CASWELL FILE 7-2-92

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

JUL 2 1992

JUL - 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Poly (hexamethylenebiguanide) (PHMB);Review of Metabolism Protocols submitted by the Registrant (ICI Specialty Chemicals)

Caswell No: 676
Submission: S419961
DP Barcode: D179567

FROM: Timothy F. McMahon, Ph.D., Toxicologist 6/29/92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Kathryn Scanlon / PM 52
Special Review and Reregistration Division (H7508W)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head 6/30/92
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) 6/30/92

Registrant: ICI Specialty Chemicals, Wilmington, Delaware

Action Requested: Review of submitted metabolism protocols in support of reregistration of PHMB.

Summary:

ICI Specialty Chemicals submitted metabolism protocols for PHMB in response to the Agency's request following a May 21, 1992 meeting between representatives of Toxicology Branch II, HED, and ICI. These protocols were designed to investigate the bioavailability and excretion of PHMB following oral dosing in rats. Recommendations of Toxicology Branch II from review of these protocols is presented below.

1) Title: PHMB: Bile Duct Cannulation in the Rat, CTL Study # URO360

The purpose of this study is to examine excretion of orally administered PHMB in bile duct-cannulated rats. To study this, two male and 2 female Wistar rats which have undergone surgery to exteriorize the bile duct will be given an oral dose of 20 mg/kg (2 MBq/kg) PHMB in a dose volume of 4ml/kg. Rats will then be housed in individual metabolism cages for collection of bile, urine, and feces at 6 (no feces collection), 12, 24, 36, and 48 hours. Rats will then be killed by Halothane anesthesia and discarded. Radioactivity in excreta samples will be analyzed by direct liquid scintillation counting, except feces, which will be analyzed following sample oxidation. Radiochemical purity of administered PHMB and dose preparation are to be determined by a yet to be defined chromatographic method. Following analysis for excreted radioactivity, samples will be stored frozen for possible future use in identifying the nature and extent of PHMB biotransformation.

Recommendation: Toxicology Branch II recommends that at least 3 rats/sex instead of the current 2/sex be used for biliary excretion studies. While this is a special study not specifically designed to meet § 85-1 guideline requirements, the use of only 2 rats per sex does not provide an adequate database for future use by the Agency. If the recommended change is incorporated into the above protocol, it will be considered acceptable.

2) Title : PHMB: Bioavailability of different molecular weight fractions, CTL study # URO392

In this study, the bioavailability of various molecular weight fractions of PHMB (< 1000, 1000-4000, and > 4000) will be examined following a single oral dose to various groups of rats. Rats (3 males/dose group) will be administered single oral doses of the above-listed molecular weight fractions of PHMB (20 mg/kg nominal dose, 2 MBq/kg, in a volume of 4 ml/kg). Dosed rats will be housed in individual metabolism cages for collection of urine and feces at 6 (no feces), 12, 24, 36, 48, and 72 hours. After the last sample collection, rats will be killed by Halothane anesthesia and blood samples obtained. The gastrointestinal tract plus contents will be removed and analyzed for residual radioactivity, as will urine and feces.

Recommendation: According to the registrant (page 3 of study # URO392), this study is designed in part to meet § 85-1 for metabolism studies. For this study to partially fulfill the guideline requirements, the following modifications must be incorporated into the protocol:

a) Four to five rats per dose group should be used instead of the current 3 rats per dose group.

b) Rats should be held in metabolism cages for 7 days or until ≥ 90% of administered radiolabel is excreted.

Tissue residue analysis would also normally be required at study termination, but this will be investigated in study # URO 361 below. Thus, it will not be required in # URO392.

3) Title: PHMB: Excretion balance study in the rat. CTL study # URO 361

In this study, disposition of a single oral 20 mg/kg dose (2 MBq/kg) of PHMB will be investigated in male and female Wistar rats. As only low molecular weight material is expected to be absorbed, it is proposed that low molecular weight material be used in this study. PHMB will be orally administered in deionized water to groups of 5 male and 5 female rats. Rats will then be individually housed in metabolism cages for collection of urine and feces at 6, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours. Following the last collection time point, rats will be sacrificed by Halothane anesthesia and duplicate blood samples obtained. The liver, kidney, spleen, gonads, lungs, heart, brain, and samples of abdominal fat, muscle, and bone will also be obtained for measurement of residual radioactivity. Urine and fecal radioactivity will be determined by direct liquid scintillation counting, while tissue radioactivity will be determined by liquid scintillation counting following either sample oxidation or solubilization. Radiochemical purity of test substance and dose preparations will be determined by an as yet to be determined chromatographic method.

Recommendation: This protocol is acceptable. However, if significant absorption of other molecular weight fractions is also observed from study # URO 392, they may also require investigation according to the above protocol.

Conclusions:

Toxicology Branch II has reviewed the submitted metabolism protocols for PHMB in rats. These protocols appear to be acceptable in design. Specific recommendations for each protocol are made above. It is to be noted that study #'s URO 361 and URO 392 are designed to partially fulfill § 85-1 guideline requirements, while study # URO 360 is not.