CASWELL FILE

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Company Response on CHO/HPRT mutagenicity assays and 2-generation reproduction study on Harmony

To: V. Walters, PM-25
Registration Division, TS-767C

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Chemical: Harmony

Firm: Dupont

Caswell No: 573S

Dupont responded to EPAs comments concerning the two remaining supplementary studies, the CHO/HPRT mutagenicity assay study # HLR 240- 84, and the 2-generation reproduction study study # HLR-432-85.

1. For the CHO/HPRT mutagenicity assay, EPA had called the study supplementary because it was not clear why 7 mM was used as the highest concentration when the test compound was soluble in DMSO at up to 700 mM. Dupont's reply is given verbatem below:

a. The dimethylsulfoxide (DMSO) solvent, the harmony test chemical and positive indicator solutions were added to the treatment medium in a volume of 30 microliters (0.030 ml) giveing a final treatment culture medium volume of 3 ml. The limit of Harmony solubility in DMSO was 700 mM. When 0.030 ml of the 700 mM stock solution was added to make 3 ml of culture medium, the final harmony concentration was 7 mM. The final DMSO concentration, 1%, is the highest level of solvent normally used in this assay.

b. Harmony test concentrations of 7, 6, 5, and 3 mM precipitated in culture medium, which demonstrated harmony's limit of solubility.

c. The 7 mM harmony test concentration reduced cell plating efficiency by at least 30%, which demonstrated harmony's toxicity.

The symbol "p" used in the original table indicated that there was a precipitate present.
Since the study appeared to achieve both a decrease in survival

of about 30% at the top dose, and had reached the limit of solubility, the EPA question has been satisfactorily answered, and the study can be upgraded from unsatisfactory to satisfactory.

2. In the 2-generation reproduction study histopathology was not performed on any parental generation animals. Dupont responded with several points to this deficiency.

a. Rats in the 2-year study, exposed to the same levels of Harmony as those in the reproduction study for a longer period showed no gross or microscopic reproductive tissue abnormalities.

b. In the reproduction study there were no effects that showed the reproductive system as the target.

c. Two subsequent reproduction studies in which similar sulfonyl urea compounds were tested showed no effects on the reproductive system when examined histopathologically.

d. In numerous other previous multigeneration studies on other materials when conducted in combination with long-term studies, showed no selective toxicity of the reproductive tract of only pregnant rats but no effect in non-pregnant rats.

e. The rats in the teratology study were exposed to 800 mg/kg as a bolus by gavage and no abnormalities of the reproductive system were found when subjected to gross examination.

f. Pathology exams of the F_{2b} weanlings exposed in utero and during lactation did not show any reproductive system abnormalities.

After reviewing Dupont's arguments, and the fact that no reproductive effects occurred during the study, EPA is satisfied that analyzing the P generations histopathologically for this study would not have added additional information to what was already gathered, and will upgrade the study from supplementary to core minimum.

Conclusions:
Both studies are now considered satisfactory and will be upgraded to core minimum and acceptable.

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