CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Propyzamide, [frequently designated as Pronamide or by the trade name "Kerb"]

Chemical Code # 694, Document Processing Number (DPN) # 317
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August 7, 1987
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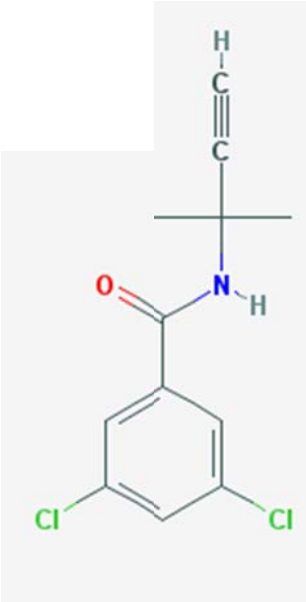
DATA GAP STATUS

Combined toxicity, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effects.
Oncogenicity, rat:	See combined, rat (above), possible adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effects.
Developmental toxicity, rabbit:	No data gap, no adverse effects.
Gene mutation:	No data gap, no adverse effects.
Chromosome effects:	No data gap, no adverse effects.
DNA damage:	No data gap, no adverse effects.
Neurotoxicity:	Not required at this time.

All record numbers for the above study types through 293856 (Document No. 317-0147) were examined. This includes all relevant records indexed by DPR as of 8/15/16.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: t20160815 propyzamide.docx



Revised by H. Green & M. Silva, 9/14/90; Kishiyama & Silva, 4/14/92; Kishiyama and Silva, 9/20/93, Silva, 5/6/94, 6/9/95, 11/9/01, Green, 10/16/14, and Aldous, 3/28/16.

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

The adjacent chemical structure of propyzamide is taken from pubchem.ncbi.nlm.nih.gov.

PROPYZAMIDE

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METABOLISM AND PHARMACOKINETICS **

317-089 186210 "Metabolism of ^{14}C Pronamide in Rats, Supplement A to: ^{14}C-Pronamide (Kerb® Herbicide): Pharmacokinetic Study in Rats," (Smith, S.; Rohm and Haas Company, Agricultural Products Development Department, Spring House, PA; R & H Company Report #: 89R-163; R & H Toxicology Report #: 89R-163A; R & H Technical Report #: 34-93-57; 7/15/93). ^{14}C-Pronamide (radiopurity = 99.8%), non-radiolabeled Pronamide (99.2% pure) and non-radiolabeled Kerb® Technical Herbicide (93.1% pure) were administered by gavage to Crl:CD®Br rats (5/sex/dose/ treatment group) in the following ways: Groups A (Males) & B (Females) = 2 mg/kg and Groups E (M) & F (F) = 100 mg/kg pronamide (radiolabel combined + non-radiolabel). Groups A, B, E, F all received a single radiolabeled gavage dose of pronamide and were terminated after 7 days. Pulse Groups I (M) & J (F) received 2 mg/kg dose of radiolabeled pronamide after pretreatment for 14 days with a daily diet containing 20 ppm non-radioactive Kerb® Technical Herbicide. The radiolabeled material was also administered by gavage in 0.5% aqueous carboxymethyl cellulose. The metabolite profile for urine samples was the same over dose and sex. The actual profile had more polar and highly oxidized known pronamide metabolites. Unknown metabolites were very low concentration (3.34% of dose). All significant metabolites were identified. Feces showed differences in metabolite profile over dose. Low and pulse doses were similar but were different than high dose. Activity as pronamide was 66% at 100 mg/kg but was 21% at 2 mg/kg and in pulse. Metabolite 4 was 18% in the low and pulse doses but was 3% in the high dose. The level of metabolites in the low and pulse doses (% sample activity) was twice the level in the high dose feces. Although the metabolite levels in the low and pulse doses were twice the levels observed in the high dose feces, the actual ppm level of residues were significantly higher at the high dose. Metabolite profile in feces was similar over sex. Metabolite profile for feces was different from that of urine. Fecal metabolites were less polar, less highly oxidized known metabolites of pronamide. Overall no unknown component exceeded 4.2% of the dose, with 73 to 89% of the activity in feces

identified. Storage stability for feces extracts and urine showed that no degradation occurred on storage. Overall metabolic fate of pronamide in rat urine and feces has been identified and all major metabolites were identified. This study is not acceptable but is upgradeable upon submission of data from experiments C, D, G and H. No adverse effect. M. Silva, 9/11/02.

[Re-examination of Pronamide (Propyzamide) Metabolism Record No. 186210, previously designated by Dr. Silva as a valid supplementary study.] This re-examination identifies major residues in excreta following low dose levels of 14C-ring-labeled propyzamide. The sex of rats and the presence or absence of pre-treatment with unlabeled propyzamide did not affect disposition of a low labeled dose. As a result, data from the low dose male and female groups, with or without pre-treatment with unlabeled propyzamide, are considered here together. [High dose treatments, previously noted by Dr. Silva to lead to poor absorption (i.e. 66-68% of label found as unchanged propyzamide in feces) are not further discussed here]. Low-dose studies found 45-59% of residues in urine, compared to 34-39% in feces. In urine, a single metabolite accounted for roughly 15-19% of administered label: the 3,5-dichloro hippuric acid (designated in the report as metabolite 10 or Roman numeral X). This structure is consistent with cleavage of the original amide bond, followed by glycine conjugation. The next-most abundant urinary metabolite appears to have arisen in steps: first by a covalent bonding of the proximal alkyne carbon to the amide oxygen to form a 5-membered ring, leaving what was previously the distal alkyne carbon connected to the new ring with a double bond. Subsequent step-wise oxidation of that distal carbon to a carboxylic acid yielded a metabolite designated SS47-70, comprising 3-5% of administered label. Another 3-4% of administered dose (designated metabolite VIII) was determined by investigators to have derived (at least in part) from SS47-10. Metabolite VIII retained the general structure of parent propyzamide, except that the triple-bonded carbon pair was oxidized in a series of steps to the carboxylic acid. Most other urinary metabolites were intermediates between parent and metabolites SS47-10 or VIII. In urine, parent propyzamide represented only 0.1 to 0.2% of administered dose. In contrast, parent propyzamide was the largest component of fecal extracts (9-11% of administered dose). The two most common fecal metabolites identified were metabolite IV (alpha-hydroxyketone attached to the dimethyl carbon; comprising 7-8% of administered dose) and metabolite III (the alcohol precursor to SS47-70, comprising 4-6% of administered dose). Aldous, 3/23/16.

