Rec'd 31463

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

MEMORANDUM JUN 15 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby, Product Manager #21
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 6/14/82

SUBJECT: Unscheduled DNA Synthesis Mutagenicity Assay of Captan.
Accession #244432

TOX Chem. No. 159
Acc. No. ~~244432~~
Study No. 239-1246

Chemical: Captan Technical

Background:

Captan was one of many pesticides tested in a battery of mutagenicity assays by SRI Laboratories under EPA contract (EPA No. 68-01-2458). It was originally reported that captan caused unscheduled DNA synthesis (UDS) in WI-38 cells in culture after metabolic activation by mouse liver S-9 mixture. This submission (stating that captan does not cause UDS in WI-38 cells) is a retraction of the original report.

Laboratory: SRI International
333 Ravenswood Avenue
Menlo Park, California 94025

Contract Officer: Michael D. Waters, Ph.D.
EPA, Research Triangle Park
North Carolina 27711

Recommendation:

Captan does not induce unscheduled DNA synthesis in WI-38 cells under the conditions of this experiment. This study is acceptable for regulatory purposes; although the metabolic activation system is not very effective.

REVIEW

Materials and Methods:

The WI-38 cells were incubated in suspension with captan technical in DMSO and tritiated thymidine for 3 hours without metabolic activation and for 1 hour with metabolic activation. The DNA was extracted and the incorporation of the labeled thymidine was counted.

Metabolic activation system: S-9 microsomal fraction from male mice (no induction pretreatment was described).

Dosage: Six replicate samples were tested at five doses plus negative (solvent) and positive controls.

Results:

Without Metabolic Activation

	Captan Concentration ($M \times 10^{-6}$)						
	0	3.1	6.3	12.5	25	50	Positive Control
Average cpm/ug DNA	55	52	48	29	8	3	1281

With Metabolic Activation

	Captan Concentration ($M \times 10^{-6}$)											
	0	3.7	11.1	12.3	33.3	37	100	111	300	333	1000	Positiv Control
Trial 1 Average cpm/ ug DNA	119	161	130	-	158	-	108	-	141	-	-	386
Trial 2 Average cpm/ ug DNA	66	-	-	72	-	73	-	71	-	61	64	277

Discussion:

The study without metabolic activation is acceptable and shows that the positive findings in the previous study were an artifact caused by the abnormally low control values.

Taking this study by itself, it is possible that the doses were too high and the cellular toxicity indicated by the decreasing thymidine incorporation into DNA is obscuring the genotoxic effects, however, in conjunction with the first study, which had lower doses, this may be interpreted as an acceptable negative study.

The metabolic activation system studies still are inconsistant and the positive control is not as active as it could be. Part of the problem may have been with the metabolic activation system: uninduced mouse liver S-9 fraction. In fact, SRI's report states that since this study was performed they have better results using a induced rat liver S-9 mixture for metabolic activation. There most likely is no cause for concern here, other studies using metabolic activation systems have shown a decrease in mutagenic activity. We do not feel that we could learn much by repeating this study.

William R. Schneider, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

OPP:HED:TOX: W.SCHNEIDER:sb 6/14/82 X73710 Rm. 816 #ml4