CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

OXYFLUORFEN

SB 950-225, Tolerance #381
Chemical Code # 1973

5/7/87
Revised 7/6/88, 10/30/89, 5/23/90 and 12/31/92

I. DATA GAP STATUS

Combined rat:	No data gap, no adverse effect
Chronic dog:	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, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effects

Chromosome Effects: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

In the one-liners below
** indicates acceptable study
Bold face indicates possible adverse effect

File name: T921231, revised 12/31/92 by [redacted]

Rectified with Library printout through document 381-130, Record # 096022. Records numbered 900000+ were also examined.

These pages contain summaries only. Individual worksheets should be reviewed as they may contain additional effects.

II. TOXICOLOGY ONE-LINERS

COMBINED

RAT

** 046, 048 014958, 014959, 014960 "A Twenty-four Month Oral Toxicity/carcinogenicity Study of RH-2915 in Rats." (1/3/78, Biodynamics, Project No. 75-1111A) Oxyfluorfen, 4 lots 85.7% or 82.2%; fed for 24 months at 0, 2, 40 or 800(685)/1600 ppm (dosage of high dose group graduated in steps from 400 to 565 to eventually 685 ppm during first 5 weeks, latter level to week 49, then to 800 ppm weeks 49 to 57, and finally to 1600 ppm at week 57 to term of study) to 50/sex/group; Long Evans rats; marginal decrease in weight gain in high dose males and all treated females; no oncogenicity or major toxicity indicated; initially reviewed as Unacceptable, apparently upgradeable - additional data needed to document dosages administered. Original review by [redacted], 7/86. Review by [redacted], 5/6/87, addressed additional data. Document 381-086, Record # 061735, contained the SOP for diet preparation and confirmed that the diet analysis was for diet aged in the animal room. Records for diet preparation had been requested from the contract laboratory by the registrant. [redacted], 7/6/88. Document 381-106, Records 074406, 074413 and 074408 contain data for diet preparation, food consumption and individual body weights. The collective data have been evaluated as acceptable with no adverse effect. The NOEL = 40 ppm (reduced body weight). [redacted], 10/20/89.

080 051383 Supplementary data in support of 046 14958. Attachment 1 contains analyses of oxyfluorfen technicals used in rat combined and other studies. Attachment 2 of this record

presents feed analyses from a later study. These data were considered in 5/6/87 [redacted] review.

080, 086 056329, 061613 "RH-2915 (Goal - Technical) Three Month Dietary Toxicity Study in Rats." (Rohm & Haas, 10/26/82 and 6/28/82 (Histopathology report), Protocol No. 81P-806) Supplementary data in support of 046:014958. Oxyfluorfen, technical, 72.5%, fed in the diet to 15/sex/group Long Evans rats in increasing concentrations to 800, 1600 and 3200 ppm active ingredient with these levels for weeks 5 - 13; no apparent NOEL - dose-related body weight decrements in males at 800 - 3200 ppm (6 to 21%), in females at 3200 ppm (7%). Increased liver weights in males at 800 ppm and above, in females at 1600 ppm and above. Initial submission did not contain the histopathology report (DPR Record # 061613). Microscopic changes were seen in the liver, adrenals and kidneys. Some change was seen at all dose levels. [redacted], 5/6/87 and [redacted], 7/1/88.

028 002980 "90-Day Feeding Study - Rats: RH-915." (Litton Bionetics, 1/25/74) Study examined with respect to 046:014958. "Charles River" strain. Investigators concluded that "No compound-related histopathology is apparent except for hepatic centrilobular swelling which is believed to be a functional response to some toxic stress" (pp. 5-6). At 5000 ppm, 3/10 males and 1/10 females had centrilobular swelling vs none in respective controls (p. A-34), suggesting a mild liver compensatory response at this high dose. Modest weight losses were observed in this study at 5000 ppm in both sexes (Table 1). These investigators determined that "Dietary levels of 200, 1000, and 5000 ppm seem appropriate for the planned longer study" (p. 6). Study addressed in [redacted] review, 5/6/87.