317-0125 247108 This is an exact copy of 317-089 186210, above.

317-0091 186212 Yih, R. Y. and Swithenbank, C., "Propyzamide: Identification of metabolites of N-(1,1-dimethylpropynyl)-3,5-dichlorobenzamide in rat and cow urine and rat feces," Agricultural and Food Chemistry 19 (2) pp. 320 ff., 1971. This is a Rohm and Haas published report which preceded the 1993 unpublished Rohm and Haas report (see Record No. 186210, above). It is apparent that the metabolic scheme used in 186210 derived mainly from earlier work such as Yih and Swithenbank. The most novel observation in the present record is that the dominant urinary metabolite in the cow is the α-hydroxyl carboxylic acid (metabolite XII in either of the two records), which appears to be only a transitory intermediate in the rat. No DPR worksheet. Aldous, 3/25/16.

317-0124 247107 Smith, S., "Rat Metabolism of ^{14}C-Pronamide," Rohm and Haas Company, Spring House, PA; 06/25/1991. Technical Report 34-91-43. Various metabolites were evaluated

from pooled urine samples of both sexes following gavage dosing of ^{14}C-propyzamide at high dose (100 mg/kg/day), low dose (2 mg/kg/day), and pulse groups (20 ppm unlabeled propyzamide in diet for 2 weeks, followed by a single labeled gavage dose of 2 mg/kg/day). The present study achieved a partial separation of metabolites, although not to the level of detail achieved in Record No. 186210, above. The primary additional information of this report is that low dose groups (included pulse groups) excreted about 7-10 times more label during day 1 as they did at day 2, indicating relatively rapid clearance. This clearance appeared to be general for all metabolites, allowing for considerable sample variability. In contrast, 100 mg/kg/day males and females displayed a plateau for days 1-2, with a reduction to less than 20% of peak levels by day 3. As this study provides only marginal information above what was already reviewed in Record No. 186210, there is no need for a worksheet on this record. Aldous, 3/25/16.

##317-0127 248152 "Pharmacokinetic Study in Rats," 02/21/1991. This volume is not currently available for DPR Data Review Group review. Since DPR Record No. 186210 adequately covers major metabolites, and Record No. 247107 generally assesses kinetics, it is unlikely that information from record 248152 be critical to understanding metabolism of propyzamide. Aldous, 3/25/16.

317-0091 186212 Yih, R. Y. and Swithenbank, C., "Propyzamide: Identification of metabolites of n-(1,1-dimethylpropynyl)-3,5-dichlorobenzamide in rat and cow urine and rat feces," Agricultural and Food Chemistry 19 (2) pp. 320 ff., 1971.

In summary, data from Record Nos. 186210 and 247107 collectively satisfy current requirements for an acceptable animal metabolism study. Aldous, 4/8/2016.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat **

**317-0147 293848 Gingrich, S. L. and J. R. Parno, "Kerb Technical - Acute Dermal Toxicity Study in Male and Female Rats," Rohm and Haas, Spring House, PA, 11/16/94. Laboratory Study # 94R-178. Six Crl:CD®BR rats/sex were dosed once by dermal application of 2.0 g/kg Kerb Technical (propyzamide), 95.7% a.i., Lot # 02525. This test article was moistened with distilled water (1 :1.5 w/v), then applied to shaved dorsal skin, and secured for 24 hours under a cuff, prior to cleansing the test site. LD50 > 2.0 g/kg (no deaths occurred). Clinical signs included red-stained fur around eyes for up to 6 days, and red-stained fur around muzzle for the duration of the study. This was attributed by investigators to testing methodology rather than to test article. Toxicity category: III. Study is acceptable. Aldous, 8/12/16.

Acute dermal toxicity **

**317-0147 293848 Gingrich, S. L. and J. R. Parno, "Kerb Technical - Acute Dermal Toxicity Study in Male and Female Rats," Rohm and Haas, Spring House, PA, 11/16/94. Laboratory Study # 94R-178. Six Crl:CD®BR rats/sex were dosed once by dermal application of 2.0 g/kg Kerb Technical (propyzamide), 95.7% a.i., Lot # 02525. This test article was moistened with distilled water (1 :1.5 w/v), then applied to shaved dorsal skin, and secured for 24 hours under a cuff, prior to cleansing the test site. LD50 > 2.0 g/kg (no deaths occurred). Clinical signs

included red-stained fur around eyes for up to 6 days, and red-stained fur around muzzle for the duration of the study. This was attributed by investigators to testing methodology rather than to test article. Toxicity category: III. Study is acceptable. Aldous, 8/12/16.

