

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
NAPROPAMIDE

Chemical Code # 001728, Tolerance # 00328
SB 950 # 081

November 12, 1987

Revised: 1/12/88; 7/25/89; 3/30/90; 9/14/90; 1/7/92; 2/25/92; 4/7/92; 12/12/95; 4/24/95

I. DATA GAP STATUS

Onco/Chronic rat:	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Onco mouse:	No data gap, no adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox :	Not required at this time

Toxicology one-liners are attached.

All record numbers through 146939 volume 113 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T970424

Revised by: Luthra, 11/87; Revised by M. Silva, 1/88, 7/89, 3/90 & 9/90; Kishiyama & Silva, 1/7/92, M. Silva, 2/25/92, 4/7/92, 12/12/95, 4/24/97.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC/ONCO, RAT
(Combined)

**** 099 127353**, "Two-Year Chronic Toxicity /Oncogenicity Study with R-7465 in Rats", (J.C. Pettersen and J.A. Walberg, CIBA-Geigy Corporation Environmental Health Center, T-13276, 7/2/91). R-7465 Technical (purity = 94.1%) was fed in diet to Sprague-Dawley rats (50/sex/dose) at 0, 250, 1100 or 5000 ppm for approximately 19-22 months. A set of 10/sex/dose (interim sacrifice) and 20/sex (10000 ppm group) were terminated at 12 months. Chronic NOEL = 250 ppm (Decreased body weights and/or food consumption were observed at \geq 1100 ppm. Emaciation was increased, primarily in females at 5000 ppm. Indications of anemia were evident at \geq 5000 ppm. Liver weights were increased in males at \geq 5000 ppm. Increased incidence in kidney cysts and progressive glomerulonephropathy severity were observed in males at \geq 5000 ppm. Hepatic foci of discoloration and serum GGT levels were increased in males at \geq 5000 ppm.) **Possible adverse effect:** Oncogenicity NOEL = 1100 ppm (Hepatocellular adenomas and carcinomas were induced, primarily in males and spongiosis hepatitis was increased in both sexes at 5000 ppm.) Acceptable. (Kishiyama & Silva, 12/5/95).

**** 049, 050 033618, 033619**, "24 Month Chronic Feeding Study in Rats : Devrinol Technical Final Report", (Hazleton Laboratories, 12/12/78). Napropamide, 94.6%, lot WRC 4059-17-1, was fed in the diet to Sprague Dawley rats for 106 weeks at 0, 10, 30 or 100 mg/kg/day, 60/sex/group, 10/sex/group used for interim sacrifice at 52 weeks. Adverse effects were marginally significant increases in hepatocellular carcinomas and hepatic neoplastic nodules in males and significantly lower body weight in females at 100 mg/kg/day. Oncogenic NOEL = 30 mg/kg/day, systemic NOEL = 30 mg/kg/day, decreased body weight in females. Originally the study was evaluated as unacceptable (CNA 9/25/85), however the information requested by DPR regarding the number of sections/tissue for histopathology was provided as well an information indicating that devrinol causes no ophthalmological effects in dogs. Therefore, the study is now ACCEPTABLE. M. Silva, 7/20/89.

071 065654 This volume contains the number of sections per tissue for study 065 059691. (M. Silva 7/20/89).

065 059691. This volume contains individual clinical observations for study 033618, 033619. (M. Silva, 1/11/88).

065 059691 This volume contains: Hazleton Laboratories America, Inc. "Summary of Neoplasia in Untreated Control Sprague-Dawley Rats," which contains the historical control data for incidence of hepatic neoplastic nodules in Sprague-Dawley Rats. (M. Silva, 1/11/88).

066 059691 This volume contains individual tissue mass observations, food consumption and body weights for study 33618, 33619. M. Silva, 1/11/88.
113 146939 This volume contains a rebuttal from Zeneca which addresses the incidence of hepatic tumors and the incidence of spongiosis hepatitis. M. Silva, 4/23/97.

EPA one-liner: Minimum core grade, systemic NOEL = 30 mg/kg/day, body wt. inhibition, oncogenic NOEL > 100 mg/kg/day (HDT).

001 020168 Summary of 049 33618, JR(G), 3-29-85.

