12-17-80

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

TOX R 001353

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg.#677-350; Methane Arsonic Acid; Miscellaneous Data
CASWELL#549A; Accession#243449-55

FROM: William Dykstra, Toxicologist WDD 12/11/80
Toxicology Branch, HED (TS-769)

TO: Richard Mountfort (23)
Registration Division (TS-767) WJP

Recommendations:

1) Toxicology Branch requests historical data on the anomalies and all variations in this strain of rat to aid in the evaluation of the teratology phase of the study. In addition, detailed descriptions of anomalies observed in the study; i.e., renal agenesis and rugae of the palate are requested to be submitted. Tables should be presented on a per litter basis with appropriate statistical evaluation. Additional detailed tables should be submitted on a per fetus basis with appropriate statistical evaluation. Only summary tables were submitted without statistical evaluations.

2) Toxicology Branch requests that statistical analyses of the data of the reproduction phase of the study be performed and submitted for evaluation. No statistical analysis of the data was indicated in the report.

3) The reproduction/teratology study will be reviewed when the data requested in #1 and #2 are submitted.

4) The study on MAA and its salts in human gastric juices is acceptable as core-minimum data.

Review:

1) Methane Arsonic Acid; Three-Generation Reproduction Study in Rats (Raltech Studies #T-511, T-601 and T-602; Final Report; November 26, 1979)

Test Material: Arsul sample; MAA, 99+% assay; 907-96-301; 7/25/75

A complete review of this study will be made when recommendations #1 and 2 are satisfied.

2) Methane Arsonic Acid (MAA) and its Salts in Human Gastric Juices (Raltech; May 7, 1979)

Purpose of the Experiment

In previous toxicity studies with MAA, only the acid form of MAA was fed and the question arose whether the disodium salt of MAA is equivalent to its acidic form. It was reasonsed that equivalency would be established if it could be shown that both the acid form of MAA and its disodium salt are identical when they are added to aqueous or gastic juice solutions; that is, if a common species could be shown to be present and that the species form was governed primarily by the pH of the medium.

Discussion

From the pka_f of MAA (4.05) in human gastric juice solutions and pH's (1.15-1.46) of these solutions, it can be calculated, based on the chemical equilibrium of MAA in aqueous solutions, that the species of MAA in human gastric juices is predominantly in its acidic form, regardless of which solute, MAA or its disodium salt, is added. For example, to calculate for MAA in gastric juice sample #2, pH = 1.46:

$$pka_f = pH - \log \frac{[MAA]}{[MAA^-]}$$

and

$$\log \frac{[MAA]}{[MAA^-]} = pka_f - pH = 4.05 - 1.46 = 2.59$$

$$[MAA]$$

leads to $\frac{[MAA]}{[MAA]} = 389$

and $\frac{[MAA]}{[MAA]_{total}} = \frac{[MAA]}{([MAA] + [MAA^-])} = 99.7\%$

Therefore, in gastric juice sample #2, 99.7% of MAA exists in the acidic form.

Direct identification of the MAA species in human gastric juices was made possible by means of C-13 NMR spectroscopy, in which the C-13 NMR chemical shifts of the C-13 (naturally occurent or enriched) nucleus of the molecules of MAA and its anionic species were measured. This revealed the species form of the solute molecules in each gastric juice sample. Possible interference due to other materials in gastric juices appeared to be insignificant, especially when C-13 enriched (90%) MAA and its disodium salt were used.

The C-13 NMR chemical shifts did vary when solution ionic strength changed from 0.01 to 3.0 M. However, the ionic strengths of the human gastric juice samples tested (seven

samples) were approximately in the range of 0.1 to 0.4 M. The effects of variations in ionic strength on chemical shifts within this range were so small that they did not affect the identification of MAA species in these human gastric juices.

The C-13 NMR chemical shifts of MAA and its disodium salt in aqueous and human gastric juice solutions were found to be essentically identical under the same conditions of pH and ionic strength. The chemical shifts were found to decrease with increasing pH from acidic to basic, paralleling the conversions of MAA species from acidic, to neutral, and then to basic.

Conclusion:

The consistent correlation between the measured and calculated chemical shifts of MAA and its disodium salt in human gastric juice samples clearly identifies the MAA species to be the acidic form.

Classification: Core-Minimum Data

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