Acute inhalation toxicity, rat **

**317-0147 293843 Bernacki, H. J. and J. S. Ferguson, "Kerb Technical Acute Inhalation Toxicity Study in Rats," Rohm and Haas, Spring House, PA, 12/03/93. Laboratory Study # 94R-104. Six Crl:CD®BR rats/sex were exposed nose-only for 4 hours to 2.1 mg/L of Kerb Technical (propyzamide), 95.7% a.i., Lot # 02525. Exposure was via an air jet mill generator, achieving chamber concentration of 2.1 mg/L, with MMAD = 2.9 µm and GSD = 2.0. LC_{50} > 2.1 mg/L (no deaths at this dose). The only signs observed were passive behavior at 3 hrs post-exposure. No treatment-related lesions were reported at necropsy. Study is acceptable. Toxicity category: IV. Aldous, 8/15/16.

Primary eye irritation, rabbit **

**317-0147 293854 Gingrich, S. L. and J. R. Parno, "Kerb Technical - Eye Irritation Study in Rabbits," Rohm and Haas, Spring House, PA, 11/16/94. Laboratory Study # 94R-180. EPA MRID# 43583904. Six adult male New Zealand White rabbits were administered a single dose of 0.1 g of Kerb Technical (propyzamide), 95.7% a.i., Lot # 02525, instilled as supplied into one conjunctival sac per animal in a standard eye irritation study. Eyes were examined by penlight at 1, 24, 48, and 72 hours, enhanced by fluorescein at the 24-hr examination. Corneal and iris scores were uniformly 0. Conjunctival redness (grade 1), swelling (grade 1) and/or discharge (grades 1-2) were observed at 1 hour in all rabbits. At 24 hours, one rabbit exhibited grade 1 swelling and another had grade 1 redness. All eye irritation scores cleared by 48 hours. Toxicity category: IV. Acceptable study. Aldous, 8/15/16.

Primary dermal irritation **

**317-0147 293851 Gingrich, S. L. and J. R. Parno, "Kerb Technical - Skin Irritation Study in Rabbits," Rohm and Haas, Spring House, PA, 11/16/94. Laboratory Study # 94R-179. Six male New Zealand White rabbits received 0.5 g Kerb Technical (propyzamide), 95.7% a.i., Lot # 02525. Application was by dermal application to clipped, intact dorsal skin. Test article was moistened with 1 ml distilled water. Site was secured under a cuff for 4 hours and then cleansed. Skin irritation was assessed at 1, 24, 48, and 72 hours after end of dosing. Mean Draize scores at 1, 24, 48, and 72 hours were 0.7, 0.3, 0.3, and 0.2. All scores were due to erythema, never exceeding a score of 2 ("well defined") for any animal at any time. No edema was observed. Toxicity category: IV. Study is acceptable. Aldous, 8/11/16.

Dermal sensitization **

**317-0147 293856 Parno, J. S., D. M. Anderson and M. G. Kemmerer, "Kerb Technical Herbicide: Dermal Sensitization Study in Guinea Pigs: Maximization Test," Rohm and Haas, Spring House, PA, 02/07/2000. Laboratory Study # 99R-196. The primary treatment group (N = 20) of female Hartley guinea pigs received Kerb® Technical herbicide (93.9% purity) as follows: day 1 induction as an intradermal treatment with 0.1 ml of 1:1 Freund's Complete Adjuvant (FCA) in mineral oil at left and right anterior sites, 0.1 ml of a 15% concentration of propyzamide in mineral oil at paired medial sites, and 0.1 ml of 15% propyzamide in 1:1 Freund's Complete Adjuvant in mineral oil at posterior sites. All treatment areas received a topical treatment with 10% w/w sodium lauryl sulfate (SLS) in petrolatum on day 8. On day 9,

residual SLS was cleansed, and the groups received topical treatments corresponding to day 1 treatments over the previously-injected sites. Topical application was by saturated filter paper patches containing 0.4 g propyzamide in 0.4 ml sterile saline. Patches were secured in place for 48 hours prior to site cleansing. On day 22, propyzamide animals were again shaved, and received challenge treatment of 0.2 g propyzamide in 0.2 ml sterile saline at naïve sites, with dressings held for 24 hours prior to cleansing. One of the 20 propyzamide animals had erythema grade 1 (scattered mild redness) at 24 hours after challenge. Two of these propyzamide animals had erythema by 48 hours after challenge, in both cases grade 1. This is a negative response (i.e. ≤ 30% response rate). Controls were functional. Study is acceptable. Aldous, Aug. 15, 2016.

NOTE: 317-0146 293842 This is a CD with the same information that was reported in printed format under Document No. 317-0147, corresponding to the above acute studies.

