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

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AUG 16 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Baquacil (10182-19); Vantocil P (10182-45)
(Polyhexamethylene Biquanide)
Record Number: 246049
Tox Chem No. 676
Project No. 9-1565

From: John H.S. Chen, D.V.M. John H.S. Chen 8/15/89
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Thru: Yiannakis M. Ioannou, Ph.D., Section Head For YMI
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and

Marcia Van Gemert, Ph.D., Branch Chief Marcia Van Gemert 8/16/89
Toxicology Branch II
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Review and Assessment of the Mouse Micronucleus Test with Vantocil IB, ICI Central Toxicology Laboratory Study No. CTL/P/2436, April 14, 1988

Reviewer's Recommendation: The study was not conducted in accordance with the acceptable procedures for performing the mouse micronucleus test as recommended by EPA (EPA Health Effects Test Guidelines 560/6-83-001). Therefore, no conclusions can be reached regarding the potential of Vantocil IB to induce clastogenic effects on the mouse bone marrows. This study is unacceptable in the present form and may be upgraded on resolution of the reported deficiencies.

Tox Chem No. 676 | Last Updated _____ | Current Date 8/ /89

Baquacil (10182-19); Vantocil P (10182-45)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	Core Grade Doc. No.
Mutagenicity - mouse micronucleus test; ICICTL; #CTL/P/2436; 4/14/89	Vantocil IB (Lot No. BX 2125 Ex. Grangemouth; 100% purity [redacted]	MRID 410969-01	Positive response in male mice at the 400 mg/kg dose level at the 48 hours sampling time only. However, the extended reading of an additional 2000 PCE did not confirm the initial finding and no statistically significant differences were observed. Dose levels tested: 250 & 400 mg/kg b.w. (Deficiencies are identified in the detailed review).		Unacceptable

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Guideline Series 84: MUTAGENICITY

Reviewed by John H.S. Chen, D.V.M. John H.S. Chen 4/15/89
Section I, Toxicology Branch -HFAS (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, PH.D. FOR YMI Alan C. Levy 8-16-89
Section I, Toxicology Branch -HFAS (H7509C)

DATA EVALUATION REPORT

CHEMICAL: Baquacil Swimming Pool Sanitizer and Algistat; Vantocil P Microbiocide

Tox. Chem. No.: 676

EPA File Symbol: 10182-19

STUDY TYPE: In vivo micronucleus assay in the mouse bone marrows
MRID Number: 410969-01
ACCESSION NUMBER:

SYNONYMS/CAS No.:

SPONSOR: ICI Americas, Inc.
Wilmington, DE 19897
TESTING FACILITY: ICI Central Toxicology Laboratory

TITLE OF REPORT: 'Vantocil' IB: An Evaluation in the Mouse Micronucleus Test

AUTHOR(S): C.R. Richardson, V. Randall, and S.L. Beck

STUDY NUMBER(S): CTL/P/2436

REPORT ISSUED: April 14, 1989

CONCLUSION(S) - Executive Summary:

Vantocil IB had positive response in male mice at the 400 mg/kg dose level at the 48-hour sampling time only. The value obtained for the control male group at 48 hours was low compared with the control values at the other two sampling times and so extended reading of an additional 2000 polychromatic erythrocytes was performed to examine this apparent difference further. The extended reading did not confirm the initial finding and no statistically significant differences were observed.

Dose levels tested: 250 and 400 mg/kg b.w.

Study: Unacceptable
(Deficiencies are identified in the detailed review)

A. MATERIALS

1. Test Material: Name: 'Vantocil' IB
Description (e.g. technical, nature, color, stability):
Colourless liquid with specific gravity of 1.04
Batch #: BX 2125 Ex. Grangemouth Purity: 100% [redacted]
Contaminants: if reported, list in CBI appendix
Solvent used: Sterilized double deionised water
Other comments:

2. Control Materials:
Negative/Route of administration:
Sterilized deionised water/ single dose by the intragastric route/10 ml/kg

Vehicle/Final concentration/Route of administration:
Same above

Positive/Final concentration/Route of administration:
Cyclophosphamide/single dose by the intragastric route/65 mg/kg b.w.

3. Test compound:
Route of administration: Single dose of 'Vantocil' IB by the intagastric route at the dose levels of 250 and 400 mg/kg b.w.
Dose levels used:

4. Test animals:
a. Species mouse Strain C57BL/6JFCD-1/AlPK Age 9-11 week old
Weight _____ Source: Animal Breeding Unit, ICI

b. No. animals used per dose: 5 males 5 females
c. Properly maintained? (Y) / N (circle one)

B. TEST PERFORMANCE

1. Treatment and Sampling Times:
a. Test compound
Dosing: X once _____ twice (24 hr apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hr _____ 12 hr
X 24 hr X 48 hr X 72 hr (mark all that are appropriate)
_____ other (describe):