CHRONIC, DOG

Rangefinding Study:

097 123740 "Napropamide: Dose Range Finding Study Preliminary Toxicity Study in Dogs by Repeated Oral Administration for 6 Weeks", (T.G. Smith, Huntingdon Research Centre Ltd., CTL Study Number: ISN/306, 4/1/93). Napropamide, purity not stated, was administered at concentrations of 0, 500, 750 and 1000 mg/kg/day to 1 dog/sex/group for 6 weeks. NOEL \leq 500 mg/kg (Liquid feces in all dose groups. Vomiting, reduced food consumption, reduced body weight gain and increased liver weight were observed at 1000 mg/kg.) Based on these observations, 1000 mg/kg is considered a suitable high dose for a one year dog study. These data are supplemental. (Kishiyama & Silva, 12/5/95).

Subchronic Study:

082 088714 "An Oral Dose Rangefinding Study of Devrinol Technical in the Beagle Dog, T-12921, Volume 1: Final Report," (Sauerhoff, M.W., Bio-Research Laboratories, Ltd., 4/22/87; project #: 82657). Devrinol Technical (Batch #: 4921-27-24, purity = 94.7%) was fed to Beagle dogs (2/sex/group) in gelatin capsules at 0 (vehicle = gelatin capsule), 30, 60, 125, 250 or 500 mg/kg/day. After 2 weeks, treatment for animals at 30 mg/kg/day was increased to 1000 mg/kg/day (due to lack of effects at 30 mg/kg/day). No adverse effect indicated. NOEL = 500 mg/kg/day (Decreased food consumption and body weight at 1000 mg/kg/day). These data are considered supplemental. M. Silva, 8/23/90.

Chronic Study:

** 102 137180, "Toxicity to Dogs by Repeated Oral Administration for 52 Weeks," (Smith, T.G., Huntingdon Research Centre Ltd., England, HRC Project ID ISN/317; March 3, 1995). Napropamide (purity = 94.9%) was administered to Beagle dogs (4/sex/dose) via gelatin capsules at 0, 50, 250 or 1000 mg/kg/day to 4 beagle dogs/sex/group for 52 weeks. NOEL = 50 mg/kg/day (There was increased vomiting in both sexes at 1000 mg/kg and increased liquid feces in both sexes at \geq 250 mg/kg. Bodyweights were decreased in both sexes at 1000 mg/kg. Liver weights were increased at 1000 mg/kg. Albumin and cholesterol were decreased and AP was increased in both sexes at 1000 mg/kg. GPT was decreased in both sexes at \geq 250 mg/kg. Monocytes were increased and MCHC was decreased at 1000 mg/kg in both sexes. Platelets were significantly increased at \geq 250 mg/kg. Specific gravity values were elevated in both sexes at \geq 250 mg/kg. There was an increase in retinal pseudopapilloedema in females at 1000 mg/kg.) Acceptable. No adverse effect. M. Silva, 12/1/95.

072 070914 "A 52-Week Toxicity Study of Devrinol Technical in the Beagle Dog," (Bio-Research Laboratories, LTD., Canada; project #: 82658, 10/19/88). Napropamide technical (Lot #: WRC 4921-27-24; 94.6% pure) was administered orally (by capsule) to 5 Beagle dogs/group/sex at 0 (gelatin capsules), 10, 70 or 500 mg/kg/day for 52 weeks. NOEL > 500 mg/kg/day (no significant effects were observed at any dose). **Napropamide was not tested at a high enough dose to determine whether or not there are adverse chronic effects in dogs.** The study was previously unacceptable, but possibly upgradeable (M. Silva, 3/22/90 & 9/14/90) upon submission of a dose justification and review of the new mouse oncogenicity study (DPR volume/record #: 088/089835). After consideration of the dose justification and the result of the mouse oncogenicity study, it does not appear that there is enough information to evaluate the chronic toxicity of napropamide in beagle dogs. Therefore, this study is now considered unacceptable and not upgradeable. M. Silva, 3/27/92.

098 127739 This volume contains a status report for the definitive chronic toxicity study in dogs (reviewed at DPR; 102/137180). No worksheet. M. Silva, 12/5/95.

ONCOGENICITY, MOUSE

** 088 089835, "18-Month Dietary Mouse Oncogenicity Study with R-7465", (J.C. Pettersen & J.A. Walberg, CIBA-GEIGY Corp., Environmental Health Center, Report no: T013272, 7/19/91). Napropamide (purity = 94.3%) was administered at concentrations of 0, 60 450, 3500 or 7000 ppm/day to 50 CrI: CD* (ICR) BR mice/sex/group for 18 months. Systemic NOEL = 450 ppm (Decreased body weight and body weight gain was reported in both sexes at \geq 3500 ppm.) both sexes. Increased relative and absolute liver weights and relative kidney weights in males at \geq 3500 ppm.) There was no evidence of oncogenicity. The report was initially reviewed as unacceptable (M. Silva, 12/24/91) due to insufficient information on diet preparation and little characterization of test material in diet. Upon submission of the requested data, the study has been upgraded to acceptable. M. Silva, 2/24/92.