SUBCHRONIC STUDIES

Oral toxicity, rat: **

**317-0134 273314, "Pronamide Technical (no clay): Three-Month Dietary Toxicity Study in Rats," (D. M. Anderson, *et al.*, Rohm and Haas Company, Toxicology Department, Spring House, PA., Report No. 88R-053, September 15, 1989). Ten Crl:CD® BR rats per sex per group received KERB™ Technical (96.4% pronamide) in the diet at 0 (basal diet), 40, 200, 1000, and 4000 ppm for 3 months. In a recovery phase, an additional 10 per sex per group received treated diet at 4000 ppm for 3 months then control diet for 1 month, and ten additional control animals per sex were necropsied after 4 months. Group mean achieved dosages of KERB™ Technical were 2.5, 12.3, 60.0, and 254.0 mg/kg/day for males and 3.1, 15.0, 74.6, and 289.2 mg/kg/day for females at 40, 200, 1000, and 4000 ppm, respectively. No treatment-related clinical signs were recorded at any treatment level during the 3-month dietary phase or the 1-month recovery phase. At 1000 ppm, one female was found dead during treatment week 3, and 1 male was sacrificed moribund during treatment week 13. Group mean bodyweight and food consumption was significantly reduced for females at 1000 ppm and for males and females at 4000 ppm during the 13-week treatment period vs controls. Following the 3-month treatment period, group mean serum clinical chemistry results included significant increases for glutamic oxaloacetic transaminase activity and alkaline phosphatase activity in high dose males; for cholesterol and total protein in 1000 ppm males and high dose males and females; for albumin in high dose males and females; and for globulins, triglycerides, and urea nitrogen in high dose females (note that triglycerides for high dose males were significantly decreased) vs controls. At the end of the 3-month treatment period, significant increases in group mean values were noted for relative liver and kidney weights in both sexes at 1000 and 4000 ppm (absolute liver weights were also significantly increased in both sexes at 4000 ppm); for relative adrenal weights in both sexes at 4000 ppm and in females at 1000 ppm; for relative brain weights in both sexes at 4000 ppm and in males at 1000 ppm; and for relative testes weights in males at 4000 ppm vs controls. Treatment-related histology included centrilobular hepatocyte hypertrophy in the liver at 1000 ppm (7/10 males and females (minimal severity)) and 4000 ppm (all males (slight to moderate severity) and all females (minimal to slight severity)) along with minimal amounts of focal or multifocal dark brown pigment in bile ducts of high dose males (5/10) (the pigment was negative for bilirubin) vs controls (0/10 for both findings). An increased incidence of hypertrophy of the zona glomerulosa of the adrenal glands was noted in both sexes at 1000 ppm (minimal severity)

and 4000 ppm (minimal to slight severity) vs control, the incidence was 2/10, 1/10, 2/10, 6/10, and 10/10 for males and 0/10, 0/10, 1/10, 4/10, and 9/10 for females at 0, 40, 200, 1000, and 4000 ppm, respectively. Minimal to slight hypertrophy of individual cells in the adenohypophysis of the pituitary was noted in males at 1000 ppm (8/10) and 4000 ppm (10/10) vs controls (the finding (minimal severity) was also noted in 5/10 males at 0, 40, and 200 ppm). The incidence of hypertrophy of the follicular epithelium of the thyroid was increased in both sexes at 4000 ppm vs controls, the incidence was 2/10, 2/10, 5/10, 4/10, and 10/10 for males and 0/10, 1/10, 0/10, 2/10, and 7/10 for females at 0, 40, 200, 1000, and 4000 ppm, respectively (the severity was minimal to slight at 4000 ppm and minimal for all other groups). Minimal to slight increased numbers of zymogen granules were noted in peri-insular acini of the pancreas in 7/10 males and 4/10 females at 4000 ppm vs 0/10 or 1/10 for the other groups (0/10 for the controls of both sexes). NOEL = 200 ppm (12.3 mg/kg/day for males and 15.0 mg/kg/day for females) based on liver weight and histology. No adverse effect. Acceptable. (Green, 11/25/13).

317-011; 961140; "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Rats for a Period of Three Months"; (J.F. Borzelleca and P.S. Larson; Department of Pharmacology, Medical College of Virginia; no Study No.; 11/27/67); Ten CD strain rats/sex/group were fed in the diet 0, 50, 150, 450, 1350, or 4050 ppm of RH-315 (lot no. WDW 10:75, purity assumed to be 100%) for 13 weeks. One female in the 1350 ppm treatment group died during the 13th week. The mean body weights for the 4050 ppm group were less than those of the controls (males for weeks 1 and 2, females, week 1 through week 13, $p<0.05$). Although the hematocrit and hemoglobin values for the 4050 ppm females were less than those of the controls at 4 and 13 weeks, the values were within a reasonable physiologic range. The mean absolute and relative liver weights for the 150 ppm females and above are significantly greater than those values for the controls ($p<0.05$). The relative liver weight for the 4050 ppm males is greater than that of the controls ($p<0.05$). The mean absolute and relative testes weights of the 4050 ppm group are greater than that of the controls ($p<0.05$). There were no treatment-related lesions noted in the histopathology examination. **No adverse effect indicated. Data are insufficient to establish a NOEL. Study unacceptable,** not upgradeable (numerous deficiencies in regard to analysis of dietary preparations, parameters not evaluated and individual animal not presented in the report). (Moore, 8/8/01)

Oral toxicity, non-rodent:

No acceptable study on file.

Dermal toxicity, 21/28-day or 90-day: **

**317-0131 271018, "Pronamide Technical: 28-Day Dermal Toxicity Study in F344/DuCrl Rats," (B.L. Yano and M.D. Dryzga, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI., Study ID: 051127, December 1, 2005). Ten F344/DuCrl rats per sex per group were dermally treated (clipped, intact, semi-occluded skin) with pronamide technical (95.9%) at 0 (0.5% aqueous methylcellulose), 100, 500, and 1000 mg/kg/day 6 hours per day, 7 days per week for 28 days. All animals survived to scheduled necropsy. One high dose male had slight scaling at the treatment site on test days 22 and 29. Group mean bodyweight for mid and high dose males was significantly reduced on test days 22 and 28 compared to controls. At study termination, mean bodyweights for mid and high dose males were 10.2% and 12.0% lower than controls respectively, and bodyweight gains were