INERT INGREDIENT INFORMATION IS NOT INCLUDED

b. Negative and/or vehicle control
Dosing: ___x___ once _____ twice (24 hr apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hr _____ 12 hr
___X___ 24 hr ___X___ 48 hr ___X___ 72 hr (mark all that are appropriate)
_____ other (describe):

c. Positive control
Dosing: ___X___ once _____ twice (24 hr apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hr _____ 12 hr
___X___ 24 hr _____ 48 hr _____ 72 hr (mark all that are appropriate)
_____ other (describe):

2. Tissues and Cells Examined:

___X___ bone marrow _____ other (list):

No. of polychromatic erythrocytes (PCE) examined per animal: 1000
No. of normochromatic erythrocytes (NCE; more mature RBCs) examined per animal:
Other (if other cell types examined, describe):

3. Details of slide preparation: The animals were killed by cervical dislocation at 24, 48, and 72 hours after receiving a single dose of the test material. Femurs were removed. The iliac end of the femur was removed and a fine paint brush wetted with a solution of albumin (6%) was dipped into the marrow canal. The brush was rinsed in physiological saline between animals of the same group and a separate brush was used between groups to avoid cross contamination. Four streaks of marrow suspension were then applied to appropriately labeled, clean dry microscope slides. The slides were allowed to air dry and stained with polychrome methylene blue and eosin.

4. Preliminary cytotoxicity assay (reported results, e.g. include dose range, signs of toxicity - e.g. MTD considerations, clinical signs; no. animals): The test material was initially administered as a single intragastric dose to two females at 2500 mg/kg. Both animals died immediately. Two female mice were then dosed at 500 mg/kg, one of which survived and one was killed due to toxic effects. A further five females and five male mice were dosed with 500 mg/kg, of which two female and two male mice died. From these observations, 500 mg/kg was taken to represent the median lethal dose. The 80% and 50% of median lethal dose were calculated to be 400 and 250 mg/kg. Therefore, the MTD was determined to be 400 mg/kg. The other dose level used in this assay was 250 mg/kg (Appendix D and E attached).

5. Micronucleus assay (reported results, e.g. include induction of micronuclei; appropriateness of negative, solvent and positive control micronucleus frequencies; ratio of PCE/NCE; sex differences (if any); appropriateness of dose levels and route; statistical evaluation; include representative table, if appropriate):

There were no significant differences in micronucleated polychromatic erythrocyte (MN-PCE) frequencies between the groups treated with the test material and the negative (vehicle) control at the 24, and 72 hours sampling times. However, the incidence of MN-PCE in mice treated with Vantocil IB showed an isolated, statistically significant increase ($P<0.01$) over control at the top dose level (400 mg/kg) at the 48 hours sampling time in male mice only. In contrast, the positive control compound (cyclophosphamide dosed at 65 mg/kg) gave significantlly increased ($P<0.01$) frequencies of micronucleated polychromatic erythrocytes in the bone marrows of both male and female groups at the 24 hours sampling time.

The data from individual aniaml are shown in Appendices F.G.H. Group data are shown in Tables 1-5. Although a statistically significant increase in the MN-PCE was found in male mice at the 400 mg/kg dose level at the 48 hours sampling time, no significant differences were observed at this dose level when the extended reading of an additional 2000 polychromatic erythrocytes was performed in this study (See Tables 2 & 3). In addition, no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes was observed at either dose level of Vantocil IB at any of the sampling times investigated, when the sexes were combined (See Table 1).

6. Reviewer's discussion/conclusions (include e.g. rationale for acceptability or not; necessity for repeat, if appropriate; address any discrepancies with author conclusions):

A. The positive control compound (cyclophosphamide) apparently induced marked increase of the PCE with micronuclei in the bone marrows of both males and females, indicating the sensitivity of the assay system to a known clastogen.

B. The spontaneous rates of micronuclei in the PCE of the vehicle control group were found from 0.24 %(females) to 0.4% (males) in this study. These results are within the normal range for performing the mouse micronucleus assay as described by Heddle et al. (Mutation Res. 123: 61-118, 1983);

C. However, the evaluation of this study cannot be accomplished due to the following deficiencies:

i. No analytical information was provided to confirm the intended concentrations of the test material in solution.

ii. Individual clinical observations, toxic or pharmacological effects of test material on test aniamls were not included.

iii. Two doses were used; however, for determination of a dose response at least 3 doses should be assayed.

iv. The number of normochromatic erythrocytes per 1000 PCE was not co-determined for the cytogenetic analysis in this study. In addition, determination of the ratio of PCE to NCE can provide an indication of a possible general activity of the test material on bone marrows for this study.

Therefore, the report is inclusive and unacceptable in the present form. However, the study may be upgraded on resolution of the reported deficiencies.

7. Was test performed under GLPs (is a quality assurance statement present)? (Y) / N (circle one)

8. CBI appendix attached (Y) / N (circle one)

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RIN 4292-93 BACUACIL 111801

Page_____ is not included in this copy.

Pages 8 through 21 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ Description of the product manufacturing process.

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