048 033627, "Lifetime Oral Study in Mice - Devrinol Technical." (International Research and Development Corp., 12-22-78) Devrinol technical, 94%, was administered in the diet to CD-I mice at 0, 10, 30 or 100 mg/kg/day, 60/sex/group, 10/sex/group used for interim sacrifice. No adverse effects indicated. NOEL = 100 mg/kg/day (HDT). UNACCEPTABLE, upgrade appears unlikely [must address DPR concerns and EPA audit results]. Dose levels are not justified, high dose does not appear to be high enough, no analysis of treated diet. (CNA, 9-20-85). NOTE: This study was classified as an unacceptable "combined" study in the 9/20/85 review. The dosage range employed does not explore the range of chronic toxicity, hence the report can only be re-considered for acceptability as an "oncogenicity" study. DPR recommendations for the repeat study remain as indicated in the 9/20/85 review. (CNA 10-28-87. M. Silva, 1/11/88).

093 112624 This volume contains supplemental information for study 088 089835: Method of diet preparation; data for homogeneity of napropamide in diet; method of diet analysis and stability data; diet sampling methods and diet concentration data. M. Silva, 2/25/92.

061 055174, "Six Week Range-Finding Study in Mice," (IRDC, 6/30/76) was provided as justification for dose selection for study 33627. Choice of doses for the definitive study did not logically follow from results of the pilot. (M. Silva, 1/11/88).

EPA one-liner: Minimum core grade, invalid by FDA audit, oncogenic NOEL > 100 mg/kg (HDT), NOEL = 30 mg/kg/day, decrease in body weight gain, females.

001 020167 Summary of 048 033627, JR(G), 3-29-85.

REPRODUCTION, RAT

** 051 033620 "Three Generation Reproduction Study in Rats - Devrinol Technical." (International Research and Development Corp., 12-22-78) Devrinol technical, 94.6%, was administered to CD rats in feed for a 3 generation study (2 litters/generation) at 0, 10, 30 or 100 mg/kg/day (15 males and 30 females/dose group--mated 1:2 by simultaneous caging). Sporadic mean body weight decrease was observed for dams and pups at 100 mg/kg dose level. Pup NOEL = 30 mg/kg/day, reduced pup weight. Parental NOEL = 30 mg/kg/day, decreased weight gain. Reproductive NOEL = 100 mg/kg/day. Originally the study was unacceptable (CNA, 9/19/85), however the information requested by DPR exams has been provided. Therefore the study is upgraded to acceptable status. M. Silva, 7/20/89.

071 065653. Information on selection of pups for necropsy in study 033620. (M. Silva, 7/20/89).

063 057823. This volume contains individual animal data for study 033620. (M. Silva, 1/11/88).

EPA one-liners: Minimum core grade: Parental NOEL = 30 mg/kg/day, decreased weight gain, Reproductive NOEL = 100 mg/kg/day (HDT), Fetal NOEL = 30 mg/kg/day, decreased pup weight gain.

001 963303 Summary of 051 033620. (JR(G), 3-29-85).

TERATOLOGY, RAT

** 086 095690, "A Teratology Study in CD* Rats with R-7465 Technical", (L.S. Meyer, CIBA-GEIGY Environmental Health Center, Report no. T-13274, 8/14/90). R-7465 Technical (Napropamide, purity = 94.3%) was administered by gavage at 0 (0.5% Tween 80), 100, 300, or 1000 mg/kg (limit test) to 26 Sprague-Dawley (CrI: CD* (SD) BRVAF/PlusT) mated female rats (26/dose) during gestation days 6 through 15. There were slight, transitional effects on dam body weights and food consumption at 1000 mg/kg. It is questionable whether an MTD was reached but since a limit test was performed, the dose range is acceptable. Maternal NOEL \geq 1000 mg/kg/day. Fetotoxicity was not apparent at any dose level. Developmental NOEL = 1000 mg/kg/day. ACCEPTABLE. (Kishiyama & Silva, 12/16/91).