086 061614 "Goal Thirteen Week Subacute Study by Dietary Administration in Rats." (Nomura Research Institute, 1981; translated from Japanese in 1982). Goal technical, 72.5%, Lot 2-3985; fed in the diet to Fischer 344 rats, 10/sex/group, at 0, 200, 1000 or 5000 ppm for 13 weeks; NOEL = 1000 ppm for all but yellow pigment in the tubular epithelium and lumena of kidneys at 200 ppm in several animals of both sexes. Supplementary data for 014958. [redacted], 6/30/88.

CHRONIC

DOG

** 060 036683, also 036681 "104-Week toxicity study in dogs [RH 2915]." (Hazleton, April 9, 1981) Oxyfluorfen, tech. (approx. 72% purity). Nominal doses of 0, 100, 600, and 2000 ppm in diet to beagle dogs 6/sex/treatment group and 10/sex/controls; 2/sex/group sacrificed at 1-year. Liver was apparently the primary target organ. The most sensitive feature was "Bile pigmented hepatocytes", observed in both sexes at 600 and 2000 ppm, and possibly in the nominal lowest dosage in males (100 ppm), suggesting that the "NOEL" for males would be slightly lower than 100 ppm. Also, hepatocellular vacuolization (noted in females only) and Kupffer cells with pigmented vacuoles (noted in males only) were observed at 600 and 2000 ppm. Initially reviewed as "Unacceptable but possibly upgradeable" on receipt of additional information requested in part VI.A. of the review, including historical data to determine if a NOEL could be established ([redacted], 2/19/87). Supplemental submissions in 381-106, Records 074409, 074410 and 074411, provided diet analyses (indicating the actual doses were somewhat lower than nominal), diet preparation and spinal cord histopathology. No historical control data are available from the conducting laboratory. Considering the collective data, study is upgraded to acceptable status. No adverse effect indicated. [redacted] and [redacted], 10/25/89.

ONCOGENICITY

MOUSE

****381-061 036684** "RH-2915 herbicide [Oxyfluorfen]: Twenty month dietary feeding study in mice" (IRDC, 10/26/77) Oxyfluorfen, tech., lot PL 75/8006, 85.7%. Doses of 0 (untreated controls), 0 [ethanol controls (1.4 ml/kg diet during first 56 wk, then 4.1 ml/kg diet during balance of study)], 2, 20, and 200 ppm oxyfluorfen, in diets of CD-1 mice (60/sex/group, including 5/sex/group allocated for 12-month interim sacrifice). Study is considered to

indicate a "**possible adverse effect**". This was due in part to the relatively low NOEL of 2 ppm for liver effects (especially necrosis) in males. Also there was an increased incidence of hepatocellular carcinomas noted by investigators in high dose males: this was not statistically significant on pairwise comparisons, however a significant linear trend was noted, and the possibility of a neoplastic effect cannot be ignored. The following treatment effects were not considered as bases for "possible adverse effects": Females were not definitely affected at the middle dose level. Findings limited to the high dose included hyperplastic nodules (F), hepatocyte regeneration/hyperplasia (M,F), lymphocytic infiltration (M), hypertrophy (M, generally limited to 12-month sacrifice), and hyaline bodies (M, exclusively limited to 12-month sacrifice). Study is **acceptable**, with various deficiencies as noted in CDFA reviews. The original CDFA review by [redacted] (2/18/87) considered the study to be unacceptable and did not consider the study to be upgradeable. The Registrant nevertheless responded by addressing itemized deficiencies. Some acceptability issues were discussed in the CDFA rebuttal response of 7/6/88 by [redacted], and some aspects of the study were then considered to be acceptable (dose selection, high frequency of autolysis, limitations of hematology and clinical chemistry). The CDFA rebuttal response of 10/25/89 by [redacted] noted additional data on diet preparation (document 381-106, records 74405 and 74407), and considered issues relating to dose preparation verification to be resolved, however CDFA was not satisfied with the presentation of histopathology data. The study was accepted following review of a presentation of individual and summary histopathology data (114:088093). [redacted], 5/23/90.

NOTE: This reviewer ([redacted]) has no information to indicate that EPA accepted this study. Apparently the EPA Peer Review Committee which reviewed these data has elected to regulate oxyfluorfen as an oncogen, based on the positive linear trend in hepatocellular carcinomas in male mice. Also, EPA apparently rejected the analysis by Newberne and Rogers (DPR record 381-061:036685), and commissioned an independent evaluation of the slides by Squires et al. DPR does not have a copy of the Squires review. The latter evaluation apparently confirmed the highly significant positive trend for hepatocellular carcinomas as determined by the IRDC investigators. The EPA Peer Review Committee also determined that the MTD was not achieved in this study, so that a replacement study is required. DPR will need a copy of the replacement

study when it is completed, and requests to be advised of the status of that study in the interim. [redacted], 5/23/90.

