CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MEFLUIDIDE, DIETHANOLAMINE SALT

Chemical Code # 1955, Tolerance # 386
SB 950 # 238

August 8, 1986
Revised 4/13/87, 7/14/88, 11/27/90, 10/5/93, 11/21/94

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effect.
Oncogenicity, rat:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.

Gene mutation: No data gap, no adverse effect.

Chromosome effects: No data gap, no adverse effect.

DNA damage: No data gap, no adverse effect.

Neurotoxicity: Not required at this time.

Toxicology one-liners are attached.

All record numbers through 128948 and 987274 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T941121
Revised by Stanton Morris, 11/21/94

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

The studies reviewed below were conducted with either the free acid or the diethanolamine salt of mefluidide. The diethanolamine salt is the registered active ingredient in California. Possible toxicological differences between the free acid and diethanolamine salt were not considered in the following reviews. The free acid and diethanolamine salt have been grouped by the US EPA (Morris, 10/5/93).

COMBINED, RAT

386-004 987263, "Two Year Feeding study in Rats", (International Research and Development Corporation, Mattawan, MI, study no. 102-208, report no. 225, 6/14/79). Mefluidide (MBR 12325) technical, purity 93%, fed in the diet to 50/sex/group at 0, 600, 1800 or 6000 ppm over two (2) years starting at in utero from a reproductive study. **ADVERSE EFFECT**: retinal degeneration. Eye effect NOEL = 600 ppm. Systemic NOEL not demonstrated with decreased body weight gain in all dose groups [see #037396]. No evidence for oncogenic effect. The study identified as record # 987263 was initially reviewed by Christopher (7/1/85) and found to be unacceptable due to lack of diet analysis and no justification for in utero exposure. Additional information (volume & record # 034 059985) was submitted 7/27/87 consisting of diet analysis, explanation for variances in weight at outset and discussion for using in utero animals. UNACCEPTABLE with no dose justification - (NOEL not demonstrated with decreased body weight gain in all dose groups). (Updated, Kishiyama, 6/24/88 and Gee, 7/14/88).

EPA one-liner: Oncogenic NOEL > 6000 ppm (HDT) Sys, NOEL < 600 ppm (body weight loss), retinal degeneration noted at all levels and control. Levels tested in Charles River CD strain 0, 600, 1800 and 6000 ppm. Minimum for oncogenic and minimum for systemic.

386-001 987262, appendix to 987263. Individual histopathology and summary tables prepared by Experimental Pathology Laboratories, Inc., 7/26/79. Supplement IV.

386-025 037389, duplicate of 987262.

386-005 987264, appendix to 987263. Individual histopathology continuation of Table 30 (individual animal results) from 987263.

386-006 987265, appendix to 987263. Individual histopathology continuation of Table 30 of 987263. Also contains Table 31, "Correlations of gross and microscopic findings."

386-025 037393. Text changes for 987263.

386-034 059985, addendum to 987263. Diet analysis, justification for in utero exposure and age/weight variation.

386-026 037396, "One Year Oral (Diet) Toxicity Study of MBR-12325 in Rats", (Riker Laboratories Inc., experiment no. 0280CR0012, IRDC no. 102-028, 9/3/81). Mefluidide (MBR-12325), purity not stated, fed 0, 60, 200 or 600 ppm to 20/sex/group. 1 year study to determine NOEL for body weight as requested by EPA. Study does establish NOEL at 200 ppm. SUPPLEMENTARY DATA, no necropsy or histopathology. (Gee, 3/17/86).

EPA one-liner: The request was for a NOEL for body weight. NOEL = 600 ppm. Core grade = minimum.

386-034 059986, addendum to 037396. Feed analysis. No worksheet. Gee, 7/14/88.

SUMMARY: Although no one document on file is adequate due to flaws in the report, the collective data, including the 1-year study to establish the NOEL for body weights, are adequate to address the effects of chronic feeding in the rat. No oncogenic potential was identified. Gee, 7/14/88.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

CHRONIC TOXICITY, DOG

**** 386-026 037397**, "Twelve Month Diet Feeding Study of MBR-12325 in Dogs", (Riker Laboratories, experiment no. 0280CD0021, 11/1/82). Technical MBR-12325 (Mefluidide), purity 93% and 91% at pre-study and post-study, respectively, fed at 0, 60, 600 or 6000 ppm in the diet to Beagle dogs, 6/sex/group for one year. **Positive for adverse effects on kidney at high dose.** NOEL kidney = 600 ppm; body weight = 60 ppm. Nephrosis or degeneration of proximal convoluted renal tubular epithelium in 4/12 at high dose. Record 059988 contains the diet analyses for content, stability and homogeneity. ACCEPTABLE. (Gee, 3/17/86 and 7/14/88).

