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

009310

FEB 24 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Agency Responses to Irgasan Phase 4 Review Rebuttal Comments

Caswell No. 186-A
PC Code: 54901

HED Project No. 2-0308
Case No.: 2340

TO: Napoleon Kotey
Product Team 52
Special Review and Reregistration Division (H7508W)

FROM: Deborah L. McCall DLMcCall 2-3-92
Toxicology Branch II / Section III / (H7509C)

THROUGH: James Rowe, Ph.D., Section Head James Rowe 2/4/92
Toxicology Branch II / Section III / (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief M. Van Gemert 2/4/92
Toxicology Branch II / HED (H7509C)

BACKGROUND

The registrant, Ciba-Geigy, has submitted rebuttal comments to the Agency concerning the Phase IV review of the Oncogenicity study in rats (§ 83-2a) MRID No. 161332. The registrant outlined their responses by using the same format as the memo from W. Phang, dated 3-23-89 (see Appendix A.) The registrant also submitted 11 other reformatted study summaries to be reviewed for acceptability. Each of the comments will be addressed separately with an Agency response below, as well as the additional reformatted studies. [Note: The PWG comments from Ciba-Geigy have been discussed with the EPA consulting veterinary pathologist, Dr. Lucus Brennecke for his concurrence.]

Agency Rebuttal #1:

The Agency still feels that the technical errors noted by the contractors are a significant problem and not the writing style of the report.

The lack of summarization had no significance on the outcore of the study, but the report format did not meet FIFRA Subdivision F Hazard Guidelines.

Agency Comment # 2:

Agency agrees with study author's conclusion that the test material did not show any oncogenic effects.

Agency Comment # 4:

The decrease in erythrocyte counts of the 300, 1000, and 3000 ppm male groups at 78 and 104 weeks will be as viewed as statistically significant, but not biologically significant.

Agency Comment # 5:

The incidence of foamy macrophages will be considered as an incidental finding.

Agency Comment # 6:

The liver necrosis slides were re-read and were broken out as two separate types of necrosis (focal and zonal) by the PWG workgroup. The consultant pathologist was consulted on these revised slides; and he agreed with the PWG workgroup's conclusion that the liver necrosis findings should be classified as "incidental".

CONCLUSIONS:

The Oncogenicity study in rats is upgraded to Core Minimum with a NOEL = 1000 ppm; based on the significantly decreased body weights in male and female rats and nonneoplastic liver changes (cytoplasmic inclusions and hepatocellular hypertrophy) in males of the 3000 ppm dose group.

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PHASE FOUR REVIEW OF REFORMATTED STUDIES

(**NOTE:** This only contains additions and changes from the phase 2 response.)

Pesticide: IRGASAN

Transmitted to HED on: 10/31/91 Chemical#/Case#: 2340
Tox. Chem #: 186-A Sponsor: Ciba-Geigy

CRM: Napoleon Kotey Phone#: 308-8523

Branch: TOX II Reviewer: D. McCall DMcC 2/3/92

Completed: 2/3/92 Concurrence:

Response, by Guideline

Guideline #: 81-1 Acute oral/rat
MRID 420279-05 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is addressed. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. DATA GAP.

Guideline #: 81-3 Acute inhalation/rat
MRID 421685-01 Study # 254597

Recommendation: Based on preliminary assessment of the study, the study is tentatively acceptable for review.

Guideline #: 81-5 Primary dermal irritation/rabbit
MRID 421685-02 Study #

Recommendation: No daily observations were performed, irritation was not graded at the specified intervals (graded at 24 and 72 hours only) and study should have been continued until skin returned to normal or 14 days (which ever is shorter). Therefore, the study is unacceptable and probably cannot be upgraded. DATA GAP.

Guideline #: 81-6 Dermal sensitization/Guinea Pig
MRID 421685-03 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review. Positive controls were not used in study. No signatures were found on page 67 of the submission. Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. Study could possibly be upgraded if discrepancies are resolved. DATA GAP.