381-114 088093 (additional data for study 381-061:036684). This is an oncogenicity study entitled "Twenty month dietary feeding study in mice." Study was performed at IRDC on 4/25/77. The new submission presents individual and summary histopathology data with clearly defined bases for censoring data due to autolysis. Censored mice are identified by number. Individual data also identify special circumstances which might be used by DPR to censor certain portions of the data (based on time of sacrifice, degrees of autolysis, or evidence that diagnoses could be made despite gross autolysis of mice and/or limited autolysis in livers). Hepatocellular necrosis was elevated in males in dose-related fashion at the two higher dose levels. Females were not definitively affected at the middle dose level. Findings limited to the high dose included hyperplastic nodules (F), hepatocyte regeneration/hyperplasia (M,F), lymphocytic infiltration (M), hypertrophy (M, generally limited to 12-month sacrifice), and hyaline bodies (M, exclusively limited to 12-month sacrifice). This completes the requirements established by DPR for an "upgrade" to "acceptable" status for this study. The study nevertheless has several weaknesses, such as inconclusive evidence that an MTD was achieved. [redacted], 5/23/90.

381-061 045069 A Rohm and Haas summary of 061:036884, above.

381-061 036685 A second evaluation of liver slides from study, 061:036884, above, by P. Newberne and A. Rogers. They found a substantially lower incidence of hepatocellular carcinomas than did the IRDC pathologists, but this evaluation found elevated hyperplastic nodules in high dose males. This evaluation was considered in all reviews of that study, but was discussed primarily in the original CDFA review ([redacted], 2/18/87).

REPRODUCTION

RAT

048/062 14961 "Three generation reproduction study of RH-2915 [Oxyfluorfen] in rats" (4/28/77, Biodynamics) Oxyfluorfen, 4 lots 82-86%; @ 0, 2, 10 or 100 ppm diet 10 males/20 females per control and test groups; Long-Evans rats; no reproductive toxicity seen and teratology data of questionable use; **Unacceptable, incomplete** (compound intake not supported by diet analysis, abortion data not presented, unexplained breeder deaths, fetus rather than litter used as experimental unit, litters not culled; histopathology on F_{3a} generation, 10/sex, but not on parents.) [redacted], 7/85.

** 130 089918, "Goal* Technical Herbicide: Two-Generation Reproduction Study in Rats", (H. M. Solomon, et al., Rohm and Haas Company, Toxicology Department, Report # 90R-007, August 26, 1991). The test article was Goal* Technical Herbicide with 71.4% purity. The test material was administered in the diet through 2 generations with 1 litter per generation at nominal concentrations of 0 (Certified Purina Rodent Chow # 5002M), 100, 400, and 1600 ppm with 25 Crl:CD*BR rats per sex per group. Treatment began approximately 10 and 14 weeks pre-mating for P1 and F1 parents, respectively. Treatment was continuous through mating, gestation and lactation to sacrifice. A marginal P1 group mean body weight reduction (1.8% to 8.0%) was noted for both sexes at 1600 ppm. F1 parental body weights at the high dose were significantly lower than control values at the start of dosing due to delayed development of the F1a pups; these rats continued to lag behind controls in body weight. Parental histopathology revealed, in the kidneys: increased pelvic/papillary urothelium hyperplasia (males), pelvic and/or collecting ducts/papilla mineralization (both sexes), and dilatation (both sexes) of the collecting ducts at 1600 ppm. In the liver, hepatocellular hypertrophy was reported for both sexes at the high dose. Parental NOEL = 100 ppm (liver and kidney (pelvic mineralization) findings at 400 and 1600 ppm). Reproductive NOEL = 400 ppm (reduced pup weight and delayed pup weight gain and smaller litter sizes 1600 ppm). **Acceptable with no adverse effect indicated**. [redacted] and [redacted], 10/23/92)

124 096022 Adverse effects disclosure for 089918 for decrease in body weight and mean number per litter at the high dose. No worksheet. [redacted], 10/26/92.