EPA one-liner: Minimum. NOEL = 60 ppm (weight loss); LEL = 600 ppm (cortical nephrosis).

386-034 059988, addendum to 037397. Diet analysis.

ONCOGENICITY, RAT

See COMBINED RAT above.

ONCOGENICITY, MOUSE

386-002 987267, "Lifetime Carcinogenicity Study in Mice", (International Research and Development Corporation, report no. 102-026, 5/14/1979). Mefluidide, purity 93%, fed at 0, 600, 1800 or 6000 ppm in diet to 60/sex/group for 18-19 months. **Positive adverse chronic**

effect of liver toxicity. No evidence of oncogenicity. NOEL for hepatotoxicity is 600 ppm. UNACCEPTABLE. (J. Christopher, 7/1/85). Evaluated as possibly upgradeable with submission of pathology data adjusted according to time of death, complete histopathology for the mid dose group and organ weights. Rebuttal (#059987 in 034) discusses the requirements for an oncogenicity study as opposed to a combined and contains diet analyses. See Summary statement below. (Updated, Kishiyama and Gee, 7/14/88).

EPA one-Liner: Guidelines. Pathology report: No microscopic lesions compound related were observed from the 600 or 1800 ppm groups.

386-024 037387, Addendum to 987267. Memo from IRDC to 3M prior to report issue, reporting liver findings.

386-024 037388, Addendum to 987267. Liver pathology report only (1978, Riker Labs). Liver hypertrophy at 6000 ppm. (Gee, 3/17/86).

386-008 987266, Addendum to 987267 (1978, IRDC) Summary of 2 consulting pathologists with IRDC pathologist’s evaluation of liver findings. Conclusions are "reparative or regenerative response to toxic liver injury". Marginal at 1800 ppm. No evidence of carcinogenic effect. NOEL: 600 ppm for hepatotoxicity.

386-024 037398, Addendum to 987267 (1981, IRDC) - pathology for 600 and 1800 ppm groups.

386-034 059987, Addendum to 987267. Response to Dr. Christopher’s review and includes diet analysis.

386-024 037391, Duplicate of 987267.

The following is a summary of the MEFLUIDIDE onco mouse study report and various supporting documents:

Significant adverse effects consisted of increased mortality in the 6000 ppm (high) dose group and liver nodular hyperplasia in the 6000 and 1800 (intermediate) dose groups. The liver alterations were called "reparative or regenerative responses to toxic liver injury" and no oncogenic effect was claimed. Two consultant pathologist re-read the slides and generally agreed with the diagnoses of the IRDC pathologist. While no oncogenic effects were found, the reduced survival in the high dose group confounds interpretation. The pathology data need to be adjusted according to time of death rather than be lumped into singular incidence values irrespective of time of death or sacrifice. Appropriate statistics could then be performed. In any event, the report is still incomplete and unacceptable due to study conduct deficiencies originally outlined in Dr. Christopher's review. F. Martz, 4/16/86.

Summary: When all documents are considered and the study is reviewed for oncogenicity only, some of the initial deficiencies noted are not major ones. The high dose was close to that stated by EPA as a "limit" test for oncogenicity and a target organ (liver) and a NOEL were established. With submission of the diet analysis and review of the collective data, the requirement for an oncogenicity study in the mouse is fulfilled. Gee, 7/14/88.

REPRODUCTION, RAT

** 386-003 987268, "Multigeneration Reproduction Study in Rats", (International Research and Development Corporation, study no. 102-027, 4/17/79). Mefluidide (MBR 12325 technical), purity 93%, fed in the diet at 0, 600, 1800 or 6000 ppm to 20 males and 40 females for 3 generations, 2 litters each. A positive adverse effect was noted - decreased weaning weights at the high dose by J. Christopher, 6/28/85. At day 0, mean fetal weights were comparable but less weight was gained during days 14-21 of lactation period. Since this is when pups were consuming treated feed, it is considered evidence that a MTD was reached and no adverse effect is found. Body Weight NOEL = 600 ppm for adults; 1800 for pups but still unacceptable with no diet analysis; inadequate necropsy (no F0, 5/sex/group for F1 and F2). (Parker, 6/28/85)

Additional information (volume & record # 034 059989 and 059990) was submitted 7/27/87. These contain analysis of diets, rebuttal concerning the necropsy/histopathology question and a review of the study by Dr. Christian of Argus, written 7/23/86. Necropsies were done on 5/sex of the controls and high dose groups of F1 and F2 parental animals and F3b weanlings and histopathology on the F1 and F3b weanlings. With submission of the analysis of diets, the study is upgraded to ACCEPTABLE status. (Gee, 7/14/88.)
EPA one-liner: Guideline. NOEL = 1800 ppm. LEL = 6000 ppm - reduced pup body weight, increased female pup spleen weight.

