CASWELL FILE

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

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JAN 6 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: BAQUACIL (VANTOCIL P) --- Mutagenicity Study Submitted in Response to the Antimicrobial Data Call-In Notice. EPA Reg. No.'s 10182-19(-45).

TB Project 8-0269
Caswell No. 676

FROM: Irving Mauer, Ph.D.
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Hazard Evaluation Division (TS-769c)

Irving Mauer 12-22-87

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THRU: Judith W. Hauswirth, Ph.D., Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Judith W. Hauswirth 12/29/87

1/5/87

Registrant: ICI Americas Inc., Wilmington DE

Action Requested: Review and evaluate the following mutagenicity study, submitted in response to the Antimicrobial Data Call-In Notice:

> Vantocil P: A Cytogenetic Study in Human Lymphocytes in vitro, Study No. SV0048 (Report No. CTL/P/613), January 16, 1981, performed at the Central Toxicology Laboratory of ICI Ltd., Alderley Park, Macclesfield, Cheshire UK.

TB Conclusions: The study is UNACCEPTABLE because, among other deficiencies, only a single assay without activation was conducted, whereas at least replicate assays with and without metabolic activation are required according to current Testing Guidelines.

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TOXICOLOGY BRANCH: DATA REVIEW

Review by: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division

TB Project: 8-0269
EPA ID No: 10182-19
Date: 12/22/87

Through: Judith W. Hauswirth, Ph.D.,Head
Section VI, Toxicology Branch
Hazard Evaluation Division

CHEMICAL: BAQUACIL (VANTOCIL P)

Caswell: 676
EPA Chem: 111801

STUDY TYPE: Mutagenicity -- cytogenetics in vitro
(human lymphocytes)

CITATION: "Vantocil P": A Cytotenetic Study in Human Lymphocytes in vitro.

ACCESSION NO.: 403919-01

MRID: n/a

SPONSOR: lCl AmericaS., Inc., Wilmington, DE

TESTINTG LAB.: Central Toxicology Laboratory (CTL), Imperial Chemical Industries (ICI), Alderly Park Cheshire (UK)

STUDY NO.: SV0048 (Report No. CTL/P/61

STUDY DATE: January 16, 1981.

TB CONCLUSIONS/EVALUATION: Unacceptable. Only a single assay was conducted without activation, whereas at least replicate assays with and without metabolic activation are required according to current Testing Guidelines.

DETAILED REVIEW

Test Ariticle: VANTOCIL P, a 20% solution in glass-distilled water of polyhexamethylene biguanide hydrochloride, Batch No. ADGM/1021/79.

Procedures: Whole blood from a single male donor (with a stated previously established low spontaneous incidence of chromosome aberrations) was dispensed into 14 culture tubes containing 1% phytohaemagglutinin, a mitotic stimulant. Forty-four hours after initiation, duplicate cultures were exposed to test compound at concentrations of 0(glass-distilled water as solvent control), 1, 5, 10, 20 and 50 ug/ml. The last two cultures were exposed to 0.5 ug/ml. Thmitomycin C, a reference mutagen serving at a positive control.

Cultures were incubated a further 26 hours, treated with colchicine for two hours (to collect mitoses in metaphase stage), then 0.075 M KCL (to expand the cells and spread chromosomes for easier scoring), and finally, fixed and stained for microscopic analysis of cytogenetic abnormalities (4 slides per culture). Twenty-five cells were scored from each slide, 4 slides from each culture, 2 cultures for each dose level. Only cells with a minimum of 45 centromeres were analyzed. (The normal human chromosome number is 46.) All categories of induced damage were evaluated statistically using Student's "t" test. The mitotic index was determined for each culture.

Results: No statistically significant difference from solvent control was recorded in any category of chromosome damage in any Vantocil treatment group (Report Table 1, attached to this review). Small non-significant increases at the HDT (50 ug/ml) in gaps (5% vs. 2% in control) and tetraploid cells (3.5% vs 1.0% in control) were considered by the authors to reflect variations resulting from compound toxicity rather than a mutagenic effect. In contract, mitomycin C produced highly significant increases in all categories of chromosome damage.

A dose-related decrease in mitotic activity was recorded at all doses of test substance.

The authors concluded that Vansocil P was not clastogenic (causes chromosome breakage and/or damage) to human lymphocytes in vitro.

TB Evaluation: This 1981 study is inadequate according to current Testing Guidelines, and is considered UNACCEPtable because of the following major deficiencies:

(1) The test material was not assayed in the presence of a metabolic activation system (S 9 mix).

(2) The assay, as performed without activation, was not repeated to confirm the negative results of the single experiment run.

(3) An appropriate preliminary dose-selection test was not conducted, to ascertain the highest toxic concentration, as well as the lowest dose which is toxicologically inactive.

(4) Data to support the "low spontaneous incidence of chromosome a aberrations" of the donor were not presented.

Attachment

'VANTOCIL P': A CYTOGENETIC STUDY IN HUMAN LYMPHOCYTES IN VITRO

TABLE 1

INCIDENCE OF CHROMOSOMAL ABERRATIONS AND MITOTIC INDEX SHOWN AS A PERCENTAGE OF THE TOTAL NUMBER OF CELLS ANALYSED PER DOSE LEVEL

Treatment	No of Cells Analysed	% of Cells with Chromatid or Chromosome Gaps	% of Cells with Chromatid or Isochromatid, Breaks or Deletions	% of Cells with Fragmentation	% of Cells with Interchanges	% of Cells with any Abnormality	% of Abnormal Cells Excluding Gaps	Mitotic Index	% Incidence of Tetra-ploid Cells
Water Control	200	2.0	0.5	0	0	2.5	0.5	10.0	1.0
Mitomycin C 0.5µg/ml	200	20.5	58 ***	11	38.5 **	96.5 ***	96.0***	6.5	1.5
VANTOCIL P 1µg/ml+	200	2.5	1.0	0	0	3.5	1.0	7.0	0
VANTOCIL P 5µg/ml	200	4.5	1.0	0	0	5.5	1.0	5.0	1.0
VANTOCIL P 10µg/ml	200	3.5	0.5	0	0	4.0	0.5	4.5	0
VANTOCIL P 20µg/ml	200	3.5	0.5	0	0	4.0	0.5	3.5	0
VANTOCIL P 50µg/ml	200	5.0	1.5	0	0	6.5	1.5	1.5	3.5

** Statistically significantly different from the control mean at 1% level (t-test)
*** Statistically significantly different from the control mean at 0.1% level (t-test)