TERATOLOGY

RAT

046 14957 (and #36687, dose range finding) "Teratology study in rats with RH-2915 Technical" (11/15/77, Hazleton) Oxyfluorfen, tech. 71.4% in 0.5% methylcellulose by oral gavage at 0, 10, 100 or 1000 mg/kg/day, 25/group day 6-15; apparent maternal, fetotoxicity and embryotoxicity NOEL = 1000 mg/kg/day Unacceptable, incomplete; too few pregnant dams in high dose group (5 high dose animals died by intubation error), dose analysis not presented, fetal data not reported for both sexes and no dam or fetal examination data presented. [redacted], 7/85.

** **125 089214,** "Goal: Oral (Gavage) Developmental Toxicity Study in Rats", (H.M. Solomon and A.S. Romanello, Rohm and Haas Company, Toxicology Department, Report # 90R-008, 2/15/91). Goal*Technical Herbicide (oxyfluorfen), purity indicated as 71.4%. The test material was administered by gavage on gestation days 6 through 15 at 0 (corn oil), 15, 150, and 750 mg/kg/day with 27 mated female Crl:CD*BR rats per group. Fifteen (15) of the 27 females in the high dose group died during treatment and 1 was euthanized. Ten of the eleven surviving females in the high dose group were pregnant but all had total resorption of their litters. Necropsy revealed an increased incidence of early resorptions at 150 mg/kg/day. Mean fetal weight was reduced at 150 mg/kg/day. **Adverse effects are indicated** (early resorptions, lower fetal weight, skeletal malformations and variations in the absence of serious maternal toxicity). Developmental NOEL = 15 mg/kg/day ; Maternal NOEL = 15 mg/kg/day (staining of the perineum and/or muzzle at 150 mg/kg/day, possibly due to test article or a metabolite, and transient weight loss). Records 088992 and 096021 are adverse effects disclosures for this study. **Acceptable.** ([redacted] and [redacted], 10/21/92)

120 088992 Adverse effects disclosure for 089214 for maternal and embryo lethality. [redacted], 10/26/92.

124 096021 Adverse effects disclosure for 089214 for skeletal malformations. [redacted], 10/26/92.

TERATOLOGY

RABBIT

028 002976 "Teratology study in rabbits with RH-915" (Litton Bionetics, 2/11/74) Oxyfluorfen, 94%; given days 6-18 at 0, 5, 25 or 125 mg/kg/day to 12/group New Zealand White rabbits in 5% acacia solution; no evidence of maternal toxicity; Unacceptable, incomplete - too few pregnancies, no dose rationale or analysis, insufficient data presented, including individual body weights, litter data and necropsy. [redacted] 7/85.

** 064, 086, 106 036690, 061612, 074404 "Goal Herbicide - Teratogenicity Study in Rabbits." (Argus Research Labs, 1/22/82, 81P-87) Goal 25 (M-8180), a formulated oxyfluorfen product (approximately 26.9%), given by oral gavage at 0 (vehicle plus inerts), 10, 30 or 90 mg/kg/day, days 6 - 18 to 19/group; maternal NOEL = 10 mg/kg/day (anorexia, decreased weight gain, abortions). Maternal deaths at 90 mg/kg/day. Developmental toxicity NOEL = 30 mg/kg/day (slight increase in resorptions in 90 mg/kg/day group); initially evaluated as unacceptable and not upgradeable based upon use of the formulated material, no purity or stability data and too few litters and fetuses in the high dose group ([redacted], 7/14/86). Document 381-086 contains a rebuttal dated August 28, 1987 and a supplemental record # 061612 with characterization of the formulation and the vehicle control. The explanation for using the formulation was based upon insolubility of the technical material in commonly used gavage materials. Corn oil was rejected because of effects on diarrhea. There was an adequate number of litters in the mid-dose group. Study status was evaluated as unacceptable but upgradeable with submission of analysis of the dosing suspensions taken during the study ([redacted], 7/14/86 and [redacted], 7/5/88). Submission of 074404, analyses of dosing solutions for oxyfluorfen, upgrades the study to acceptable status with no adverse developmental effect. [redacted], 10/18/89.