086 095691, "A Teratology Study in CD* Rats with R-7465 Technical", (L.S. Meyer, CIBA-GEIGY Environmental Health Center, Report no. T-13589, 10/19/90). R-7465 Technical (napropamide, purity = 94.3%) was administered by gavage at concentrations of 0 (0.5% Tween 80), or 1000 mg/kg to 30 mated Sprague-Dawley rats for 10 consecutive days during gestation days 6-15. Food consumption was reduced 15% (measured on gestation day 9). Maternal NOEL \leq 1000 mg/kg/day. There were no treatment-related developmental effects at any dose level. Developmental NOEL = 1000 mg/kg/day. ACCEPTABLE as a supplement to CDPR record # 095690. (Kishiyama & Silva, 12/18/91).

086 095689, "A Rangefinding Teratology Probe in Rats with R-7465 Technical", (L.S. Meyer, CIBA-GEIGY Environmental Health Center, Report no. T-13273, 12/6/89). R-7465 Technical (napropamide, purity = 94.3%) was administered by gavage at concentrations of 0 (0.5% Tween 80), 500, 750, or 1000 mg/kg to mated Sprague-Dawley rats (11/group) for 13 consecutive days (days 8-20 of gestation). No significant effects were reported for dams. An MTD was not achieved, however, a limit test was performed. Maternal NOEL > 1000 mg/kg/day. No apparent gross external anomalies in pups days 0 and 4 postpartum. Developmental NOEL > 1000 mg/kg. Based on the results, high dose selection was 1000 mg/kg/day for the definitive rat study. (Kishiyama & Silva, 12/11/91).

053 033626, "Teratology Study in Rats with Devrinol Final Report." (Wil Research Laboratories Inc., 12-23-82) Devrinol technical, lot WRC 4921-27-24, was administered to mated Sprague Dawley rats by gavage on days 6 to 15 of gestation at 0, (corn oil), 30, 110 or 400 mg/kg/day, 25/group. Maternal toxicity NOEL = 400 mg/kg/day, Developmental toxicity NOEL = 400 mg/kg/day. UNACCEPTABLE. (need analytical data on dose suspension, original page 11, individual food consumption from group 2). Not upgradeable clinical observations not present (see Document/Record No. 067 060781). (JAP, 9-20-85. M. Silva, 1/11/88).

061 055175, "A Range-Finding Teratology Study in Rats with Devrinol," (WIL Research

Laboratories, Inc., 12/20/82). Study provided as a justification for dose selection for 033626. Data in the pilot study however do not justify dose selection in the definitive study. (M. Silva, 1/11/88).

067 060781. This volume contains individual clinical and mating observations for animals in study 33626. M. Silva, 1/11/88.

EPA one-liner: Minimum core grade, Teratogenic NOEL \geq 400 mg/kg/day (HDT), Maternal NOEL > 400 mg/kg/day, Fetal toxic NOEL > 400 mg/kg/day.

024 017048 Summary of 053 033626. (JR(G), 3-29-85).

TERATOLOGY, RABBIT

** 085 095688, "A Teratology Study in Rabbits with R-7465 Technical", (J. L. Minor, CIBA-GEIGY Environmental Health Center, Report No. T13270, 11/19/90). R-7465 Technical (Napropamide, purity = 94.3%) was administered by oral gavage at concentrations of 0 (Aqueous 0.5% Tween 80), 100, 300, or 1000 mg/kg/day (limit test) to mated New Zealand White rabbits (17-19/group) day 7-19 of gestation (day 0 of gestation = visual observation). Maternal NOEL = 300 mg/kg/day based on reduced body weight and food consumption and increased abortions. There were no structural and/or other abnormalities to the fetus reported. Developmental NOEL = 1000 mg/kg/day. ACCEPTABLE. Kishiyama & Silva, 12/11/91.

085 095687, "A Rangefinding Teratology Probe in Rabbits with R-7465 Technical", (J. L. Minor, CIBA-GEIGY Environmental Health Center, Report No. T13269, 10/20/89). R-7465 Technical (Napropamide, purity 94.3%) was administered by oral gavage at concentrations of 0 (Aqueous 0.5% Tween 80), 200, 400, 600, 800 or 1000 mg/kg/day to mated New Zealand White rabbits (6/group) on days 7 through 19 of gestation (day 0 = day of mating). Daily doses were based on each doe's gravid day 7 body weight. Treatment effects include reduced food consumption (days 13-19), decreased body weight gain, decreased mean fetal and placental weights. Based on the results of this study, 1000 mg/kg/day was selected as the high dose for the main teratology study. (Kishiyama & Silva, 12/9/91).