386-034 059989, addendum to 987268. Diet analysis.

386-034 059990, addendum to 987268. A critical review of 3M company MBR technical multigeneration study in rats by Dr. M. Christian, ATS.

TERATOLOGY, RAT

** 386-038 096649; "Teratology Study in Rats with Diethanolamine Salt of Mefluidide", SLS Study No. 3229.5; D.E. Rodwell; Springborn Laboratories, Inc., Spencerville, OH; 3/4/91. Groups of 25 mated female Sprague-Dawley rats were exposed on gestation days 6 through 15 to the diethanolamine salt of mefluidide (28.78% w/w, stated purity, Lot No. JB0624) at 0, 50, 200, or 400 mg/kg/day. The animals were sacrificed and cesarean sectioned on day 20. Maternal effects were lethality, clinical signs, and reduced body weight and food consumption at 400 mg/kg/day (maternal NOEL = 200 mg/kg/day). Increased resorptions were seen at 400 mg/kg/day (developmental NOEL = 200 mg/kg/day). There were no treatment-related malformations or developmental variations. No adverse effect was indicated. The study was unacceptable (S. Morris and J. Gee, 9/30/93) but upgraded to acceptable by submission of an adequate analysis of the test material (S. Morris and J. Gee, 11/21/94).

386-040 128936,

386-040 128941: These documents contain anayltical techniques and data for the test material used in the study at rec. # 096649. Evaluation of these data upgraded the study to acceptable (S. Morris and J. Gee, 11/21/94).

386-038 096648; "Range-finding Teratology Study in Rats with Diethanolamine Salt of Mefluidide"; SLS Study No. 3229.4; 2/22/91. This study provided the rationale for the doses in DPR doc. # 386-038, rec. # 096649. Groups of six mated female Sprague-Dawley rats were exposed by oral gavage on gestation days 6 through 15 to the test material at 0, 100, 200, 400, 600, or 800 mg/kg/day. Four females died at 800 mg/kg/day and 3 died at 600 mg/kg/day. Urine staining, tremors, hunched posture, salivation, dark material around the eyes, decreased body weight gain and food consumption were seen at 400, 600, and 800 mg/kg/day. Fetal body weights were reduced at 800 mg/kg/day (S. Morris and J. Gee, 9/30/93).

386-026 037395, "Oral Teratology Study of MBR-12325 in Rats", (Riker Laboratories, Inc., experiment number 0681TR0095, 3/22/82 and 7/27/87). Mefluidide, purity 93% and 91% at start and end of study, respectively, administered by gavage (4% gum acacia) at 0, 15, 30 or 60 mg/kg/day to Sprague-Dawley rats (26/group) on days 6 through 15 of gestation. Maternal and developmental NOEL $\geq$ 60 mg/kg/day. No adverse effect. Dose selection was not justified and no maternal toxicity reported, including body weight differences; 1/3 of fetuses for visceral exam, no necropsy data on dams. Initially reviewed as unacceptable and not upgradeable based primarily on dose selection. No analysis of dosing solutions. (Gee, 3/17/86) Records 059991 and 059992 are rebuttals and review of the study, early and late resorption data and justification of dose selection. Study remains UNACCEPTABLE and not upgradeable - no MTD. (Updated, Kishiyama and Gee, 7/15/88)
EPA one-liner: Minimum. Teratogenic NOEL > 60 mg/kg (HDT), Maternal NOEL > 60 mg/kg (HDT), Fetotoxic NOEL > 60 mg/kg. Levels tested by gavage in Sprague-Dawley strain -0, 15, 30, and 60 mg/kg/day.

386-034 059991, addendum to 037395. Justification of dose and data on early and late resorption sites.

386-034 059992, addendum to 037395. A critical review of Riker Laboratories,Inc. oral toxicity study of MBR-12325 in rats by Mildred S. Christian, Ph.D., ATS, 7/23/86.