40.0% and 45.4% lower than controls respectively. Group mean bodyweights for mid and high dose females were consistently lower than controls during the study (but were not statistically different) and were within the historical control ranges. Since concurrent control female bodyweights were frequently at the high end of or outside of the historical control ranges, the bodyweight differences were considered inconclusive and not treatment related. Male and female bodyweights and bodyweight gains at 100 mg/kg/day were comparable to controls. Group mean food consumption for mid and high dose males was lower than controls throughout the study with statistical significance for test days 8 to 15 (high dose only), 15 to 22, and 22 to 28 compared to controls. Food consumption values for low dose males and low, mid, and high dose females were comparable to controls. Histology results included very slight epidermal hyperplasia at the test site in 4, 4, 5, and 3 males and 1, 2, 1, and 4 females at 0, 100, 500, and 1000 mg/kg/day respectively, and slight epidermal hyperplasia at the test site in 1, 0, 1, and 7 males and 0, 0, 0, 0 and 0 females respectively. The hyperplasia was of minimal severity and consisted of very slight (2 to 3 cell layers thick) to slight (4 to 5 cell layer thick) thickening of the epidermis. Additionally, very slight, subacute to chronic inflammation (small numbers of neutrophils admixed with occasional lymphocytes in the superficial dermis) that was multifocal in distribution was noted in 4 males and 5 females at 1000 mg/kg/day. There were no microscopic effects noted in any tissues indicative of systemic toxicity. Systemic NOEL = 100 mg/kg/day for males based on bodyweight and = 1000 mg/kg/day for females. Dermal NOEL = 500 mg/kg/day for males based on slight dermal scaling and = 1000 mg/kg/day for females. No adverse effect. Acceptable. (Green, 9/18/14).

317-011; 961146; "Subchronic Percutaneous Toxicity of RH-315 WP in Albino Rabbits (Abraded Skin)"; (P.S. Larson and J.F. Borzelleca; Department of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University; No study no.; 4/7/70); The abraded skin of 5 New Zealand White rabbits/sex/group was treated with 0, 2.0 or 4.0 g/kg of RH-315 WP (lot no. SW 69/0610, a.i.: 75%) for 6 hours/day, 5 days/week for 4 weeks under an occlusive wrap. The test material was moistened with water into a paste prior to being applied. Additional five animals/sex/group were treated in the same manner with 0, 0.5, or 1.0 g/kg of the test material for 9 weeks. In the initial treatment, one male in the control group, two males each in the 2.0 and 4.0 g/kg groups and two females in the 2.0 and 3 females in the 4.0 g/kg groups died. Due to the high mortality, the study was discontinued and the lower dosing levels employed. Reduced mean body weight gain was exhibited by females in both the 2.0 and 4.0 g/kg groups ($p<0.05$). There were no treatment-related effects noted from the hematology and urinalysis data. The mean relative liver and kidney weights were increased for the 1.0 g/kg females. There were no apparent treatment-related lesions noted in the histopathology examination. **No adverse effect indicated. NOEL: data insufficient to establish a NOEL**. **Study unacceptable,** not upgradeable (clinical chemistry was not performed, particular hematological parameters were not evaluated). (Moore, 8/9/01)

CHRONIC STUDIES

Combined, rat ** †

NOTE: The combined, rat study was performed in two separate phases (chronic and oncogenicity) which were submitted as two studies (060/091888 & 061/091889). Together, the two submissions satisfy the combined rat data requirements (see combined, rat, below).

317-0025 036797, "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Albino Rats (Two-Year Feeding Study)", (Depart. of Pharmacology, Medical College of Virginia, 6/11/70), combined-835-rat; RH-315, lot no. SW-68-0261, analytical purity 97%, fed in the diet, 30/sex/group, for two years at 0, 30, 100, or 300 ppm; 5/sex/group sacrificed at 6 months for histopathology. No adverse effects reported. NOEL > 300 ppm. UNACCEPTABLE, not upgradable (inadequate number of animals per group, no justification of dose with no NOEL clearly established, no analysis of dose in diet, no tabulation of histopathology, no clinical observations) (Van Way, Remsen (Gee) 11/25/85).

011 961150 Abbreviated version of 036797; (Oshita, Wong, 4/19/85).

317-0060 091888 "Kerb* Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats", 12-Month Chronic Toxicity Phase, (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426S, 10/15/90). Kerb* (Technical, no clay, purity = 96.4%) was fed to Charles River rats (Crl:CDBR VAF/PLUS, 20/sex/group) at concentrations of 25, 100, or 400 ppm for the first 2 weeks, then increased to 35, 140, 560 ppm for weeks 3 and 4 and finally adjusted to 40, 200, or 1000 ppm for weeks 5 through week 52. Ten rats/sex/group were terminated at 26 weeks, while the remaining 10/sex/group were treated for 52 weeks. NOEL = 200 ppm (An increase in ketones was observed in males at 1000 ppm. Increased liver/body weight % in both sexes and kidney in males at 1000 ppm. Increased thyroid/parathyroid/brain weight % in females at 1000 ppm. Increased incidence of liver centrilobular hypertrophy in both sexes at 1000 ppm and increased incidence in follicular cell hypertrophy in thyroid in both sexes at 6 months and in females at 12 months at 1000 ppm. B-Follicular cell adenomas were observed in 1 female at 6 months and 1 male at 12 months at 1000 ppm.) Not acceptable as a chronic study. It is only acceptable when combined with data from the rat oncogenicity study 061/091889. Kishiyama & Silva, 3/11/92.