064 036689 "Goal Herbicide - Oral Range-finding Study in Pregnant Rabbits" [Pilot study for 064:36690, above]. (1/22/82, Argus Research Labs, 81P-86) Goal 25 WP (26.9% active ingredient) given by oral gavage to 4/group at 0, 31, 62, 125, 250 or 500 mg/kg/day active

ingredient suspended in water; all died at 250 and 500 mg/kg/day and 1/4 at 125 mg/kg/day; document discussing problems with getting a good suspension for dosing follows study report. [redacted], 5/7/87 and [redacted], 6/30/88.

GENE MUTATION

General Comments on Gene Mutation (842):

Rohm and Haas has now submitted 13 studies in this category. After consideration of these studies and the Rohm and Haas rebuttal of 12/5/86, DPR has found that individually none of the studies is complete and acceptable. However, taken together the studies provide a consistent picture of the genotoxicity and nothing is likely to be gained by further testing.

Two Ames assays (DPR Record Numbers 987472 and 54975) and a mouse lymphoma assay (DPR Record Number 54973) demonstrated mutagenicity with Goal Technical. The absence of mutagenicity in the Litton Bionetics Ames assay (Record Number 54972) would be expected from the lower dose levels, although the purity of the test material is not given and thus alternative explanations are possible. In any case, these four studies are compatible with each other.

An Ames assay (DPR Record Number 987473) and a mouse lymphoma assay (DPR Record Number 987471) with purified oxyfluorfen demonstrate that the active ingredient is not itself mutagenic. This is confirmed by a series of Ames assays (DPR Record Numbers 987474 and 51387) showing that other components of Goal Technical do have mutagenic activity.

The remaining assays show a lack of mutagenicity for three compounds which are impurities of Goal Technical and for RH-915, which is not identified in any way beyond the code number.

In summary, the data gap is filled by the submitted studies and there is a possible adverse effect for Goal Technical. [redacted] and [redacted], 5/7/87.

009 987472, **080 51384** "Goal Technical Microbial Mutagen Test Results." (Rohm and Haas Company, Report 80R-247, 2/3/82) Oxyfluorfen (72.5% purity) tested on Salmonella strains TA98, TA100, TA1535, and TA1537 at doses ranging from 1.0 to 7500 ug/plate ± activation with triplicate plates; one confirmatory repeat with TA100 and five repeats with TA98; Possible adverse effect-mutagenicity with and without activation in TA98, TA100, and TA1537; Incomplete, unacceptable-no individual plate data, confirming trials inadequate, cover memo ignores mutagenicity in TA1537. 51384 is a duplicate of 987472 with unrelated data appended. Reviewed-[redacted] 7/2/85, [redacted] 4/13/87.

009 987473, 080 51385 "Goal Technical, Purified-Microbial Mutagen Test Results." (Rohm and Haas Company, Report 81R-28, 8/26/81) Oxyfluorfen (99.7% purity) tested on Salmonella strains TA98, TA100, TA1535, and TA1537 at doses ranging from 1.0 to 7500 ug/plate ± activation with triplicate plates; confirmatory repeat with TA98 and TA100 only; No adverse effect reported; Incomplete, unacceptable-no individual plate data, confirming trials incomplete, no positive control without activation, high background levels for TA98 with activation. Reviewed-[redacted] 7/2/85, [redacted] 4/13/87.

009 987474, **080 51386** "Goal (Polar Fraction)-Microbial Mutagen Assay." (Rohm and Haas Company, Report 82R-80, 3/31/82) Polar Fraction (Lot # WJZ 1861) of Oxyfluorfen (Lot #2-3985, TD #81-598) tested on Salmonella strain TA98 only at doses ranging from 50 to 7500 ug/plate ± activation with triplicate plates; confirmatory repeat; Possible adverse effect-every test point in both assays was significantly elevated; Incomplete, unacceptable-not an assay of oxyfluorfen itself, only one strain tested, incomplete individual plate data, no positive control without activation, Reviewed-[redacted] 7/2/85, [redacted] 4/13/87.

081 51387 "Investigative Research Conducted on the 'Polar Fraction' of Goal Technical" (Rohm and Haas Company, 3/8/84) Oxyfluorfen (various purities) tested on Salmonella strain

TA98 at 2 to 5 dose levels with 7500 ug/plate as the high dose; ± activation with triplicate plates; Possible adverse effect-mutagenicity with and without activation in TA98 for some components of Goal technical; Incomplete, unacceptable-not intended to be a Guideline study. [redacted] 4/17/87.

