CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CAPTAN

SB 950-206, Tolerance # 103
Chemical Code, 104

November 6, 1986
Revisions: 5/5/87, 8/23/88, 1/23/89, 5/18/90, 7/22/91, 11/18/91, 7/6/92

I. DATA GAP STATUS

Chronic rat:	No data gap, no adverse effect
Chronic dog:	No data gap, no adverse effect
Oncogenicity rat:	No data gap, possible adverse effect
Oncogenicity mouse:	No data gap, possible adverse effect
Reproduction rat:	No data gap, no adverse effect
Teratogenicity hamster:	No data gap, no adverse effect
Teratogenicity rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect

Chromosome effects: No data gap, possible adverse effect

DNA damage: No data gap, possible adverse effect

Neurotoxicity: Not required at this time

Note, Toxicology one-liners are attached

In document/record number designations of the one-liners below:
** indicates acceptable study
Bold face indicates possible adverse effects

NOTE: This product has more than one registrant. This is the primary reason for often retaining more than one record number for a single study.

NOTE: All relevant record numbers up to 089224 (Document 103-256) and 098765 (Document 103-261) and all record numbers over 900000 submitted for Captan SB-950 review have been examined. These data reflect all studies in DPR library files as of 11/18/91. [redacted] 11/18/91)
Revised 7/6/92 by [redacted]

TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED (CHRONIC/ONCOGENICITY)

RAT

****073-076 925094-925097** "2-year oral toxicity/carcinogenicity study of Captan in rats" IRDC, 6/23/82. Captan technical (89%) in the diets of Charles River CD* rats at 0, 25, 100 of 250 mg/kg/day for two years; 70/sex/group; interim sacrifices of 10/sex/group at 12 and 18 months. Results: modest increase of comparatively uncommon renal tubular adenomas or carcinomas in males, with incidence of 1, 1, 3, and 4 in increasing dosage groups. Non-oncogenic effects NOEL = 25 mg/kg [Decreased body weight (M & F), hepatocellular hypertrophy (M), increased relative organ weights of liver and thyroid/parathyroid (F) and kidney (M & F)]. Prior reviews classified report as acceptable, with no adverse effect, however in 1986 CDFA had requested a full disclosure of relevant historical control kidney tumor incidence data, which the registrants had obtained from the testing facility for submission to EPA [redacted] 7/1/85, 10/21/86). This information has been supplied to CDFA (Aug. 17, 1988 submission by ICI Americas; CDFA has since assigned record No. 218:069960 to these data). The low historical incidence of renal tubular adenomas plus carcinomas in male CD* control rats from contemporary IRDC studies prompts a reclassification of study status to **acceptable, with possible adverse effect**. [redacted] 8/19/88; one-liner amended by [redacted] without a new worksheet, 11/30/88).

EPA one-liner: Tentative NOEL = 25 mg/kg/day; renal tumors in males were 1%, 1%, 4% and 6%--potential for onco effect being investigated further; minimum.

205 065864 Supplement to 925094. Section of 1/28/88 Rebuttal from Captan Task Force. This section was a discussion which dealt with long term rat studies, particularly 073:925094. This section was primarily interpretative narrative, not new data. Comments were considered in 8/19/88 CDFA review of 073:925094.

066 925078 Partial Duplicate of 073:925094 (First 42 pp. of text only.) Retain this record number.

098 016924 Almost-complete duplicate of 074:925095. Retain both records.

098 016923 Apparent exact duplicate of 073:925094. Retain both records.

028 024181 12-month interim report of 073-076:925094-925097. Retain record.

046 925090 Interim report of (negative) duodenal microscopic findings sent prior to final report of 073:925094, above.

103-028 924976 Letter (IRDC to Stauffer) on interim tumor data in adrenal and thyroid for study 103-073:925094, above. Data were negative. [redacted] 5/18/90.

CHRONIC

DOG

103-224 071019 "One year oral toxicity study in dogs with captan technical". IRDC No. 153-198, 10/25/88. Captan, tech. (90.4%), lot # WRC 4921-26-15. Doses of 0, 12.5, 60, and 300 mg/kg/day in gelatin capsules to 5 beagles/sex/group for 1 year. **No adverse effects: NOEL = 60 mg/kg/day, based on marginal increases in emesis and soft/mucoid stools in males and females. The high dose was thus not definitively toxic, however a 4-week study (223:071018) justified the selected dosages for the chronic study. **Acceptable**: Upgraded on 5/14/90 on the basis of supplementary information about the test article in Record #090597, below. [redacted] 1/23/89, 5/14/90.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "supplementary", but upgradeable on receipt of certain clarifications.

103-250 090597 (additional data to dog chronic oral toxicity study 103-224:071019). Two capsules per dose were needed due to the low density of the test material. Retention samples of the lot used in the dog study were assayed. There was no detectable change in captan content over a period of about 3 years. These data support an upgrade of the cited study to **acceptable** status. [redacted] 5/14/90.

ONCOGENICITY

RAT

028 925129 "Bioassay of Captan for Possible Carcinogenicity - Rats", (Gulf South Res. Inst., report no: NCI-CG-TR-15, 1977). Captan (lot 5X-317, Chevron, presumably technical) in the diets of Osborne-Mendel rats initially at 0, 8000 or 16,000 ppm; high dose terminated at 18 weeks; several changes in dosing levels, ending with 2000 and 4000 ppm groups. Tumors of

adrenal cortex and thyroid C-cells appeared to be possibly compound-related (but were not significant by two-way comparison tests such as Fisher's exact test). UNACCEPTABLE (many major deviations from guidelines), NOT UPGRADEABLE (insufficient useful information for scientific evaluation. [redacted] 7/10/85).

028 925086 Comments on record 028:925129 by William W. Carlton, D.V.M., Ph.D. He concluded that rat tumors were spontaneous.

047 925091 Comments on record 028:925129. Evaluation of selected tissues for neoplasms.

085 000004, "Life-Span Oral Carcinogenicity Study of Merpan in Rats", (Netherlands Org. Appl. Sci. Res., final report no. V 83.233/200153, 11/83). Captan in the diets of SPF (Cpb: WU; Wistar random) rats at 0, 125, 500 or 2000 ppm for 130 weeks; 50/sex/group; no adverse effects reported; NOEL = 500 ppm (based on decreased body weight gain); UNACCEPTABLE (Needs histopathology of lung and kidney tissue from the low and mid-dose groups, analysis of dosing material, test article characterization), POSSIBLY UPGRADEABLE. [redacted] 7/8/85).
EPA one-liner: Systemic NOEL > 2000 ppm (HTD); onco NOEL=insufficient data to assess effect (statistically significant increase of tumors in the pancreatic islet cells of males reported); supplementary.

086 000103. Appendix to 085:000004. Signs, grossly visible masses, ophthalmoscopic examinations, body weights.

087 000104. Appendix to 085:000004. Food intake, hematological findings, white blood cell counts, organ weights.

088 & 089 000105 & 00016. Appendices to 085:000004. Macroscopic observations.

090 to 295 000107 to 000112. Appendices to 085:000004. Macroscopic and microscopic observations of lesions suspected of tumors.

MOUSE

Mouse oncogenicity studies provide definitive evidence for duodenal hyperplasia and neoplasia in mucosal tissues, as indicated below. Other GI mucosal areas have been indicated in some studies. Effects in the duodenum are predictable at 6000 ppm and above in the diet, however the dose effect relationship is not well established at lower levels. Study 103-241:074479 (Wong, Z.A. and Bradfield, L.G., Jan. 9, 1981 study, SOCAL 1150) was re-classified as acceptable. There is no indication of oncogenic responses in tissues other than GI tract mucosae of mice, in contrast with rat findings suggesting a possible weak oncogenic response to high doses in the kidney. [redacted] 11/6/86, revised 5/18/90.