**** 061, 081 091889, 131700** "Kerb* Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats", 24-Month Oncogenicity Phase, (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426M, 11/2/90). Kerb* (Technical, no clay, purity = 96.4%) was fed in diet to Charles River Crl:CD*BR VAF/PLUS rats (60/sex/dose) at 0 (vehicle = acetone), 25, 100, or 400 ppm for the first 2 weeks, then increased to 35, 140, 560 ppm for weeks 3-4 and finally to 40, 200, or 1000 ppm weeks 5-105 or 106. Chronic NOEL = 200 ppm/day (Decreased body weight primarily in females and increased relative liver weight in females at 1000 ppm.) Oncogenicity NOEL = 200 (Testes showed increased gross pathology and benign interstitial cell tumors at 1000 ppm. Sertoliform tubular hyperplasia and sertoliform tubular adenomas were observed in ovaries at 1000 ppm. Both sexes had increased centrilobular hypertrophy and eosinophilic alterations in liver and males had increased hepatocellular adenoma and carcinoma at 1000 ppm. Thyroid effects were follicular

cell adenoma in both sexes and follicular hyperplasia in females at 1000 ppm.) Acceptable. M. Silva, 6/2/95.

058 091885 & 091886 The discussion in this volume refers to the combined (chronic and oncogenicity) study: "Kerb* Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats", (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426M, 11/2/90). 058/091885 "Perspective on the Increased Incidences of Thyroid and Testicular Tumors Produced by Kerb Herbicide in Rats," states why the registrant believes the increased incidence of adenomas in the rat chronic study occurred by an indirect, non-genotoxic mechanism. Document 058/091886 is a letter from Rohm & Haas Company to EPA which included incidence data for the control and treated groups from the combined study (091888 & 091889) along with historical controls from the laboratory conducting the study. Included in both documents is risk assessment information. These data are supplemental. M. Silva, 3/16/92.

063 089234 "Kerb* Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats," Supplement - Histopathology Photomicrographs - 87RC-062K, (Kulwich, B.A. and Harris, J.C., Hazleton Laboratories America, Inc., Vienna, VA, 2/4/91). This volume contains photomicrographs of histopathology from thyroid, liver, testes and ovary from study 091889. No worksheet. M. Silva, 3/17/92.

317-0072 118047 Historical data were submitted by the registrant 7/11/92 to state that the hepatocellular carcinomas and adenomas in study 061/091889 were incidental and not related to propyzamide administration. DPR maintains that the lesions are compound-related in light of the tumors and related effects in liver that occur in most, if not all chronic and subchronic studies in more than one species. M. Silva, 2/24/94.

Chronic, dog **

** 317-0062 089232, "Pronamide (Kerb* Technical Herbicide): 52 Week Oral (Dietary) Toxicity Study in the Beagle Dog", (J.P. Briffaux, Hazleton France (HF), HF Study No. 616/503, 2/20/91). Pronamide (Kerb* herbicide; technical), purity = 96.8%, was administered in the feed at concentrations of 0, 300, 875, or 1750 ppm to 6 Beagle dogs/sex/group for 52 weeks. NOEL = 300 ppm/12 mg/kg/day (Body weights at 1750 ppm were significantly lower than control in both sexes. Food consumption was also decreased throughout most of the study in both sexes. Platelet counts were significantly increased at 1750 ppm in females. Alkaline phosphatase, gamma glutamyl transpeptidase and alanine aminotransferase (females only) were significantly increased at 1750 ppm. Serum albumin was significantly decreased in both sexes at 1750 ppm. Adrenal weights, absolute & relative to brain weight--females and relative to body weight--both sexes were significantly increased at 1750 ppm. Liver weights absolute & relative to brain weight--females and relative to body weight--both sexes were increased at $\geq$ 875 ppm. Both sexes had liver histopathology at $\geq$ 875 ppm and kidney histopathology at 1750 ppm. (Kishiyama & Silva, 3/2/92).

066 111520 "Pronamide (Kerb* Technical Herbicide): 52 Week Oral (Dietary) Toxicity Study in the Beagle Dog," (Y. Guichard, Study Pathologist, Hazleton France (no date). This volume contains photomicrographs of liver and kidney histopathology from study 089232. The data are supplemental (no worksheet). M. Silva, 3/17/92.

062 089233. Range-finding Study for 089232. "Kerb* Herbicide - 4 Week Oral (Dietary Administration) Toxicity Study in the Beagle Dog", (J.P. Briffaux, Hazleton France (HF), HF Study No. 616/502, 2/11/91). Pronamide (Kerb* herbicide; technical), purity = 96.8% was administered in the feed at concentrations of 0, 1250, 2500 or 5000 ppm to 2 Beagle dogs/sex/group for 4 weeks. NOEL < 1250 ppm/day (Thymus weights, both absolute and relative, were decreased in both sexes at all doses. Relative liver weights were increased in both sexes at ≥ 2500 ppm. There was also decreased body weight and food consumption at ≥ 2500 ppm. Some clinical chemistry and hematological effects were observed at 5000 ppm.) This was range-finding for the definitive chronic dog study DPR # 089232). (Kishiyama & Silva, 2/25/92).

024, 046 036796, 066119, "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Beagle Dogs (Two-Year Feeding Study)," (Department of Pharmacology, Medical College of Virginia, 6/13/68). FH-315 (lot no. SW-68-0261; purity = 97%) was fed in the diet at 0, 30, 100 or 300 ppm (4/sex/group) for 104 weeks (1/sex/group was sacrificed at 52 weeks). No adverse effect indicated. NOEL > 300 ppm (no significant effects were observed at any dose). This study was originally reviewed as unacceptable by J. Gee, 11/25/85 since it lacked an MTD (dose justification), an analysis of dose in the diet, clinical observations and a tabulation of histopathology. An analysis of dose in the diet as well as information on stability, homogeneity and concentration verification was received by CDFA (Volume/record#: 046 066119) and found to be acceptable. The study remains UNACCEPTABLE, however, since there was no acceptable dose justification and no ophthalmological exam included in the report. The study is not upgradeable. (M. Silva, 9/28/88)

046 066119, This volume contains information about preparation of propyzamide in the diet as well as information on its stability, homogeneity and concentration in feed. It also contains information on the analysis of propyzamide technical.