081 54972 "Mutagenicity Evaluation of RH-2915 75-332. Final Report." (Litton Bionetics, Inc., 1/16/76) Oxyfluorfen (RH-2915 75-332, no purity given) tested on Salmonella strains TA98, TA100, TA1535, TA1537, TA1538 (Ames assay) and yeast strain D4 (gene conversion) at 0, 5, 50, 250, and 500 ug/plate ± activation; No adverse effect. Incomplete, unacceptable-Test material not characterized, replicates not specified, no confirmatory repeat assay, dose levels not high enough, no GLP. [redacted] 4/20/87.

081 54975 "In Vitro Microbial Assays for Mutagenicity Testing of RH-2915." (Life Science Department, NRI, 6/80) RH-2915 (Oxyfluorfen) Technical (72.0% purity) tested on Salmonella strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538 and E. coli strain WP2 Hcr- Try- at 0, 10, 50, 100, 500, 1000, and 5000 ug/plate ± activation; Possible adverse effect-mutagenicity with and without activation in TA100 and TA1538 and mutagenicity in TA98 and TA1537 only with activation; Incomplete, unacceptable-only single plates for each dose level, no confirmatory assay, no GLP or signoff sheets. [redacted] 4/21/87.

028 32744 "In vitro and subacute in vivo host-mediated assay for mutagenesis. Final report." (1/25/73, Litton Bionetics, LBI Project 2390) Compound RH-915 (no purity stated, no compound identification) tested on Salmonella strains TA1530 and G-46 with 0% or 5% solutions on sensitivity discs; 5 plates/dose; no activation. No mutagenicity. Unacceptable, incomplete -not guideline strains, no metabolic activation, no dose rationale, test material not identified, no confirmatory assay, and multiple other protocol deficiencies. Reviewed-[redacted] 7/2/85, [redacted] 4/27/87.

028 32743 "In vitro and subacute in vivo host-mediated assay for mutagenesis. Final report." (1/25/73, Litton Bionetics, LBI Project 2390) Compound RH-915 (no purity stated, no

compound identification) at 0, 0.1, 1.0, or 10.0 mg/kg/day for 5 days by oral gavage to mice; mice were injected with Salmonella strain TA1530 or G-46 after last dose and sacrificed 4 hours later; 5 plates were prepared from the peritoneal cavity fluid of each animal. No mutagenicity. Unacceptable, incomplete -no rationale for dose selection, no information on mice used, not guideline Salmonella strains, number of replicates not indicated, no evidence that bacterial cells were actually exposed to the test material. Reviewed-[redacted] 7/2/85, [redacted] 4/27/87.

081 54977 "Mutagenicity Evaluation of RH-34672. Final Report." (Litton Bionetics, Inc., 9/77) 2-chloro-5'-ethoxy-2'-nitro-4-trifluoromethyl-diphenyl ether = RH-34672 (99% purity, Intermediate/Isomer of Oxyfluorfen) tested on Salmonella strains TA98, TA100, TA1535, TA1537, TA1538 (Ames assay) and yeast strain D4 (gene conversion) at 0, 0.1, 1.0, 10.0, 100.0 and 500.0 ug/plate ± activation; No adverse effect. Incomplete, unacceptable-Test material is not oxyfluorfen, replicates not specified, no confirmatory repeat assay, dose levels may not be high enough, no GLP, study labeled "un-audited". [redacted] 4/23/87.

081 54978 "Mutagenicity Evaluation of RH-34672. Final Report." (Litton Bionetics, Inc., 9/77) 6-chloro-alpha, alpha, alpha-trifluoro-m-tolyl-3-ethoxy-4-nitrophenyl ether = RH-42382 (98% purity, Intermediate/Isomer of Oxyfluorfen) tested on Salmonella strains TA98, TA100, TA1535, TA1537, TA1538 (Ames assay) and yeast strain D4 (gene conversion) at 0, 0.1, 1.0, 10.0, 100.0 and 500.0 ug/plate ± activation; No adverse effect. Incomplete, unacceptable-Test material is not oxyfluorfen, replicates not specified, no confirmatory repeat assay, dose levels may not be high enough, no GLP, study labeled "un-audited". [redacted] 4/23/87.