125 043865, "Identification of a Preneoplastic Alteration Following Dietary Administration of Captan Technical to CD-1 Mice", (Environmental Health Ctr. (Stauffer), report no: NCI-CG-TR-15, 9/23/85). Captan technical, 0 or 6000 ppm in diet (lifetime exposure with interim sacrifices, also recovery groups following 6 or 12 month exposures). No NOEL determined in study (duodenal adenomas, adenocarcinomas and focal epithelial hyperplasias were characteristic features at 6000 ppm). Non-neoplastic effects also observed in nonglandular stomach epithelium (hyperplasia, ulcers, and erosions) in mice killed during first several months of study. Study does not satisfy data requirements for a mouse oncogenicity study, however useful data were provided. [redacted] 9/26/86).

028 033944, "Bioassay of Captan for Possible Carcinogenicity - Mouse", (Gulf South Res. Inst., report no: NCI-CG-TR-15, 1977). Captan tested at 0, 8000 or 16,000 ppm in the diet; B6C3F1 mice dosed for 80 weeks, then observed for 11 weeks; 10/sex in concurrent control group (additional pooled controls considered for statistics), 50/sex/test article group. **Possible adverse effect**: dose-related incidence of duodenal mucosal hyperplasia and duodenal tumors. Incidence of adenomatous polyps plus adenocarcinomas in duodena of males was 0/68, 3/43, and 5/46 for pooled controls, 8000 ppm and 16000 ppm groups, respectively. Corresponding female incidence was 1/68, 1/49, and 3/48, respectively. **Unacceptable** (several major variations from guidelines), **not upgradeable**, but useful information. [redacted] 7/10/85).

028 925085 Comments on record 028:033984 by William W. Carlton, D.V.M., Ph.D. He concluded that the duodenal tumors noted in the study were probably treatment related, due to the relative rarity of such tumors in mice.

****103-241 074479** (the 38 page "main text" of part 1 of the report was previously reviewed under CDFA record 103-099:016925). Wong, Z. A., and Bradfield, L. G., "Lifetime oncogenic Feeding Study of Captan Technical (SX-944) in CD-1 Mice (ICR derived)", (Chevron, Env. Health Ctr., report no: SOCAL 1150, Jan. 9, 1981). Captan (90.7%) given in the diet at 0, 2000/6000, 6000/10,000 or 10,000/16,000 ppm to Swiss CD-1 mice for 113 weeks; 80/sex/group; lesser dose for first 4 weeks, greater dose for remainder of study. There was no NOEL in this study. At the lowest dose level (6000 ppm) and above in both sexes, treatment elicited duodenal mucosal hyperplasia, adenomas, and adenocarcinomas. This was a **possible adverse effect**. Related effects were mucosal hyperplasia in stomach and jejunum (apparently in both sexes at all dose levels), and increased adenomas and adenocarcinomas in the jejunum in 10000 ppm males. Body weights were reduced (dose-related) in both sexes at all doses. Distended abdomens, presumed to reflect poor nutritional status, were observed in all groups of males, as well as in high dose females. The high dose was apparently above the MTD in both sexes, based on reduced body weights, reduced survival, changes in clinical observations incidence in both sexes, and changes in incidences of several histological parameters. **Acceptable**. This full report addresses major CDFA concerns regarding individual data and dosing material analysis. Those concerns were based on the limitations of the brief "main text" of the report originally submitted. [redacted] 7/2/85), 5/18/90).

EPA one-liner: Onco NOEL < 6000 ppm; significantly increased incidences of duodenal adenomas and adenocarcinomas in both sexes; guideline.

099 016925 Record number for the 38-page "Main Text" of 103-241:074479, above. The 1985 CDFA review cited this record number.

106 024899 Exact duplicate of 099:016925. Retain both record numbers.

028 925084 Proposed protocol for 016925.

019 925087 Protocol for 016925.

019 925088 Earlier version (10/24/80) of 099:016925. Retain record No.

028 924974 Draft document of summary pathology data for 099:016925.

106 024547, "Lifetime Oncogenicity Study of Captan in Mice", (Biodynamics, report no: Project # 80-2491, 4/6/83). Captan (89%) tested on CD-1 mice at 0, 100, 400, 800, or 6000 ppm for 22 months; 100/sex/group. **Possible adverse effect**: hyperplasia and neoplasia in mucosal g.i. tract, principally in duodenum at 6000 ppm in both sexes. Incidence of duodenal adenomas or primary carcinomas in males (79-90 examined per group) was 0, 3, 0, 0, and 4 mice/group with increasing dosage. Corresponding incidence in females (83-93 examined per group) was 0, 0, 1, 1, and 4. These duodenal tumors are rare in control mice, and no explanation is available for the unexpectedly high incidence in 100 ppm males. These data support data from other studies, which establish detectable, treatment-related duodenal tumor effect at 6000 ppm and above in both sexes. **Unacceptable** (Appendices II and III missing, no analysis of dosing material provided, no individual animal data, historical incidence data on adenomas, polyps and carcinomas in jejunum and ileum not provided), **Upgradeable**. [redacted] 7/2/85).

EPA one-liner (for 106 24547): Survivorship is low; GI neoplasms are likely due to the administration of captan; guideline.

135 050697 Response to questions raised in the course of CDFA Health Assessment Group review of 106:024547. Response discouraged the practice of combining stomach and small intestinal neoplasia in risk assessment evaluations. A new fate table was provided, also new tables of correlations between gross and histopathology data. Histopathology table was re-written, incorporating minor changes made on re-examination of tissues since the final report was written (pages with changes were identified). No CDFA re-review was necessary from SB-950 Data Review Group, since the data requirement is filled, and the possible adverse effect (duodenal adenomas) has already been identified and the revised data do not change the conclusion. [redacted] 8/17/88.

072 925093 Exact duplicate of 106:024547. Retain both record numbers.

028 024180 Protocol for 106:024547.

049 925092 Interim report for 106:024547.

028 925083, "Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", (Bionetics, report no: NCI-DDCP-CG-1973-1, 8/68). Captan tested in B6C3F1 and B6AKF1 mice. Public document presenting results of testing 130 pesticides. Captan given by oral gavage at 215 mg/kg from 7 to 28 days of age, thereafter in the diet at 560 ppm for 18 months; vehicle controls and untreated controls; 18/sex/group; no adverse effects reported; UNACCEPTABLE (several major variations from guidelines), NOT UPGRADEABLE. [redacted] 7/10/85).

028 925130 Publication version of 925083.

028 033945, "Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", (Bionetics, report no: PB-223 159, 8/68). Captan tested in B6C3F1 and B6AKF1 mice. Public document presenting results of testing 130 pesticides. Captan given as single subcutaneous injection (1000 mg/kg) in the nape of the neck at 28 days of age, observation continued to 18 months; 18/sex/strain/group; no adverse effects reported; UNACCEPTABLE (several major variations from guidelines), NOT UPGRADEABLE. [redacted] 7/10/85).

035 925079 General discussion of captan-induced oncogenicity.

033 925081 Discussion of oncogenicity: no clear connection with other record numbers.

REPRODUCTION

RAT

EPA accepts the two IRDC studies, (023 925109 and 077 925116) as acceptable for fulfillment of the reproductive effects data requirement (see March 1986 Guidance Document). This reviewer [redacted] notes that the protocols for the studies are not identical to 1982 guidelines, the most important difference being the lack of histopathological exams of parental animals. There is no significant likelihood that a repeat study with such exams of parents would reveal information which would have a bearing on reproductive risk, inasmuch as no effects on fertility or gestational length were attributable to dose up to 500 mg/kg/day. The conservative NOEL determination of 12.5 mg/kg/day should provide an adequate basis for safety factor estimation. These two studies have been ACCEPTED by CDFA to fill the rat reproduction data requirement: while no one study alone fills the data gap, the two aforementioned studies provide sufficient data to be considered collectively as adequate and complete. [redacted] 11/6/86.