317-0011 961143 "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Beagle Dogs For a Period of Three Months," (Department of Pharmacology, Medical College of Virginia, 1967). Propyzamide technical (RH-315, Lot no. WDW 10:75, purity = 100%) was administered in diet to beagle dogs (1/sex/group) for three months at 0, 450, 1350 and 4050 ppm. No adverse effect indicated. NOEL = 1350 (A decrease in weight gain, elevation in serum alkaline phosphatase and enlarged livers was observed in both sexes). There was no mortality nor were there hematological, urinalysis or histopathologic effects observed. This subchronic study is supplementary to 024 036796**.** (M. Silva, 9/29/88)

011 961152, Abbreviated version of 036796; (Oshita, Wong, 4/18/85).

Oncogenicity, mouse ** †

**00317-0113 215467 Stebbins, K. E. and K. J. Brooks, "Pronamide (Propyzamide): 18-Month Oncogenicity Study in Cd-1 Mice (3 Parts)," Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, 11/22/04. Pronamide (95.9% pure) was fed in diet to CD-1 mice (50/sex/dose) at 0 (diet only), 5, 50, and 250 mg/kg/day for 18 months to evaluate the potential for oncogenicity. Concentrations were adjusted periodically to maintain

doses for males and females. Actual intake was close to nominal. Systemic NOEL = 5 mg/kg/day (there were slight decreases in body weights in both sexes at 250 mg/kg/day). Increased absolute and relative spleen and adrenal weights at 250 mg/kg/day (M), absolute and relative liver weight gains at ≥ 50 mg/kg/day (both sexes), and absolute and relative kidney weights at ≥ 50 mg/kg/day (F) were observed. Gross effects on liver in both sexes, in kidneys (F) and in skin and subcutis (M) were observed at 250 mg/kg/day. Decreased amount of fat was observed at ≥ 50 mg/kg/day in females. There were non-neoplastic histopathological effects in livers of males at ≥ 50 mg/kg/day and in females at 250 mg/kg/day. There were non-histopathological effects observed in gallbladder, adrenal glands, heart, and lungs of both sexes at 250 mg/kg/day and in lungs of females and salivary glands of males at 250 mg/kg/day. Possible adverse effect: there was an increased incidence in both hepatocytic adenomas and carcinomas at 250 mg/kg/day. Acceptable. Silva, 1/31/05.

026 036798, "Eighteen Month Study on the Carcinogenic Potential of Kerb (RH-315) in Mice (31-78 Week Period)", (Depart. of Pharmacology, Medical College of Virginia, 8/30/74), Kerb Technical (batch SW 71/0225, 97% active ingredient); 125/sex/group fed 0, 1000, or 2000 ppm in diet for 78 weeks; positive controls DEN and AAF. **Adverse effect** indicated: increased incidence of liver neoplasms in males at 1000 and 2000 ppm. NOEL < 1000 ppm. UNACCEPTABLE (only 2 dose levels, no analysis of dosing material, very limited histopathology) (Van Way, Remsen (Gee) 11/25/85) Rebuttal information, 12-3-86, justifies dosage, but does not change status; histopathology still deficient. (J. Carlisle, 8-6-87)

011 916157; This is a 30 week interim report on 036798 (Oshita, Wong 4/18/85) **027 036799**, "Kerb: Chronic Toxicity Study in the Mouse", (MIT Animal Pathology Laboratory, Cambridge, MA., # 81RC-157, 8/10/82), combined-835-mouse, technical grade Kerb 95-99%, lot no. 3874, fed in the diet to 42 males/group at 0 or 2500 ppm for 6 months; at 0, 20, 100, 500, or 2500 ppm to 42 males/group for 15 or 18 months and to 63 males/group for 24 months. **Adverse effects**: liver changes and oncogenicity reported. NOEL = 20 ppm. UNACCEPTABLE and not upgradable (deficiencies: use of male mice only, nominal versus analytical concentrations in diet) (Van Way, Remsen 11/25/85; Rebuttal information, 12-3-86, clarifies purpose of study, but does not change status; J. Carlisle, 8-6-87).

Conclusion: Although neither combined mouse study is acceptable, together they adequately address the issue of oncogenicity in mice, and fill the oncogenicity data gap. They do not qualify as combined studies although they provide useful chronic toxicity information. (J. Carlisle, 8-6-87)

GENOTOXICITY

Bacterial reverse mutation assay **

Records 036805 and 51357 were not individually accepted, primarily due to lack of repeat trials. Since each study was otherwise valid, the two studies collectively address the data requirement. Aldous, 4/8/16.

317-0031 036805, "Mutagenicity of Kerb (propyzamide) in Bacteria", (Japan Institute of Environmental Toxicology, 8/10/78), mutagenicity-842-Salmonella typhimurium and

Escherichia coli, Kerb (propyzamide) 93.7%; dissolved in DMSO; reversion assay with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100 and Escherichia coli WP2 hcr, 2 replicates, at 0, 10, 50, 100, 500, 1000, or 5000 µg/plate; with/without S9 rat liver fraction (Aroclor induced) activation; positive controls 2AA, AF-2, 2-nitrofluorene, beta-propiolactone, and 9-aminoacridine. No mutagenicity reported. UNACCEPTABLE and not upgradable (no repeat trial to verify findings). (Van Way, Remsen (Gee) 11/22/85).