TERATOLOGY, RABBIT

** 386-016 987269, "A Teratology Study in Rabbits with Technical MBR 12325 (Lot No. 9)", (Riker Laboratories Inc., experiment no. RBT-14, report no. 55, 5/7/75; 3M, 5/12/89). MBR 1235 (Mefluidide), purity not stated (lot no. 9 in some of the IRDC studies show purity as 93%), administered orally (gastric intubation) at 0 (4% gum acacia), 60, 30, or 15 mg/kg/day to 16-20/group from days 6 through 18 of gestation. No adverse effect identified. Maternal and developmental NOEL $\geq$ 60 mg/kg/day. Initial review by Christopher (6/27/85) classified as "unacceptable". Additional data in 059993, 059994 and 059995 provided dosage justification, clinical observations (not complete and with multiple discrepancies) and revised tables of raw data. This study did not determine a NOEL but #59993 shows that doses of 100 mg/kg and above resulted in mortality. Still was considered unacceptable but upgradeable (analysis of dosing solution, individual fetal/litter findings, resolution of the discrepancies in 059994 and 059995 concerning the fate of several does, revision of the report). Updated by Kishiyama, 7/1/88 and Gee, 7/14/88). Submission of record numbers 095391 and 959392 (analytical data on dosing solutions and individual maternal and fetal data) upgrades the study to ACCEPTABLE status. (Gee, 11/27/90).

EPA one-liner: NOEL = > 60 mg/kg/day (highest dose tested). No core grade.

386-036 095391,
386-036 095392, Analytical data on dosing solutions and individual maternal and fetal data for 987269.

386-034 059993, Appended summary, " A 14 Day Dose Finding Oral Intubation study in Rabbits with Technical MBR 12325, Lot No. 9", (Report no. 475R0015, 1/17/1975). MBR (Lot No.9), purity not stated, administered by oral intubation at 800, 400 and 200 mg/kg

and later included an additionaldose at 100 mg/kg to 4, 3, 4, 3 (2 plus 1 from 400 mg/kg group) female rabbits, respectively. Deaths of 4/4, 3/3, 4/4 and 1/3 at levels 800, 400, 200 and 100 mgs, respectively. Animals in 800, 400 and 200 mg levels showed tremors. Supplementary data to justify dose selection for teratology study. (Kishiyama and Gee, 7/14/88).

EPA one-liner: NEL = <100 mg/kg/day (range finding); 1/3 deaths at 100 mg; tremors at 200 mg/kg/day.

386-034 059994, addendum to 987269. Clinical observations.

386-023 037385, duplicate of 987269.

386-034 059995, "Critical Review of Rabbit Teratology Study of MBR 12325 (experiment no RBT-14)", (Mildred S. Christian, Ph.D., ATS, Argus Research Laboratories Inc., 7/23/86). Dr. Christian states, "the study can be defended as providing adequate information for EPA regulatory use, as required at the time of conduct. On basis of the report and raw data reviewed, the study was designed in conformance with the 1966 FDA requirements for studies of this type". Addendum also includes revised tables for 016 987269. (Gee, 7/14/88)

GENE MUTATION

Bacteria

** 386-037 096364, "Mutagenicity Test on Diethanolamine Salt of Mefluidide in the Salmonella/Mammalian-Microsome Reverse Mutation Assay (Ames Test) with a Confirmatory Assay", HLA Study No. 12322-0-401R, T.E. Lawlor, Hazleton Laboratories America, Inc., Kensington, MD, 2/12/91. The diethanolamine salt of mefluidide (28.8% stated purity) was assayed for induction of reverse mutations at the histidine locus of Σαλμονελλα τψπηιμυριυμ tester strains

TA98, TA100, TA1535, TA1537 and TA1538. Two trials per strain were conducted with or without S9 metabolic activation (ArchlorT-induced rat liver microsomes) in triplicate at 0 (deionized water), 100, 333, 667, 1000, 3330, and 5000 µg/plate (based on weight not actual content of a.i.). There was no treatment-related effect on revertants. No adverse effect was indicated. The study was unacceptable (S. Morris and J. Kishiyama, 9/14/93) but upgraded to acceptable by submission of the test material batch number and missing pages (S. Morris and J. Gee, 11/21/94).

386-040 128936,
386-040 128941: These documents contain anayltical techniques and data for the test material used in the study at rec. # 096364. These data were evaluated with doc. # 386-040, rec. # 128948 (S. Morris and J. Gee, 11/21/94).