**023 925109, "Three Generation Reproduction Study in Rats", (IRDC, report no: 153-096, 1/7/81). Captan (89%) given in the diet at 0, 25, 100, 250 or 500 mg/kg/day for a 3 generation study; first and third generations mated twice, second generation mated 3 times; 15 males/group, 30 females/group. Parental NOEL = 25 mg/kg/day (dose-related reduction in body weight at 100 mg/kg/day and above). Reproductive effects NOEL not observed (modest, but often statistically significant reductions in pup body weights at 25 mg/kg/day (LDT) and dose-related reductions in pup body weights at higher dosages. Decreased pup survival during lactation occasionally at 250 and consistently at 500 mg/kg/day). This study is ACCEPTABLE in conjunction with study (077:925116, below). For EPA one-liner, see IRDC 1982 study below. [redacted] 6/18/85).

205 065866 Rebuttal arguments dated 1/28/88, referring to [redacted] review of reproduction study 023:925109. Comments were acknowledged in CDFA Rebuttal Response of July 1988, however no additional worksheet was required (study was already ACCEPTABLE as of 11/06/86 review).

066 925114 Partial duplicate of 023:925109. Record No. must be retained.

103-036 925111 Interim report for 023:925109.

077 925116, "One-Generation Reproduction Study in Rats with Captan", (IRDC, report no: 153-190, 10/11/82). Captan (tech., 89%) in the diet at 0, 6, 12.5 or 25 mg/kg/day (weekly adjustment of dietary concentration on basis of dietary intake) for one generation. This study is supplementary to 023:925109. 15 males/group, 30 females/group. No statistically significant effects reported; investigators noted non-statistically significant decreases in group mean pup body weights at 25 mg/kg/day during lactation (See Table 5 of report), and established 12.5 as the (conservative) NOEL. That NOEL is now acknowledged by EPA (see below). The original review by [redacted] had set the NOEL at 25 mg/kg/day. CDFA now accepts the more conservative NOEL of 12.5 mg/kg/day, as employed by EPA. [redacted] 6/26/85).
EPA one-liner: NOEL = 12.5 mg/kg/day; LEL=25 mg/kg/day (decreased mean litter weights); in combination with the 81 study considered minimum.

023 925110 Protocol for 077:925116. Duplicated in 036:925112.

066 925113 Partial duplicate of 077:925116 Record No. must be retained.

TERATOGENICITY

HAMSTER

** 072 925107, "Teratology Study in Hamsters", (IRDC, report no: 415-005, 1/17/83). Captan tech. [89%] given by oral gavage to golden Syrian hamsters at 0, 50, 200 or 400 mg/kg/day on days 5-10 of gestation; 30 females/group. Maternal NOEL = 50 mg/kg/day (deaths of four 400 mg/kg/day dams, and of one 200 mg/kg/day dam, also additional clinical signs observed at 400 mg/kg/day. Dose-related maternal weight losses at 200 and 400 mg/kg/day, respectively.) Developmental toxicity = 50 mg/kg/day (slight decrease fetal body weight at 200 mg/kg/day). Substantial fetal body weight decrements, increase in post-implantation losses, various malformations and developmental retardations (especially reduced ossification) at 400 mg/kg/day. Study initially classified unacceptable [redacted], 7/12/85) due to lack of test article characterization; no justification of choice of test animal; and concerns about low offspring weights, reduced fetal weights, and reduced ossification. [redacted] (9/15/86) later examined the report, and identified a possible adverse effect: increased incidence of fused ribs, which appeared to be treatment related and lacking a NOEL. [redacted] (10/10/86) concurred with [redacted] that a developmental NOEL had not been demonstrated. Rebuttal comments (document No. 103-139) provided additional information on test article (I.D. number and purity), choice of test animal, other clarifications, and historical data on fused rib incidence in hamsters. [redacted]contacted Dr. C. Willhite (Calif. Dept. Health Services) about fused rib incidence in his experience. All available information was considered to support a change in study status to **acceptable, with no adverse effect**. ([redacted], 5/4/87).

EPA one-liner study disposition: minimum. [Note that teratology did not enter into the bases for the special review, which culminated in a March, 1986 EPA Reregistration Guidance Document: see p. 6 of that document].

019 925104 Amendment to 072:925107.

036 925099 Comments on 072:925107. Review of animal studies.

036 925100 Pilot for 072:925107.

036 925101 Unamended report of 072:925107.

071 925108 Summary of 072:925107.

139 [no record number] Part of rebuttal responses of 11/26/86 and 12/31/86 concerned principally with interpretation of apparent increase of fused rib incidence in 072:925107.

113 035466 A 9/5/85 rebuttal response to early CDFA review(s). These contentions were considered by [redacted] in 9/15/86 CDFA review. [redacted] 9/18/88).

113 035467 A table taken from a manuscript by Frakes, Sharma, Willhite, and Gomez, submitted to show how frequent and/or variable fused rib incidence was in hamsters. This information was considered by [redacted] in 9/15/86 CDFA review. [redacted] 9/18/88).

113 035468, 035469, and 035470 "Maternal toxicity: A possible etiological factor in embryo-fetal deaths and fetal malformations of rodent-rabbit species". (By K. S. Khera, Teratology 31:129-153, 1985). Submitted with 9/5/85 rebuttal to show association of fused ribs and multiple malformations with maternal toxicity in several species. This information was considered by [redacted] in 9/15/86 CDFA review. [redacted] 9/18/88).

RAT

023 033942, "Three Generation Reproduction Study in Rats", (Teratology subsection - IRDC, report no: 153-096, 1/7/82). Captan (89%) given in the diet at 0, 25, 100, 250 or 500 mg/kg/day on an ongoing basis to male and female rats, and continuing on days 0 through 19 of gestation; teratology study conducted on 3rd mating of F1 females in a reproduction study (023:925109). 21-26 pregnancies/group. No teratogenic effects, however there was a small but significant decrement in mean fetal body weights in the 500 mg/kg/day group. UNACCEPTABLE, POSSIBLY UPGRADEABLE (Requires that adequate assessment of developmental delays was made and that it be reported. Test article purity analysis should be obtained if possible). (C. [redacted] 6/18/85, 7/20/88).

205 065866 Rebuttal arguments referring to [redacted] review of reproduction study 023:925109. Comments relevant to the teratology portion of that study (given CDFA volume/record No. 023:033942) were addressed in a 7/20/88 CDFA review.

MOUSE

036 033940, "Inhalation Teratology Studies with Captan and Folpet - C57B1/6 and AKR Mice - Subcutaneous and Oral Routes", (Bionetics, 3/78). Captan given by gavage at 100 mg/kg/day to C57B1/6 mice on days 6-14 of gestation or by subcutaneous injection at 100 mg/kg/day to C57B1/6 mice (days 6-14 of gestation) or to AKR mice (days 6-15 of gestation). Summary data only. Possible adverse effects in injection study: malformations of eye, jaw and face following subcutaneous administration to C57B1/6 mice. UNACCEPTABLE, NOT UPGRADEABLE, data not usable for risk assessment due to non-standard route of administration. [redacted], 7/12/85).

036 925105, "Inhalation Teratology Studies with Captan and Folpet - CD-1 Mouse - Intragastric Subcutaneous or Inhalation Routes", (EPA, 3/78). Captan by oral gavage or by subcutaneous injection at 100 mg/kg/day on days 6-15 of gestation or by inhalation at 483 ug/M^3 on days 6-13 of gestation to CD-1 mice; summary data only; no adverse effects reported; UNACCEPTABLE, NOT UPGRADEABLE. [redacted] 7/12/85).