081 54979 "RH-34,670 Technical; Microbial Mutagen Assay" (Rohm and Haas Company, Report No. 81R-166, 10/2/81) RH-34,670 (unidentified impurity of Goal technical, no purity stated) tested on Salmonella strains TA98, TA100, TA1535, and TA1537 at 0, 0.1, 1, 10, 100 and 500 ug/plate ± activation; No adverse effect. Incomplete, unacceptable-Test material is not oxyfluorfen, no individual plate data, no confirmatory repeat assay, no positive control agent for nonactivation, no GLP. [redacted] 4/23/87.

081 54973 "Mutagenicity Evaluation of RH-2915 Technical in the Mouse Lymphoma Forward Mutation Assay" (Litton Bionetics, Inc., Rohm & Haas Report No. 82RC-37, 6/82) Oxyfluorfen (RH-2915 Technical, no purity given) tested on L5178Y mouse lymphoma cells at 62.5, 125.0, 250.0, 500.0, and 1000.0 ug/ml without activation and doses ranging from 1.95 to 50.0 ug/ml with activation. Possible adverse effect-small and erratic but repeatable increases in mutant frequency with activation. Incomplete, unacceptable-Test material incompletely characterized, no individual plate data, no confirmatory repeat assay in the absence of activation, no signoff sheet. [redacted] 4/20/87.

009 987471 "Mutagenicity Evaluation of RH-2915, Pure, TD-81-308 in the Mouse Lymphoma Forward Mutation Assay" (Litton Bionetics, Inc., Rohm & Haas Report No. 81RC-165, 2/82) Oxyfluorfen (99.7% purity) tested on mouse L5178Y (TK+/-) cells at 0, 62.5, 125.0, 250.0, 500.0 or 1000.0 ug/ml in duplicate treatment flasks for 4 hours ± metabolic activation; tables show cytotoxicity greater than 50% at all levels ± S9. No mutagenicity. Unacceptable, incomplete - too much cytotoxicity for doses shown, doses less than 62.5 ug/ml mentioned in text but no data given, no confirmatory assay. [redacted], 7/3/85.

CHROMOSOME MUTATION

General Comments on This Category:

Three studies have been submitted in this category. Record 14962 is unacceptable because of several deficiencies, including the failure to identify the test material. For a full discussion of Record 987475, see the DPR comments on the Rohm and Haas rebuttal. [redacted], 5/7/87. The data gap is filled by 089215. [redacted], 10/26/92.

048 14962, 028 2978 "Subchronic Cytogenetic Study. Compound RH-915. Final Report." (Litton Bionetics, Inc., LBI Project No. 2372, 1/24/73-record 2978, Revised 10/22/76-record 14962) Compound RH-915 (no purity stated, no compound identification) given to groups of 5 male rats

by oral intubation at doses of 0, 0.1, 1.0, or 10.0 mg/kg/day for 5 days; animals killed on day 5; 50 bone marrow cells/rat scored for chromosome aberrations; No adverse effect reported; Incomplete, unacceptable-no identification of test compound, no purity, no females tested, no justification of dose selection, no justification for the single sample time. Reviewed-[redacted] 7/3/85, [redacted] 4/21/87.

009 987475 "Goal Technical Cytogenetic Study in Rats." (3/10/75, Rohm & Haas, Report No. 81R-261) Oxyfluorfen (72.5% purity) given at 0, 0.12, 0.48, or 1.19 mg/kg by single oral gavage to 8 Sprague-Dawley male rats/group with sacrifices at 4, 24 and 48 hours, as well as 5 daily intubations with sacrifice 6 hours after the last dose administration. No mutagenicity demonstrated. Unacceptable, incomplete - toxicity or cytotoxicity ambiguous; no 24 hour sample time for the quintuplicate dosing; extreme variability including control data; no females tested. Reviewed-[redacted] 7/5/85, [redacted] 4/27/87.

