabolites.

Response:

The registrant stated that the reported decomposition in this study did not interfere with metabolite identification. The 2 primary metabolites (the glucuronide and sulfate conjugates of 2,5-dichlorophenol) were present in significant amounts, and could not have been formed from decomposition products. The minor peaks present, which could have represented decomposition products of 1,4-dichlorobenzene, were present in amounts substantially below the 5% threshold specified by § 85-1.

Conclusion:

The registrant has adequately addressed the issue.

Issue 6:

In tables 1a-1c of the original review, percentage recovery in urine was shown for male and female rats and male mice exposed orally or by inhalation to radiolabeled 1,4-dichlorobenzene. These values were compared to those obtained from urinary metabolite identification (Table 4 of the original review). It was noted that for male rats dosed with 150 and 300 mg/kg 1,4-dichlorobenzene, the percent recovered as various urinary metabolites (from Table 4) did not approximate the percent of radioactivity recovered in Tables 1a-1c. Specifically, 23.8% and 14.9% of the administered dose recovered in urine was unaccounted for from urinary metabolite identification in these dose groups.

Response:

The registrant acknowledged that summation of the three major metabolites did not account for all of the radioactivity due to the uncharacterized material. Discrepancies would also arise as a result of the selection of certain pooled samples prepared for metabolite identification.

Conclusion:

The registrant's response partially explains the discrepancies between total urinary radioactivity recovered and total metabolites identified in urine. However, discrepancies of 14.9% and 23.8% are significant in these types of studies. It would serve no useful purpose to reject the present metabolism study based on this deficiency alone, as the registrant has adequately addressed other concerns raised from the original review. Thus, although the response of the registrant to this deficiency is not considered fully adequate, the study will not remain as supplementary data based upon this fact alone.

Based on the registrant's response to the above issues, the previously reviewed metabolism study (MRID # 416978-01) is upgraded to **core minimum** data.