RABBIT

023 925103, "Effect of Technical Captan on Pregnancy of the New Zealand White Rabbit", (Huntingdon, report no: CHR/15/8114, 5/12/81). Captan (89%) given by oral gavage at 0, 6, 12, 25 or 60 mg/kg/day on days 6-28 of gestation; 8-12 pregnant/group at termination; no adverse effects reported; Apparent maternal NOEL = 25 mg/kg (transient weight loss, also anorexia, reduced fecal output and reduced water intake at 60 mg/kg/day). Apparent developmental toxicity NOEL = 60 mg/kg. UNACCEPTABLE: inadequate numbers of pregnant dams in the two highest dose groups, inadequate justification of dosage levels, with dosages possibly too low. Also, no analysis of dosing solutions (or alternative surrogate data). APPARENTLY NOT UPGRADEABLE. [redacted] 7/20/85).
EPA one-liner: Teratogenic NOEL > 60 mg/kg/day (HTD); minimum.

036 925102 Protocol for 925103.

042 925106 Summary of 925103.

[No document/record numbers] Rebuttal comments sent with 11/24/86 cover letter from Chevron. No new data on study. Discussed in 5/5/87 CDFA Rebuttal Response.

103-256 089224, "Captan: Teratogenicity Study in the Rabbit", (D.J. Tinston, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report # CTL/P/3039, 2/13/91). Captan, 91.2% w/w purity, was administered by gavage on gestation days 7 through 19 at 0 (corn oil), 10, 30, and 100 mg/kg/day to 20 artificially inseminated New Zealand White female rabbits per group. **No "adverse effects". Maternal NOEL = 10 mg/kg/day (Reduced maternal food consumption and body weight gain, dose-related, at 30 to 100 mg/kg/day. Fecal output was also markedly reduced, dose related, at 30 to 100 mg/kg/day). Developmental NOEL = 10 mg/kg/day (characterized by variants or minor abnormalities, namely: partially ossified odontoid, presence of 27 pre-sacral vertebrae, and an increase in incidence of 13th ribs of normal length). High dose developmental findings were decreased fetal weights, increased total numbers of major malformations (without any characteristic pattern of effects), slight

increase in early and late resorptions (statistically significant when early and late resorptions were considered together), and increased ossification delays (most convincingly demonstrated in lower lumbar vertebrae and in the forepaw phalanges). **Acceptable**. (H. Green and [redacted] 7/22/91).

MONKEY

036 033939, 2-paragraph report begins p. 9 of Tab "Reference 130", (Lab not identified, 3/78, summary only). Captan given by oral gavage to Macaca monkeys at 6.25, 12.5 or 25 mg/kg/day on days 22-32 of gestation; 7 females/group; no adverse effects reported. NOT UPGRADEABLE. No apparent reason to repeat a monkey teratogenicity study. [redacted] 7/12/85). EPA one-liner: Terata NOEL $\geq$ 25 mg/kg (HTD); fetotoxic NOEL = 12.5 mg/kg; (No core grade given.)

MUTAGENICITY

GENE MUTATION

It is clear from the one-liners below that Captan is mutagenic in bacterial systems and in mammalian in vitro systems under some conditions. Although none of the bacterial gene mutation (GNMU) studies is considered acceptable according to CDFA evaluation criteria, there is no apparent reason to request additional GNMU studies from the registrants at this time: there is general agreement about the mutagenic potential of Captan under conditions of several microbial assays. In general, systems without "S9" activation are more active in demonstrating in vitro mutagenic potential than systems with activation. Apparently captan is inactivated to non-mutagenic derivatives by blood, plasma, or other body fluids (see 034 925126 under "Microbial Systems" or 034 925156 under "Mammalian Systems", below). An in vivo mouse somatic cell mutation assay has been accepted by CDFA and is negative. One mammalian in vitro test (034 925156) claims a positive effect, and further information is needed about that study as indicated in the one-liner. [redacted] 11/6/86.

Microbial Systems

034 925125, "Mutagenicity Screening of Pesticides in the Microbial System - Reversion Assay - Salmonella typhimurium", (Inst. Env. Tox. (Japan), 6/75, Tab reference 74,; for other tests reported in same article, see under 034:033947 a publication presenting results of testing 166 pesticides). Captan (not fully characterized) tested at 50 ug/plate on S. typhimurium strains TA1535, 1536, 1537 and 1538; increased mutation frequency reported in two E. coli reversion assays; UNACCEPTABLE, NOT UPGRADEABLE (no activation system, other deficiencies). [redacted] 7/11/85).

034 925132, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in vivo Studies - reversion - S. typhimurium", (SRI, sponsor report no: 600/1-77-028, 5/77, Tab reference 78). Captan ("technical grade or equivalent") tested at 0 to 50 ug/plate on S. typhimurium strains TA100, TA1535, TA1537 and TA1538 +/- S9; triplicate platings; increased mutation frequency in TA1535; UNACCEPTABLE (no positive control for non-activated system, no characterization of test article, no individual plate counts reported), NOT UPGRADEABLE, but useful information. [redacted] 7/11/85).

029 925133, "Survey of Mutagenicity of Various Pesticides", (Swiss Fed. Res. St., 10/72. - published information). Ames assay with uncommonly used strains; Adverse effects reported, but only summary data provided; UNACCEPTABLE (test article not characterized, not currently used strains). [redacted] 7/11/85).

034 925131, "Evaluation of Some Pesticides for Mutagenicity - Salmonella typhimurium Tester Strains of Ames", (Swiss Fed. Res. St., 1975 - published information). Ames assay with uncommonly used strains; Positive for limited point mutation assay (TA1535), but negative for mouse micronucleus test. UNACCEPTABLE: not a thorough point mutation test battery, only summary information provided. [redacted] 7/12/85).

034 925127 "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test Assay of 300 Chemicals", (Univ. Calif., 1975, p 5, publication). Ames assay in which captan was reported to increase mutation frequency in strains TA98, TA100 and TA1535; UNACCEPTABLE (test article not characterized and probably not technical; no individual data). [redacted], 7/11/85).

034 925126, "Mammalian Host and Fluid-Mediated Mutagenicity Assays of Captan and Streptozotocin in Salmonella typhimurium", (Western Mich., Univ., 1976, publication). Captan at very high concentrations (10^4 ug/ml) in whole blood mutagenic to Salmonella strain TA1950. Evidence that captan is largely inactivated by RBCs, plasma, and/or other tissue or fluid compartments. UNACCEPTABLE (not a regulation mutagenicity study), however useful data. [redacted] 7/11/85).

034 925124, "Induction of Point Mutations by Different Chemical Mechanisms in the Liver Microsomal Assay", (Univ. Heidelberg, 1976, publication). Captan (apparently not tech. grade) tested at 0, 1, 10 or 20 mg/ml with S9 on Salmonella; positive mutagenic response in strains G46, TA1535 and TA1537; UNACCEPTABLE (not a regulation mutagenicity study), however useful data. [redacted] 7/11/85).

034 925123, "Screening of Pesticides for Mutagenic Potential Using Salmonella typhimurium", (Univ. Kentucky, 1976). Captan (apparently an analytical grade, source not given) tested in

Ames assay at levels up to 50 ug/plate +/- S9; positive mutagenic response in TA1535, especially without S9; also positive in TA1537; UNACCEPTABLE (not a regulation mutagenicity study), however useful data. [redacted], 7/11/85).

034 925180, "Induction of Forward Mutations to Colicin E2 Resistance in Repair Deficient Strains of Escherichia coli: Experiments with Ultraviolet Light and Captan", (Tab Ref. 79, Univ. Sussex, 1973). Captan (recrystallized "Orthocide") tested on E. coli strains WP2, WP2uvrA, CM561 and CM611 at 0, 0.1, 1, 2, 3 or 4 (and possibly other concentrations, judging from the figures) ug/ml without metabolic activation; report indicates captan increases mutation frequency at doses as low as 0.1 ug/ml; UNACCEPTABLE (not a regulation mutagenicity study), however useful data. [redacted] 7/15/85).