** 125 089215, "Acute Test for Chemical Induction of Chromosome Aberration in Mouse Bone Marrow Cells In Vivo", (Ramadevi Gudi, SITEK Research Laboratories, Rockville, MD. Report # 0158-1541, February 6, 1991). Goal Technical Herbicide, 71.4% purity. A single dose of the test material was administered by gavage at 0 (corn oil), 0.5, 2.5, and 5.0 g/kg with 21, 15, 21 and 21 CD-1 mice per sex per group respectively. Seven (7), 5, 7, and 7 mice per sex per group at 0, 0.5, 2.5, and 5.0 g/kg, respectively, were sacrificed at 6, 24, and 48 hours post-treatment. **No increase in chromosomal aberrations**. **Acceptable**. ([redacted] and [redacted], 10/21/92)

DNA/OTHER GENOTOXICITY

General Comments on This Category:

Rohm and Haas has submitted five studies for this category, of which the Unscheduled DNA Synthesis assay (DPR Record Number 987476) was evaluated as complete and acceptable. The

negative result in the assay was supported by a negative result in the same assay with the polar fraction of Goal Technical which was shown to contain the components responsible for gene mutagenicity. Although a positive effect was found in a bacterial repair assay (DPR Record Number 54976), it carries less weight than the negative results for the following reasons: 1) the study is incomplete and unacceptable, 2) the effect occurred only at very high dose levels (5 and 20 mg/well) in which there was precipitation, and 3) the inhibition measurements were minimal.

In summary, the data gap is filled and there is no clear evidence of an adverse effect. [redacted] and [redacted], 5/7/87.

** 009 987476 "Evaluation of RH-2915 (TD 81-561, Lot No. 7530) in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay. Final Report." (3/23/82, Litton Bionetics, Report No. 82RC-20) Oxyfluorfen (73% purity) at 0, 0.10, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0 or 25.0 ug/ml in triplicate, to limits of solubility in medium and limits of cytotoxicity; no evidence of UDS induced by

test substance; Complete, acceptable. Reviewed-[redacted] 7/2/85, [redacted] 4/27/87.

009 987477 "Evaluation of Polar Fraction from Lot 2-3985 (TD 81-562, WJZ 1861) in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay. Final Report." (3/23/82, Litton Bionetics, Report No. 82RC-21) The polar fraction of Goal Technical (identified as a mutagen in gene mutation studies) tested at 0, 0.10, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0 or 25.0 ug/ml in triplicate with cytotoxicity at 10 ug/ml. No evidence of UDS induced by test substance; Complete, unacceptable-test material is not Goal Technical. Reviewed-[redacted] 7/5/85, [redacted] 4/27/87.

028 32742 "In vitro and subacute in vivo host-mediated assay for mutagenesis. Final report." (1/25/73, Litton Bionetics, LBI Project 2390) Compound RH-915 (no purity stated, no compound identification) tested at 0, 0.1, 1.0 or 10 mg/kg day for 5 days by oral gavage to mice; mice were injected with Saccharomyces strain D-3 and sacrificed 4 hours later; 5 plates were prepared from the peritoneal cavity fluid of each animal. No adverse effect reported-recombination frequency elevated at middle dose but not at the high dose. Incomplete, unacceptable-test material not identified, no dose rationale or analysis, no information on mice used, exposure schedule not justified, no evidence that yeast cells were actually exposed to the test material. Reviewed-[redacted] 7/2/85, [redacted] 4/27/87.

028 32741 "In vitro and subacute in vivo host-mediated assay for mutagenesis. Final report." (1/25/73, Litton Bionetics, LBI Project 2390) Compound RH-915 (no purity stated, no compound identification) tested on Saccharomyces strain D-3 with 0% or 5% solutions. No increase in recombination frequency. Unacceptable, incomplete -test material not identified, no dose rationale, no explanation of exposure method or duration, no individual data, no metabolic activation, no confirming experiment. Reviewed-[redacted] 7/2/85, [redacted] 4/27/87.

081 54976 "In Vitro Microbial Assays for Mutagenicity Testing of RH-2915." (Life Science Department, NRI, 6/80) RH-2915 (Oxyfluorfen) Technical (72.0% purity) tested on matched B. subtilis strains, H17 (repair-competent) and M45 (repair-deficient) at 0, 50, 100, 500, 1000,

5000, and 20,000 ug/well; Possible adverse effect-greater growth inhibition in M45 at the highest doses; Incomplete, unacceptable-no activation assay, little information on cell culture conditions, no GLP or signoff sheets. [redacted] 4/21/87.

NEUROTOXICITY

Not required at this time.