386-040 128948: This document contained a complete copy of the study at rec. # 096364. Evaluation of these data upgraded the study to acceptable (S. Morris and J. Gee, 11/21/94).

386-008 987271, "Mutagenicity Study with S-12207, S-15017, S-15733, S-22241, S-22242 - Concomitants in Technical Mefluidide F5401-Lot 502", (Riker Laboratories Inc., 3M report no. 154, 1/31/78). Melfluidide (technical, purity not stated). Salmonella (5 strains) were tested at 1, 10, 100 or 1000 ug/plate +/- S9. No mutagenic effect reported. UNACCEPTABLE with insufficient information - inadequate methods, single plate, no repeat trial, concentrations used not justified with no evidence of toxicity at the high concentration in any strain. (Christopher, 6/27/85).

EPA one-liner: Negative at highest level tested (1000 ug/plate) in TA-1535, TA-100 and negative to 100 ug/plate in TA-1535, TA-1538 and TA-98.

386-008 987273, "Evaluation of MBR 12325 Technical (Free Acid) in the Salmonella/mammalian-microsome Mutagenicity Test". (Riker Laboratories Inc., report no 199, 5/25/77). Mefluidide (MBR-12325 technical (free acid), purity not stated). Salmonella, strains TA1535, TA1537,

TA1538, TA98 and TA100 were tested at 1, 10, 100 or 1000 ug/plate +/- S9. The test was repeated with preincubation in liquid suspension for 20 minutes prior to plating. No mutagenic effect reported. UNACCEPTABLE with insufficient information - inadequate methods, concentrations not justified with no evidence of cytotoxicity at the high concentration in any strain. (Christopher, 6/27/85).

386-008 987272. Summary (very brief) of 987273.

387-023 037382. Duplicate of 987272.

386-026 037399, "Genetic Toxicology Studies with EL-565 (Compound 151065)", (Lilly Research Laboratories and Company, study no. 821115-GPA-1969, 3M Agrichemicals report no. 278, January 1983). El-565 (Mefluidide);(Lilly compound 151065), purity not stated. Eight strains of S. typhimurium and two strains of E. coli were tested for mutagenicity at 0.1-1, 1-10, 10-100 and 100-1000 ug/ml +/- S9 using the gradient plate assay devised by Lilly. Evidence that the test compound diffuses in agar as described are requested. Note: this assay is frequently used at Lilly but not enough description is included to evaluate adequacy. No evidence of a mutagenic effect. UNACCEPTABLE but UPGRADEABLE - diffusion test must be substantiated, no repeat trial, need % purity of test article - introductory synopsis states that the genotoxicity studies were performed with technical material. (Gee, 3/17/86); (updated, Kishiyama, 7/6/88).

EPA one-liner: Negative for mutation. Acceptable.

Mammalian Cells

386-026 037401, "The Effect of EL-565 (Compound 151065) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells",(Lilly Research Laboratories, study 820908MLA1969, 12/1982). EL-565, purity not stated. Mouse L51784 Tk cells were exposed for 4 hours to 1, 25, 50, 100, 250, 500, 750 or 1000 ug/ml +/- S9. At the highest concentration, growth was reduced to 72% of control without activation and to 69 - 92% with activation in a preliminary cytotoxicity assay. No mutagenic effect. UNACCEPTABLE - no

repeat trial, test article not described, induction of rat liver with 100 mg/kg aroclor rather than 500 is not justified. (Gee, 3/18/86).

EPA one-liner: Negative for mutation. Acceptable

CHROMOSOME EFFECTS

** 386-037 096365, "Mutagenicity Test on Diethanolamine Salt of Mefluidide in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", HLA Study No. 12322-0-437, H. Murli, Hazleton Laboratories America, Inc., Kensington, MD, 2/11/91. The diethanolamine salt of mefluidide (stated purity 28.8%, w/w, batch no JB0624) was tested without metabolic activation at 0, 360, 720, or 1080 µg/ml (trial 1); 0, 721, 1080, or 1440 µg/ml (trial 2); or with S9 metabolic activation (microsomes from Aroclor 1254-induced male Sprague-Dawley rat livers) at 0, 360, 720, 1080, or 1440 µg/ml. Duplicate cultures of Chinese hamster ovary (CHO) cells were exposed to the test material for 7.25 (trial 1) or 17.25 (trial 2) hours without S9 or 2 hours with S9. The -S9 cultures were washed and incubated with 0.1 µg/ml Colcemid* for 2.5 hours. The +S9 cultures were washed and incubated in complete medium for 7.75 hours with 0.1 µg/ml Colcemid* being present for the last 2.5 hours. The cultures were then washed, dried, stained, and 100 metaphase cells / replicate were cytogenetically scored for chromosome aberrations. There were no treatment-related increase in chromosome aberrations. No adverse effect was indicated. The study was acceptable (J. Kishiyama and S. Morris, 9/22/93).