034 033947, "Mutagenicity Screening of Pesticides in the Microbial System - Reversion Assay - E. coli", (Inst. Env. Tox. (Japan), 6/75., Tab Ref. #74). Same publication also reports positive Salmonella reversion assays (see 034 925125, also under "GNMU" heading), and positive Rec assay in Bacillus subtilis strains (see 034 33946 under "DNA" section of this tox summary)

[redacted] 7/11/85. Publication. Captan at 50 ug/plate (without S9) reported to be definitively mutagenic to WP2 strain of E. coli; UNACCEPTABLE (test article not defined and appears not to be technical captan, no individual data).

034 033949, "Evaluation of Certain Pesticides as Chemical Mutagens in vitro and in vivo Studies - Reversion using E. coli", (Tab Reference 78 - SRI, 1977). Captan ("technical grade or equivalent") tested at 0-50 ug/plate on E. coli strain WP2; triplicate platings, increased mutation frequency reported with and without metabolic activation; UNACCEPTABLE (lacks individual plate data, lacks adequate characterization of test article). Useful data, UPGRADEABLE. [redacted] 7/12/85).

034 925183, "Mutagenic and Recombinogenic Action of Pesticides in Aspergillus nidulans - Mitotic Cross-Over and Non-Disjunction in Seeding Conidia", (Tab Reference 82 - publication from Italian Univ., 1976). Captan tested on Aspergillus nidulans haploid strain 35 at 2000 ug/filter paper triangle; report claims increase in point mutation frequency, but offers no data; UNACCEPTABLE (test article not characterized, no data provided). [redacted], 7/15/85).

042 925184 Comments on use of Aspergillus; no captan data.

034 024553 Review article which discusses mutagenicity of many pesticides, including captan.

Drosophila Systems

034 925138, "Mutagenicity Tests and Toxicity Tests with Captan in Drosophila - Sex Linked Recessive Lethal (Topical Application)", (Tab Reference 95, see also No. 33956, Fed. Tech. Univ.-Zurich, 1972, publication). 0.15 or 0.3 ul of a 3% captan solution applied topically to 40-50 D. melanogaster males/group; one application to assess frequency of recessive sex-linked lethals in F_1 generation; no adverse effects reported; UNACCEPTABLE (not tech. captan, dosages not justified, and apparently not optimized, too few flies to demonstrate an effect). [redacted] 7/16/85).

034 033956, "Mutagenicity and Toxicity Tests with Captan in Drosophila - Sex Linked Recessive Lethal (Application by Injection)", (Tab Reference 95, see also No. 925138, Fed. Tech. Univ.-Zurich, 1972. publication). A single injection of 0.2 ul of 1.5, 5 or 80 ppm captan solutions given to D. melanogaster males to assess for recessive lethal effects; no adverse effects reported; UNACCEPTABLE (Not technical captan, dosages actually applied not verifiable). [redacted] 7/16/85).

034 925137, "Mutagenicity Tests with Captan and Folpet in Drosophila melanogaster - Complete and Mosaic Sex-Linked Recessive Lethal Mutation Assays", (State Univ. Leiden, 1973). Publication in which a captan formulation reported to be negative in D. melanogaster sex-linked recessive lethal, II-III translocations and dominant/lethal tests; UNACCEPTABLE (tech. captan comparable to USA products not used, dosage levels not justified). [redacted], 7/16/85).

034 925157, "Overview of Short-term Tests for the Mutagenic and Carcinogenic Potential of Pesticides", (Warf Inst., Madison, WI, Tab Ref. 89, prepublication). Captan tested at 2, 3 and 2000 ppm on D. melanogaster; indicated as positive at all three dose levels for sex-linked recessive lethal (by a "+" in Table 2), but no individual data presented; UNACCEPTABLE. The full report of the Drosophila sex-linked recessive lethal test portion of the report should be obtained. The information presented here is insufficient for an independent assessment. [redacted] 7/15/85).

Mammalian Systems

**019 925119, "Mutagenicity Evaluation of Captan in the Somatic Cell Mutation Assay - Final Report (Mice)", (Litton Bionetics, revised 7/81). Captan tech. given by oral gavage at 0, 100, 1000 and 5000 ppm on days 8-12 of gestation to C57B1/6J mice for somatic cell mutation assay (est. high dosage group intake = 2095 mg/kg/5-day treatment period); 50 to 52/group; 26 in positive control group; pups scored at day 12 of lactation and weaning for spots; no mutational effect observed; ACCEPTABLE. [redacted] 7/9/85).

103-019 925120 Addendum to 019:925119, above.

013-035 925142 An earlier version of 019:925119, above.

034 925156, "Comparison of 8-Azaguanine and Ouabain-Resistant Systems for the Selection of Induced Mutant Chinese Hamster Cells (using Captan)", (Tab Ref. 87, Univ. Sussex, 1975, publication). Captan formulation tested for mutation-inducing potential in a system with V79-4 male Chinese hamster cells; study reports increased frequency of forward mutations without metabolic activation, both on direct contact of captan with cells or by exposure of cells to volatiles which diffuse from a piece of captan-impregnated filter paper to the media. Investigators noted that "toxic action disappeared during incubation in media containing serum (unpublished results)" [p. 270 of report]. UNACCEPTABLE (test article not characterized, individual data not given, inadequate detail of experimental methods, especially whether calf serum was present in the medium in captan experiments). These clarifications should be submitted to CDFA as soon as practicable. [redacted] 7/15/85).

034 041607 "Mutagenic and recombinogenic action of pesticides in Aspergillus nidulans". Mutation research 46:395-402 (1977). Captan indicated as positive in a "spot test" based on occurrence of 8-azaguanine resistance. No data provided. Report supports generally accepted concept that captan is mutagenic in certain in vitro studies. No CDFA review needed. [redacted] 8/18/88.

CHROMOSOME

Several studies below indicate a potential for chromosomal damage, particularly in in vitro sister chromatid exchange (SCE) studies. One study (034 925160), was accepted by EPA but not formally accepted by CDFA. That study found positive and dose-related SCE and chromosomal aberrations in cytogenic analysis of Chinese hamster cell cultures. In vivo studies were negative, with the exception of one publication reporting rat and mouse dominant lethal studies (Vol. 35, Tab 103, Rec. Nos. 033936-033938 and 925128). More rigorous dominant lethal studies have found no evidence of captan effects on early embryonic deaths, diminishing the concern for the one published positive effect. In summary, chromosomal studies demonstrate the intrinsic potential for captan to cause chromosomal damage in certain

controlled in vitro situations. In vivo studies generally support the concept that metabolism or decomposition in the intestine or in body fluids may reduce the actual risk to humans or test animals to very low levels, as discussed in the previous GNMU section. One study (035 925177) has been accepted to fill the chromosomal effects data requirement, and several non-accepted studies have useful information. [redacted] 11/6/86.

**035 925177, "Mutagenesis Studies of Pesticide Compounds: Mouse, Heritable Translocation Test, Captan", (Tab 109 - SRI, report no; Project # LSU-3493, 5/80). Mouse heritable translocation assay. Captan tech. given at 0, 2500 or 5000 ppm in the diet to ICR/SIM male mice for 8 weeks, positive control (TEM) group included; 60-66 males/group; 2 females/male; 1 positive translocation was reported for the 5000 ppm group and one for control group (historical background was exceedingly low, hence the 1 translocation in controls was unusual); ACCEPTABLE ; however, results did not definitively find Captan non-mutagenic under conditions of study. [redacted] 7/17/85).

035 925176, "Dominant Lethal Study with Captan Technical in Albino Mice Exposed for 8 Weeks to the Chemical in the Diet", (IBT, report no: 623-05998, 1/77). Dominant/lethal study. Not guideline design; dosages not optimized. No adverse effects reported. Invalid IBT study. [redacted] 7/16/85).
EPA one-liner: IBT invalid.

071 925135 Summary of invalid IBT study described in 035 925176, above.

071 925134 Supplemental to 925135.