053 033628, "Teratology Study in New Zealand White Rabbits with Devrinol." (Stauffer, 8-6-84) Devrinol technical, 94.6%, was administered to New Zealand White rabbits by gavage on days 7-19 of gestation a 0 (corn oil), 10, 50 or 200 mg/kg/day, 14 to 20 mated per group. Maternal NOEL > 200 mg/kg/day (HDT). Developmental NOEL > 200 mg/kg/day (HDT). UNACCEPTABLE. There were 12 deaths attributed to dosing errors, the addition of animals after the main study was complete is not acceptable, no maternal toxicity noted. First reviewed by JRG as #017049 on 3/29/85 and noted positive to adverse effects. With additional data, JAP reviewed the study as #033628 on 9/30/85 and noted no adverse effects. YKL concurs with JAP. 10/27/87.

061 055172, "A Range-Finding Teratology Study in New Zealand White Rabbits with Devrinol T-11851," (Stauffer Chemical Co., 5/7/85). The correct dose was chosen for the definitive study based on the pilot study. (M. Silva, 1/11/88).

061 055173, "A Teratology Study in New Zealand White Rabbits with Devrinol," T-11898, Addendum 1: Response to Canadian Comments (Stauffer Chemical Co., 11/85). The explanation in this addendum for dosing error and addition of animals to fill dosing groups is UNACCEPTABLE. (M. Silva, 1/11/88).

EPA one-liner: Minimum core grade, Teratogenic NOEL \geq 200 mg/kg/day (HDT), Fetotoxic

NOEL = 10 mg/kg/day, resorption, Maternal NOEL = 10 mg/kg/day, mortality.

024 017049 Summary of 053 033628 (No individual values). (JR(G), 3-29-85).

GENE MUTATION

** 052 033624, "Devrinol Technical: Mutagenicity Evaluation in Salmonella typhimurium Ames Salmonella/Microsome Mutagenesis Assay." (Stauffer Environmental Health Center, 9-17-84) Mutagenicity of technical napropamide, 94.6%, was assayed in four strains of Salmonella with and without activation. No increase was found in TA1535, TA1537, TA98 or TA100 at a range of 0.037 to 3.0 mg/plate. ACCEPTABLE. Initially reviewed as unacceptable, (JR(G), 9/20/85). In view of the modifications in the amended guidelines, Federal Register 52(97)19072, May 20, 1987 for the gene mutation assay in Salmonella typhimurium requiring only a single trial and based primarily on the evidence of precipitation of the test article at the two highest concentrations, the study is upgraded to ACCEPTABLE status. The precipitation confirms that the bacteria were actually exposed to devrinol. (M. Silva, 1/7/88).

001 031824. Stauffer's very brief summary on the reverse mutation tests with and without metabolic activation system using Salmonella typhimurium strains and E. Coli. No data. UNACCEPTABLE. No worksheet. (Kishiyama, 5/12/89).

** **052 033622**, "Devrinol Technical: Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Forward Mutation Assay." (Stauffer Environmental Health Center, 3-12-84) Napropamide technical, 94.6%, was assayed for mutagenicity with L5178Y mouse lymphoma TK+/- . Activated doses were from 0.012 to 0.020 mg/ml, non activated were 0.01 to 0.08 mg/ml. An increase in the mutation frequency was observed in a concentration dependent manner with and without activation. ACCEPTABLE. (JR(G), 9-20-85).

** 060 054029, "Mutagenicity Evaluation in Chinese Hamster Ovary Forward Mutation Assay" (Stauffer Chemical Co., Farmington, Conn., Report HT-12057, 12/30/85. Devrinol, technical 94.6 % was tested in CHO for mutation at HG-PRT/ locus at 5 to 9 concentrations from 0.08 - 0.16 mg/ml (-S.9) and 0.02 -0.06 mg/ml (+ S.9). Devrinol was not mutagenic in the forward mutation assay. ACCEPTABLE. (YKL, 10/5).

SUMMARY: All studies for Gene Mutation were assessed as acceptable. Using the L5178Y cells with TK marker, there was an increase in frequency of mutation, whereas using the CHO cells with HGPRT marker, the results were negative. Both assays measure gene mutation. The contradictory results may partially be explained by period of exposure, incubation conditions, expression time and differences in the two cell lines. The tox summary conclusion is based on the positive results for gene mutation in L5178Y. (YKL, 10/87).