Guideline #: 84-2a Mutagenicity/Ames
MRID 420279-07 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID - 30398.]

Guideline #: 84-2a Mutagenicity/Gene Mutation
MRID 421685-04 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancies are resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. b) No signature was found on GLP statement page of the submission. [Old MRID - 30399.]

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID 421685-05 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID - 30401.]

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID 421685-06 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID - 30402.]

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID 421685-07 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID - 30403.]

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID 421685-08 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID- 30404.]

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Guideline #: 84-4 Other genotoxic effects
MRID 421685-09 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancies are resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. b) No signatures were found on GLP statement page of the submission. c) EPA does not usually accept published reports, please submit the final study (laboratory) report. [Old MRID - 57631.]

Guideline #: 84-4 Other genotoxic effects
MRID 421685-10 Study #

Recommendation: Based on preliminary assessment of the study, the study is tentatively unacceptable for review until the following discrepancy is resolved. a) Study information pertaining to the Code of Federal Regulations 40, §160.12, Statement of Compliance, subpart (b) was not addressed. [Old MRID - 89717.]

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WASHINGTON, D.C. 20460

Appendix A

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Irgasan: Review of Chronic Feeding / Oncogenicity Study in Rats

Caswell No. 186A EPA ID No. 100-502
EPA Record No. 230991

TO: J. Kempter / W. C. Francis, PM (32)
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 3/20/89
Pharmacologist
Section II
HFAS / Toxicology Branch II / HED (H7509C)

THROUGH: K. Clark Swentzel, Toxicologist 3/21/89
Acting Section Head
and
Marcia van Gemert, Ph.D.
Acting Branch Chief
HFAS / Toxicology Branch II / HED (H7509C)

The registrant, Ciba-Geigy Corp. has submitted a 2-year feeding/oncogenicity study in rats with Irgasan (Fat 80'023). This study has been reviewed by Dynamac Corp. and approved by Toxicology Branch II. The data evaluation report is attached, and the conclusion is as follows:

1). This study is poorly organized and written. It also contains technical errors in clinical chemistry analyses. In most cases summary data are not prepared.

2). Groups of rats (80/sex/dose) were fed Irgasan at dietary concentrations of 0, 300, 1000, and 3000 ppm for 104 weeks and 6000 ppm for 52 weeks. Under the conditions of the study, the test agent did not show any oncogenic effects.

3). A significant body weight decrease was seen in 6000 ppm females.

4). Consistent and statistically significant decreases in erythrocyte counts were seen in 300, 1000, and 3000 ppm males

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at the measuring periods of weeks 78 and 104. Decreases in hemoglobin concentration and hematocrit in treated males were also present, but they were not consistent and sometimes were not statistically significant. Clotting time in 6000 ppm males was consistently increased.

5). A significant increase in the incidence of accumulation of foamy macrophages in pulmonary alveoli of both treated males and females was seen at 104 week.

6). A significant increase in the incidence of non-neoplastic liver changes such as cytoplasmic inclusions and hepatocellular hypertrophy was seen in 3000 ppm males. An increase in the incidence of hepatic necrosis was seen in 300, 1000, and 3000 ppm males relative to the controls. It seemed to be quite odd that clinical chemistry data did not show consistent changes in SGPT or SGOT levels while the above effects on the liver were found in the treated males. In the absence of the historical control incidence of liver necrosis, the increase in the incidence of liver necrosis in 300, 1000, and 3000 ppm males could not be dismissed.

Based upon the increase in the incidence of liver necrosis, the decrease in the erythrocyte count, and the increase in the incidence of accumulation of foamy macrophages in the pulmonary alveoli, the LOEL is established at 300 ppm which was the lowest concentration tested. At the present a NOEL for chronic toxicity can not be established.

The study is classified as supplementary because it contains many technical errors, is incomplete, and is poorly organized.