034 033950, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in vivo Studies - Dominant Lethal Test in Mouse", (SRI, sponsor report no: EPA-600/1-77-028, 5/77, Tab Reference 78). Dominant lethal assay; Captan ("technical grade or equivalent") given at 0, 1250, 2500 and 5000 ppm in diet to ICR/SIM mice, TEM for positive control; after 7 weeks of dosing males paired weekly with 2 females for 8 weeks; 20 males/group; no adverse effects reported; UNACCEPTABLE (dosages not optimized: single administration or maximized dosing over a short period is standard procedure in dominant lethal studies). Useful information. [redacted] 7/12/85).

035 925173, "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse", (various publication sources on dominant/lethal assays of many compounds, 1972).

UNACCEPTABLE: (test article not clearly captan technical, no details on methods, no individual data, no evidence that dosage was optimized). [redacted] 7/16/85).

034 925158, "Cytogenetic and Dominant Lethal Studies on Captan - Dominant Lethal study in Mice", (Inst. Env. Tox.-Japan, 1977, Tab Ref. 90). Dominant lethal test. Captan given by gavage at 0, 200 or 600 mg/kg/day for 5 consecutive days to C3H male mice, EMS for positive control; males caged with 1 female every 2-4 days for 6 weeks for dominant/lethal study; 15 males/group; no adverse effect reported; UNACCEPTABLE (test article apparently not technical captan, dosages not optimized, no individual data). NOT UPGRADEABLE. Useful data. [redacted] 7/15/85).

034 925159 Comments on 925158. Dosage inadequacy not addressed.

035 925128, also designated 035:033936, 033937, and 033938 for the same report. "Dominant Lethal Assay. I. Captan", (Tab ref. 103 - FDA, 1972 publication). Dominant lethal study in rats and mice, dosage by gavage or ip injection. Every other page of report missing. Abstract claims "increases in the mean number of early fetal deaths per pregnancy, a measure of mutagenic effect, were seen in both species [rat and mouse] after ip and oral administration". Maximum dosage levels were 10 mg/kg/day ip, or 200 mg/kg/day by gavage, repeated for 5 days in each case. Unacceptable, incomplete, insufficient information to evaluate. One-liner by [redacted], 5/5/87.

035 925175, "Dominant Lethal Mutations in Mammals", (various publication sources, 1/77). No new captan data: discussion of two earlier dominant lethal studies without adverse effects. [redacted] 7/16/85).

034 033955, "Cytogenetic and Dominant Lethal Studies on Captan - in vitro Cytogenetic Study Using Human Diploid Fibroblasts", (Inst. Env. Tox.-Japan, 11/77. - Tab Ref. 90). Chromosomal aberrations, in vitro; Human fibroblasts exposed to captan at 0, 0.5, 1.5, 3.0 or 4.0 ug/ml. Negative for chromosome aberrations; UNACCEPTABLE (test article not characterized, no cultures

with metabolic activation, procedures inadequately described), NOT UPGRADEABLE. [redacted] 7/15/85).

035 041655 Letter from Dr. Shirasu to Judy MacGregor of Chevron explaining details for 034:033955, above. No need for written review: design deficien-cies of study prevent an upgrade, and study was negative. [redacted] 8/18/88.

035 925143, "Cytogenetic Test of Captan in Mouse Bone Marrow", (Tab Ref. 100, Western Mich. Univ., 1978). In vivo chromosome aberration (bone marrow). Captan formulation (50% technical); captan dosage = 250 mg/kg. No adverse effects noted; UNACCEPTABLE, NOT UPGRADEABLE (inappropriate test article, dose level not optimized, insufficient numbers of test animals, no justification for using only males). [redacted] 7/16/85).

034 033954, "Cytogenetic and Dominant Lethal Studies on Captan - in vitro Cytogenetic Using Rat Bone Marrow Cells", (Inst. Env. Tox.-Japan, 11/77. - Tab Ref. 90). In vivo chromosome aberration (bone marrow) assay; Captan (not tech.) given at 0, 500, 1000 or 2000 mg/kg in a single dose by gavage or at 0, 200, 400 or 800 mg/kg for 5 consecutive days to male Wistar rats; 5 males/group; no increase frequency of aberrations reported; UNACCEPTABLE (males only used, test article not characterized and apparently not technical, no justification of dose levels, no individual animal data, only a single sampling time), NOT UPGRADEABLE, but useful information. ([redacted] 7/15/85).

035 041656 Letter from Dr. Shirasu to Judy MacGregor of Chevron explaining details for 034:033954, above. No need for written review: design deficien-cies of study prevent an upgrade, and study was negative. [redacted] 8/18/88.

034 033948, "Evaluation of Some Pesticides for Mutagenicity - Micronucleus Test for Using Female ICR Mice", (Swiss Fed. Res. St., 1975, publications). Micronucleus test with captan; no adverse effects reported; UNACCEPTABLE, NOT UPGRADEABLE (little useful information: doses appear to be considerably below MTD). [redacted] 7/12/85).

034 925136, "Effect of the Pesticides, Dexon, Captan and Roundup, on Sister-Chromatid in Human Lymphocytes in vitro", (Tab Ref. 93, Eastern Wash. Univ., 79. publications). Captan (not characterized) tested at 0, and apparently 3, 30, and 300 ug/ml [there were discrepancies in reporting the treatment concentrations] $300X10^{-3}$ mg/ml on human lymphocytes for SCE assay; summary only; increased SCE at lowest dose and cytotoxic at higher dose levels; UNACCEPTABLE (test article not adequately identified, no metabolic activation system used, only summary data shown, inadequate sampling: only 50 cells counted from each of two persons, internal inconsistencies in report, etc.). [redacted], 7/15/85).

034 925160, "Sister-Chromatid Exchanges and Chromosomal Aberrations in Cultured Chinese Hamster Cells Treated with Pesticides Positive in Microbial Reversion Reports", (Tab Ref. 92, Inst. Env. Tox.-Japan, 11/79). [SCE and cytogenetic analysis] Captan (analytical grade) tested at 0, $6X10^{-6}$, $1.5X10^{-5}$, $3X10^{-5}$, $4.5X10^{-5}$ or $6X10^{-5}$ M on Chinese hamster cells without S9 for SCE assay; increased frequency of SCE at $6X10^{-6}$ and increased frequency of chromosome aberrations at $4.5X10^{-5}$ and above; UNACCEPTABLE (technical grade not used, no S9, no individual data shown), NOT UPGRADEABLE, but useful data. [redacted]7/15/85).
EPA one-liner: Positive LEL chromosome aberrations = $4.5X10^{-5}$ M; acceptable.

237 073026 "Lack of Induction of Nuclear Aberrations by Captan in Mouse Duodenum." (Chidiac, P. and M. T. Goldberg, Environmental Mutagenesis 9: 297-306 (1987)) Captan, several grades and concentrations (94%, 92.4%, 99% (analytical) and 50% Orthocide 50W), was fed in the diet or given by oral gavage to male CD-1 or C57Bl/6J mice at a variety of doses in mg/kg and by several dosing regimens. In general, there were 5 or 6 mice per group. The formation of nuclear aberrations (a combination of apoptotic bodies and micronuclei) were scored in 10 crypts of the duodenum per mouse. Captan did not increase the incidence of nuclear aberrations either alone or when given in combination with a known gastrointestinal tract carcinogen (dimethylhydrazine) or contaminants of captan. The **results were negative** for an adverse effect. The study provides supplemental information. **Unacceptable, not upgradeable**. [redacted] 5/14/90).

NOTE: The above volume, 237, contains various studies relating to metabolism, human exposure, and interactions with tissues or biochemical components of tissues in duodenum and elsewhere in the alimentary tract. While none of these are needed for "SB-950" purposes, some of these studies might be relevant for subsequent risk assessment. [redacted] 5/16/90.