CHROMOSOME ABERRATIONS

** 052 033623 "Devrinol Technical: Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay," (Stauffer Environmental Health Center, 9/17/84). Napropamide, 94.6%, was assayed for chromosome aberrations with L5178Y mouse lymphoma TK +/- . Activated concentrations ranged 0.002 to 0.020, non-activated concentrations were 0.005 to 0.10. There was no reported increase in the percent of cells with chromosome aberrations with and without activation. ACCEPTABLE. (JR(G)), 9/20/85).

** 052, 071 033621, 065496 "Devrinol Technical: Mutagenicity Evaluation in Bone Marrow Micronucleus - CD-I Mice", (Stauffer Environmental Health Center, Report no. T-11822, 3-12-84). Napropamide technical, 94.6%, was administered to CD-I mice (15/sex/dose) by gavage in a single dose at 0 (water), 556, 1667 or 5000 mg/kg and cells were harvested at 24, 48 and 72 hours. No effect reported. The original study 033621 was considered unacceptable since individual data were not provided, (JR(G), 9/20/85; M. Silva, 1/11/88). Individual data requested by DPR have been provided and are complete. Therefore study 033621 is upgraded to ACCEPTABLE. M. Silva, 7/20/89.

071 065496. This volume contains individual data for studies with record numbers 033621 and 054055. (M. Silva, 7/20/89).

061 063369 SB950 Response to Toxicology Comments, Stauffer Chemical Co. (3/5/87). In Appendix 6: "Mutagenicity of devrinol technical" the criteria for scoring micronuclei are listed. (M. Silva, 1/11/88).

060 054055, "Mutagenicity Evaluation in Bone Marrow Micronucleus". (Stauffer Chem. Co., Farmington, Conn.; Report# T-12813, 2/11/86). CD1 female mice, 5/group treated orally, Napropamide, 94.6% purity @ 0, 556, 1667, 5000 mg/kg. Positive control-cyclophosphamide 200 mg/kg. 2/5 died @ 5000 mg/kg. Micronucleus assay 24 hrs post-treatment. No adverse effects. Supplemental study to 052 033621. (YKL, 9/87).

DNA DAMAGE

** 083 091343 "Napropamide: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes in vivo," (Kennelly, J.C., ICI Central Toxicology Laboratory, Cheshire, UK, 7/30/90). Napropamide technical (94.3% pure; lot #: WRC4921-27-27) was administered by gavage to male Alderley Park (Alpk:APfSD) rats (2 rats/time point control and 2-3 rats/dose/time point napropamide) at 0 (corn oil), 500, 1000 and 2000 mg/kg (2000 mg/kg was the limit for a non-toxic dose). Primary hepatocytes were obtained at 4 and 12 hours (25-50 cells scored/slide for a total of 100 cells/animal). Subsequently [³H]-TdR, was added in vitro for autoradiographic analysis (4 hours). The slides were then read for autoradiography. The experiment was repeated. No adverse effect. There was no UDS effect which was significantly increased over negative controls. Positive controls functioned as expected. ACCEPTABLE. (M. Silva, 9/12/90).

052 033625, "Effects of Devrinol Technical on Human Fibroblast DNA: Alkaline Sucrose Sedimentation Studies Nick Translation Assay Using E. coli DNA Polymerase I." (Stauffer Environmental Health Center, 9-84) The effect of technical napropamide on DNA molecular weight was measured by alkaline sucrose gradient centrifugation and on DNA repair by nick translation with E. coli pol 1. Both are reported to give negative results. UNACCEPTABLE. Insufficient information on how assays were conducted. (JR(G), 9-20-85).

001 031825, (Stauffer) Very brief summary, no data, B. subtilus assayed for DNA damage/repair. UNACCEPTABLE. (JR(G), 3-29-85).

060 054030, "Effects of Devrinol on Human Fibroblast DNA" (Stauffer Chemical Co., Farmington, Conn., 5/5/86). Napropamide Technical, 94.6% purity, tested for DNA damage in vitro, ±9, using Human Fibroblasts treated @ 0, 0.08, 0.67 and 0.83 mg/ml. Adverse effect: Caused DNA damage at 2 high doses with +S.9, as measured by sedimentation at higher gradient than control, of "nucleoid" from lyse cells. Test protocol not in compliance with guidelines. Considered as supplemental data. (YKL, 10/87).

NEUROTOXICITY

Not required at this time.