386-026 37402 "The Effect of EL-565 (Compound 151065) on the In Vivo Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters", (Lilly Research Laboratories, study 821012SCE1969, 10/1982). EL-565 (Lilly compound 151065), purity not stated. Mice were given 12.5, 25, 50 or 100 mg/kg by oral gavage and sacrificed 21 hours later.100 metaphases per animal were scored. No effect on chromosomes was reported. UNACCEPTABLE: use of only females is not justified, only 3/group, justification of doses as high dose was much lower than the LD(>4000 mg/kg), no purity for test article. Not upgradeable. (Gee, 3/18/86).

EPA one-liner: No effect in SCE. Negative. Acceptable.

DNA DAMAGE

** 386-039 096792, "Genotoxicity Test on Diethanolamine Salt of Mefluidide in the Assay for Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures", HLA Study No.: 12322-0-447, M.E. McKeon, Hazleton Laboratories America, Inc., Kensington, MD, 03/22/91. Triplicate coverslips of primary rat liver hepatocytes from adult male Fisher 344 rats were exposed, in the presence of ^{3}H-thymidine (10 μCi/ml, 40 Ci/mmole), to the diethanolamine salt of mefluidide (28.8% state purity, batch no. JB0624, water solvent) for 20.5 hours (trial 1) at 0, 100, 250, 500, 1000, 2000, or 3000 μg/ml or for 18.5 hours (trial 2) at 0, 1000, 1500, 2000, 2500, 3000, or 3500 μg/ml (based on weight and not actual content of a.i.). The cells were then fixed, developed for autoradiographic analysis and stained. Net nuclear grain counts were determined microscopically for 50 cells / coverslip. The was no treatment-related increase in net nuclear grain counts. No adverse effect was indicated. The study is acceptable (S. Morris and J. Gee, 9/24/93).

386-026 37400, "The Effect of EL-565 (Compound 151065) in the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes", (Lilly Research Laboratories, studies 820803UDS1969 and 820824UDS1969, 10/1982). EL-565 (Lilly compound 151065), purity not stated. Hepatocytes were exposed for 20 hours to 5, 10, 50 100, 500 or 1000 moles/ml (calc. to be 0.3 mg/ml at high concentration; M.wt.=310). No evidence of unscheduled DNA synthesis as conducted. UNACCEPTABLE but UPGRADEABLE - Justification of concentrations used as no evidence of cytotoxicity and request purity of active ingredient. (Gee, 3/17/86).

EPA one-liner: Negative for cytotoxicity. Negative for repair synthesis. Acceptable.

NEUROTOXICITY

Not required at this time.

386-008 987274, "Demyelination Study with S-12325-2S in Chickens", (Riker Laboratories inc., experiment no. 477MO241, 11/14/77). S-12325-2S (MBR 12325 2S formulation, lot 1001, 5477), purity not stated. Hens were given 8500 mg/kg and watched for 21 days. No pathology or clinical observations included in report. No adverse effect reported. UNACCEPTABLE - insufficient information, no redosing, no dosing analysis. Wrong system to follow up on an earlier study on demyelination - should use a mammal. (Christopher, 6/27/85).

EPA one-liner: Protocol was not adequate - a second LD50 dose was not given 21 days after negative response.

These documents were reviewed:

386-023 037382
386-023 037385
386-024 037387
386-024 037388
386-025 037389
386-024 037391
386-025 037393
386-026 037395
386-026 037396
386-026 037397
386-024 037398
386-026 037399
386-026 037400
386-026 037401
386-026 037402
386-034 059985
386-034 059986
386-034 059987
386-034 059988
386-034 059989
386-034 059990
386-034 059991
386-034 059992
386-034 059993
386-034 059994
386-034 059995
386-036 095391
386-036 095392

386-037 096364
386-037 096365
386-038 096648
386-038 096649
386-039 096792
386-040 128936
386-040 128941
386-040 128948
386-001 987262
386-004 987263
386-005 987264
386-006 987265
386-008 987266
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