DNA

Captan apparently is capable of DNA damage under certain controlled conditions, such as a number of the in vitro studies below. Two studies indicated UDS effects, however a third study was negative for UDS. The latter study was acceptable for EPA, is apparently more rigorous in design and is better reported than the other two UDS studies, and the study has recently been upgraded to acceptable status by CDFA (1980 SRI study, 019 925162, see below). Three bacterial DNA damage/repair studies were positive, as was one Saccharomyces cerevisiae mitotic recombination study. One BALB/3T3 cell transformation assay (048 033941) was negative and is now determined to be acceptable by CDFA. ([redacted], 8/23/88). A recent study assessing unscheduled DNA synthesis in vivo in male rats was negative (253 095219). [redacted] 7/19/91). A new study, 261 098765, examined the binding of captan to DNA from several tissues with the finding that there may be some association. [redacted] 11/18/91).

**019 925162, "An Evaluation of the Effect of Captan on Unscheduled DNA Synthesis in Diploid Human Fibroblasts". (SRI International, report no: proj LSU 3493,7558, Nov. 1980). Captan (Sample SX-640, 90.3 to 90.5% purity) tested at 0, 3.1, 6.3, 12.5, 25 or 50 $X10^{-6}$ M without S9; and with S9 at 0, 3.7, 11.1, 33.3, 100 or 300 $X10^{-6}$ M, and repeated at 0, 12.3, 37, 111, 333, and 1000 $^{-6}$ M on human fibroblasts (WI-38) for UDS assay; S9 from mouse liver. No UDS reported with or without S9. First trial with S9 gave equivocal results (statistical significance without dose relationship). The second trial with S9 was clearly negative, and the overall conclusion is that Captan is negative in this test system. Report was initially not acceptable due to lack of characterization of test article. This information was provided in 181:062732. The report is now ACCEPTABLE and no adverse effect is indicated. ([redacted], 7/9/85, 7/14/88).

EPA one-liner: Negative with and without metabolic activation; acceptable.

**048 033941 "Morphological Transformation of BALB/3T3 Cells", (In vitro Toxicology Section, Stauffer Chemical Co., Farmington, CT, Stauffer Report No. T-10431. 4/28/81). Captan (93.7%). BALB/3T3 cells for transformation assay under two assay conditions: (a) 4-hr cell treatment in serum-free culture medium at doses of 0 to 0.1 ug/ml, and (b) 3 day treatment in medium containing fetal bovine serum with 0, 0.04, 0.08, 0.12, 0.16 or 0.20 ug/ml (Assay #1) or 0, 0.1, 0.2, 0.3, 0.4, 0.5 or 0.6 ug/ml (Assay #2). Positive controls were included in all assays. No adverse effects observed. Initial review classified study as unacceptable but upgradeable: major concerns were study design and evaluation criteria, also a question about differential survival of test cells at identical exposure conditions in two separate assays. Questions were addressed in rebuttal document (205:065865). Report is now ACCEPTABLE. (C. [redacted] 6/25/85, 7/14/87).

205 065865 Specific answers to concerns stated in CDFA review of 6/25/85 about study 048:033941. CDFA responses were given in July 1988 rebuttal response, and the change of study to acceptable status was noted in worksheet W925162.S01. [redacted], 7/4/88).

253 095219 "Captan: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes in vivo." (Kennelly, J. C., ICI Central Toxicology Laboratory, Report No CTL/P/2995, 9/13/90) Captan, batch WRC#11240-37-1, 91.2%, was given by oral gavage to male rats (Alpk:APfSD) at 0 (corn oil), 500, 1000 or 2000 mg/kg bodyweight, single dose. There were 5/dose group with 2 or 3 sacrificed at 4 or 12 hours post-treatment. Primary hepatocytes were isolated, put into culture and incubated for 4 hours with ^{3}H-thymidine followed by further incubation overnight. Unscheduled DNA synthesis detected by autoradiography. Triplicate slides were prepared with 50 cells from two slides scored for net nuclear grain counts. No evidence of induction of unscheduled DNA synthesis. **Unacceptable** (doses not justified with no sign of toxicity). Not upgradeable. [redacted] 7/19/91) ICI submitted a rebuttal dated 10/25/91 to the DPR review on the items of dose selection, analysis of dosing material and method of counting cytoplasmic grains. A response was prepared dated 7/6/92. No new data. No document or record number - ID # SBDR-131659-E. No worksheet. [redacted] 7/6/92)

034 925185, "Pesticide Induced DNA Damage and Its Repair in Cultured Human Cells", (Tab Ref. 84, Ohio St. Univ., 7/76, publications). Captan (grade not specified) tested at 0, 1, 10, 100 or 1000 uM on human fibroblast cells +/- S9 for UDS assay; UDS reported at all dose levels; UNACCEPTABLE (test article grade not specified, no individual data-only qualitative information provided). [redacted] 7/15/85).

034 033951, "Human Diploid Fibroblasts (WI-38 Cells)", (Tab Reference 78, SRI, sponsor Report no: EPA-600/177-028, 5/77). Captan ("technical grade or equivalent") tested at 0, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} or 10^{-4} M on human fibroblasts (WI-38) +/- S9 for UDS assay; adverse effects noted in report (approx. doubling of UDS at 10^{-4} M in presence of S9), but report not initially flagged by [redacted] as a significant adverse effect because report superceded by replacement study. The captan analog, folpet, was similarly a weak UDS positive compound; UNACCEPTABLE (no individual data, however the procedures appear to have been properly performed and the data are useful. [redacted] 7/12/85).

034 925161, "Repair-Deficient Bacterial Strains Suitable for Mutagenicity Screening: Tests with the Fungicide Captan", (Tab Ref. 80 [previously numbered 034 925182], Univ. Sussex, 1971, publication on bacterial DNA damage/repair in repair-deficient E. coli WP2 strains). Captan recrystallized from Orthocide tested on 5 strains of WP2 at 1 mg/filter paper; test article mutagenic in all 5 strains, most particularly in the excision repair deficient strains designated "UvrA". This mutagenic activity is evident in a volatile product of captan hydrolysis; UNACCEPTABLE, NOT UPGRADEABLE (test article not tech. captan, no individual data), but useful data. [redacted], 7/15/85).

034 033953, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in vivo Studies - DNA Damage/Repair Test Using B. subtilis and E. coli", (SRI, sponsor Report No: EPS 600/1-77028, 5/77, Tab Reference 78). Captan (technical grade or equivalent). Captan tested on E. coli and B. subtilis at 0.1 mg/disc only without S9 for a DNA damage/repair assay; test article mutagenic in both species (Table 93); UNACCEPTABLE, NOT UPGRADEABLE (no S9 inclusion, no individual data of replicates at various concentrations of captan, etc.). Useful information. [redacted] 7/12/85).

034 033946, "Mutagenicity Screening of Pesticides in the Microbial System - Rec-Assay - B. subtilis", (Inst. Env. Tox.-Japan, 6/75, Tab ref. 74). Captan (grade not specified) tested on B. subtilis at 20 ug/disc only without S9 for rec assay; test article mutagenic; UNACCEPTABLE, NOT UPGRADEABLE (only one conc. of test article, no S9 included, scanty methods detail and no individual data). Useful information provided. [redacted] 7/11/85).

034 033952, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in in vivo Studies - Gene Conversion in Mitotic Recombination in Saccharomyces cerevisiae", (SRI, sponsor report no: EPA-600/1-77-028, 5/77, Tab Reference 78). Captan ("technical grade or equivalent") Captan tested at 0.003% on Saccharomyces cerevisiae +/- S9 for gene conversion assay; captan strongly positive in this mitotic recombination test with and without S9; UNACCEPTABLE, NOT UPGRADEABLE (only a single treatment level employed, summary data only, insufficient information on methods). Useful data obtained. [redacted], 7/12/85).

034 925139, "Detection of Somatic Recombination and Mutation in Drosophila: A Method for Testing Genetic Activity of Chemical Compounds", (Mutation Research, Swiss Federal Res. Sta., 5/20/74). Not a validated study type. Did not employ tech. captan. No adverse effects indicated. [redacted] 7/16/85).

047 925186, "The Association of Captan with Mouse and Rat Deoxyribonucleic Acid", (In Vitro Toxicology Section, Stauffer Chemical Co., Farmington, CT, report no: T-10435, 4/28/81). Studies involved oral administration of [trichloromethyl] ^{14}C-captan to mice and rats. ^{14}C levels in DNA of extracted tissues were very low in initial experiments. There was a limited supply of labeled captan, and subsequent studies were limited to male mice, because comparatively high specific activities of labeled captan were required. When male CD-1 mice were treated with 156 mg/kg captan at specific activity of 50 mCi/mmol 24 hr before sacrifice, calculated trichloromethyl carbon/DNA nucleotide ranged from a high of 4.2×10^{-5} (liver) to a low of 5.1×10^{-6} (testis), with intermediate values (in increasing order of trichloromethyl carbon concentration) for duodenum, kidney, stomach, and "intestine". The possibility of a biologically important alteration of DNA exists, and this indicates a "**possible adverse health effect**", however the nature of DNA binding is not well characterized in this study. Tissues

varied substantially in the amount of label which could be removed from DNA by dialysis. In conclusion, these pilot studies indicate that captan can bind covalently to a limited extent to DNA; that there is no apparent association between such binding and oncogenicity target organ (duodenum) and that the chemical structure or physiological relevance of such binding is not defined. This study is limited in scope and is not a validated protocol to fill the "DNA damage" data requirement. Study is therefore NOT ACCEPTABLE, and NOT UPGRADEABLE, however some useful data have been provided. [redacted], 7/15/88).

261 098765 "Captan: DNA Binding Study in the Mouse." (Pritchard, D. J. and G. J. Lappin, Hazleton UK, Report No. 6531-72/299, 4/91 and ICI Central Toxicology Laboratory, UK, CTL/P/3380, 9/19/91) Groups of 100 male Crl:CD-1(ICR)BR mice were given [^{35}S]-captan (nominal dose of 900 mg/kg) or [^{14}C]-NMU (nominal dose of 80 mg/kg) by oral gavage. After six hours, animals were sacrificed and the liver, stomach, jejunum, duodenum and bone marrow samples were removed and frozen. For the liver, organs from 50 animals were pooled for two pools. For the other organs, all 100 were pooled before processing. DNA was isolated using enzymes and phenol/chloroform/propan-2-ol extraction. The Covalent Binding Index (CBI) was calculated for each organ. They were: stomach, 38; duodenum, 46; jejunum, 91; liver, 38 and bone marrow, 2.8. Samples from the liver, jejunum and duodenum were further purified by cesium chloride density gradient centrifugation. The peak fractions for DNA and for radioactivity were determined. Although there was overlap in location on the gradient, the peaks did not coincide. The results suggest some association with DNA but do not prove covalent binding. This study is considered **supplementary.** [redacted] 11/15/91.

034 041607 "Mutagenic and recombinogenic action of pesticides in Aspergillus nidulans". Mutation research 46:395-402 (1977). Captan indicated as positive for somatic recombination crossing-over, but negative for non-disjunction, in a "spot test" based on occurrence of p-fluorophenylalanine resistance. No numerical data provided. Report supports generally accepted concept that captan causes various genotoxic effects in certain in vitro studies. No CDFA review needed. [redacted] 8/18/88.

SUBCHRONIC STUDIES

INHALATION

RAT

103-247; 87655; Hext, P.M., "Captan: 90 day inhalation toxicity study in the rat" [EPA MRID #41234402]; ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. PR0735, Report No. CTL/P/2543; 8/3/89; 10 rats/sex/dose were exposed to captan at 0, 0.1, 0.5, 5.0, and 15.0 ug/l nominal for 6 hrs/day, 5 days/wk for 13 weeks and an additional 10 rats/sex/dose at 0 and 15 ug/l were allowed to recover for 4 weeks after the 13-week exposure period; no dose-related differences in body weight gain, food consumption, clinical chemistry, urinalysis, and hematology values, and organ weights were observed; no treatment-related gross observations were noted; toxicologically significant histological changes in the epithelium of lungs, larynx, and nasal cavity were observed at the 5.0 and 15.0 ug/l level (this is considered a **possible adverse effect); NOAEL - 0.5 ug/l (0.5 mg/m3 or 0.12 mg/kg/day) based on the histological changes in the respiratory tract; **Acceptable**. (Lewis, 11/27/89).

103-186 074922 Exact duplicate of first 160 pages of 103-247:087655, above (this version lacks much of the individual data).

103-246; 87654; Hext, P.M., "Captan: 3 week preliminary inhalation toxicity study in the rat" [EPA MRID #41234401]; Rat (Alpk:APfSD, Wistar derived); ICI Central Toxicology Laboratory, Macclesfield, Cheshire, UK; Study No. MR0133; Report No. CTL/P/2534; Aug. 3, 1989; 5 rats/sex/dose were exposed (nose only) to 0, 1, 5, and 25 ug/l captan nominal, 6 hours/day, 5 days/week, for 3 weeks; body weight gain and food consumption were unaffected; increased mucoid nasal discharge, salivation, and respiratory noises were observed in treated animals immediately after exposure; several statistical differences in serum chemistry and hematology values of questionable toxicological significance were observed including a dose-related decrease in albumin, total protein, and triglyceride levels in both sexes, a dose-related

reduction in creatinine in both sexes at the mid and high dose level, an elevation in alkaline phosphatase levels in both sexes at the high dose level, a dose-related elevation in phosphorus levels and reduction in calcium levels in females, a dose-related reduction in the female hematocrits, and an increase in the mean cell hemoglobin levels in the mid-dose females and the mean cell hemoglobin concentration in the mid- and high-dose females; ulceration and necrosis of the epithelium in the larynx and nasal cavity, rhinitis, and hyperplasia of the goblet cells in the nasal septum were observed at the 25 ug/l exposure level; NOEL - 5 ug/l (5 mg/m3 or 1.2 mg/kg/day) based on the microscopic lesions in the respiratory tract. (Lewis, 11/21/89).

GENERAL

035 925121, "Mutagenic, Teratogenic, and Carcinogenic 6022 Properties of Pesticides - Recent Literature: Mutagenicity Studies with Captan (Summary)"' (Tab Ref. 101 - published review sponsored by EPA (1972) of mutagenic, teratogenic, and carcinogenic effects of captan and other pesticides. (Most valid studies have been performed since that time). [redacted] 7/16/85).

034 925122, "Mutagenicity of Captan and related Fungicides". Tab Ref. 71, published review (B. A. Bridges, 1975) of mutagenic effects of captan. [redacted] 7/11/85).

035 925178. "Review of Genotoxic Activity". Tab Ref. 110, Bionetics, 1978). Review by D. Brusick for Stauffer, of mutagenic effects of captan. [redacted] 7/17/85).

017 925089 Chevron RPAR rebuttal (1980) of muta and onco effects of captan.

181 062733 "Updated summary of results of mutagenicity testing of captan technical", (Submitted by Captan Task Force), 1/2/86. Conclusions of review are consistent with conclusions in CDFA Medical Toxicology Branch Captan Tox Summaries over the past two years: Captan typically displays a weak potential for positive results in study types gene mutation

(842), chromosomal aberrations (843), and "Other genotoxic effects" (844). Components of body fluids, especially thiol-containing molecules, rapidly inactivate mutagenic capacity of captan. Most of the positive studies are in vitro tests, in which presence of an S9 activation system reduces the mutagenic activity of captan. In vivo positive results are rare, and typically weak or not reproducible. In summary, the review confirms what registrants, EPA, and CDFA have agreed to for some time (potential for mutagenicity confirmed in several different test types) however hazard is markedly reduced in in vivo situations. ([redacted], 8/17/88.)