034 51357, "Mutagenic Evaluation of Compound RH-315", (Litton Bionetics, Kensington, MD., # 2547, 8/29/75), RH-315, no purity stated; plate assay at 1, 10, 100, 500, or 1000 µg/plate with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, or TA-100, with/without S9 mouse liver (Aroclor induced) activation; positive control with activation - DMNA, AAF, or DMBA, without activation - EMS, NF, or QM. Due to high cytotoxicity, data was not collected from the 1000 µg/plate group. No mutagenic activity reported. UNACCEPTABLE (no analysis of test solutions, no confirming trial). (Carlisle 7/13/87).

Mutagenicity: In vitro mammalian cell assay **

** 317-0031 036807, "Gene Mutation in Chinese Hamster V79 Cells", (Life Science Research Roma Toxicology Centre, Rome, Italy, # 107001-M-02884, 10/29/84), Kerb Technical (no clay) 95.5-96.3%, lot no. 2-0801, TD no. 83-144; tested in 1% DMSO at 0, 2.5, 5, 10, 20, or 40 µg/ml with Chinese hamster V79 cells for HGPRT locus mutation with/without S9 rat liver (phenobarbitone and betanaphthoflavone induced) activation; 3 replicates; positive control +S9 = DMN, -S9 = EMS; cells were exposed for 3 hours. Expression times of 48, 96, and 168 hours. No increase in mutation frequency reported. ACCEPTABLE. (Van Way, Remsen (Gee) 11/25/85).

Mutagenicity: In vivo cytogenetics **

317-011 961161, "Final Report, Cytogenetic Study, Kerb Technical" (Litton Bionetics, # 2380, 4/16/73), Kerb Technical, no purity stated, in methocel fed in the diet or dosed by intubation at 0, 5, 50, or 500 mg/kg, single dose daily for 5 days; 5 males/group; positive control TEM; sampled at 5 days, examined 250 cells/dose; no chromosomal aberrations reported. UNACCEPTABLE and not upgradable (no analysis of test article nor dosing solution, only 5 animals of one sex used, criteria for scoring aberrations not apparent, no individual data, no quality assurance) (Oshita, Wong 4/22/85).

011 961159, "Final Report, Cytogenetic Study, Kerb Analytical", (Litton Bionetics, Inc., # 2381, 4/16/73), chromosome-843-rat; Kerb analytical, no purity stated; in 0.5% methocel administered by gavage or fed in the diet at 0, 5, 50, or 500 mg/kg/day, 5 males/group; single daily dose for 5 days; positive control - TEM; sacrificed at 5 days, 250 cells/dose (200 cells in high dose due to 1 death). No chromosomal aberrations reported. UNACCEPTABLE and not upgradable (used analytical grade, no test article purity stated, no dose justification, used only males and only 5 animals per dose, not clear which animals received which dosing method, no individual animal/chromosome data). (Green, Gee 8/6/87).

** 317-0031 036806, "Kerb In Vivo Cytogenetic Study in Mice", (Rohm and Haas Co., Toxicology Department, Spring House, PA., # 84R-112, 10/31/85), Kerb technical (no clay) TD

83-144, 96.8% a.i., lot no. 2-0801; in 0.5% methylcellulose given in a single peroral dose or for 5 consecutive days intraperitoneally at 0, 0.48, 1.94, or 4.84 g/kg; 30 male mice/single dose group, 10 male mice/5 day group; TEM as positive control; sampled 10 animals/single dose group at 6, 24, and 48 hours, all animals/5 day group (except high-dose group due to excessive mortality) at 6 hours. No adverse effects reported. NOEL ~ 0.48 g/kg for clinical observations. Initially unacceptable (Van Way, Remsen (Gee) 11/22/85) (used only male mice, did not analyze dosing solution until 35 days later when found 62-77% of theoretical). Re-reviewed by J. Carlisle, 7/14/87. Information in 051358 allows upgrade to ACCEPTABLE with no adverse effects.

034 051358, Provides report on analysis of dosing materials, acute toxicology information for Kerb Flowable Herbicide, and explanations in response to the deficiencies found in the original review of 031 036806, by J. Gee, 11/22/85.

031 036804, "Mutagenicity of Kerb (Propyzamide) in Bacteria", (Japan Institute of Environmental Toxicology, 8/10/78), mutagenicity-844-Bacillus subtilis, Kerb (Propyzamide) 93.7%; dissolved in DMSO; recombination assay with Bacillus subtilis M45 (Rec^-) and H17 (Rec^+) at 0, 20, 100, 200, 500, 1000, or 2000 µg/disk, negative control-Kanamycin, positive control-Mitomycin C. No **selective inhibition of the rec^-** strain reported. UNACCEPTABLE, not upgradable (deficiencies: maximum of 2000 µg/disk with no rationale for not going higher, no activation series, and no repeat trial). (Van Way, Remsen (Gee) 11/22/85).

** 317-0047 071734, "Kerb* Technical <u>In</u> <u>Vitro</u> Unscheduled DNA Synthesis Assay", (Muller, G. and Frank, J.P., Rohm and Haas Company, Toxicology Department, Spring House, PA., report No. 86R-185, 2/11/87). Kerb* (propyzamide) technical (94.2% pure, lot # 4859) was used in a 19 hour-exposure of primary rat hepatocytes (3 replicates/group) at 0.1, 0.5, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0, and 500.0 µg/ml for UDS determination (autoradiography, 50 cells scored/replicate and 150 total cells/dose were scored). Reduced cell survival at 100.0 and 500.0 µg/ml (48% and 40% of solvent control values respectively) was observed. No UDS effect. ACCEPTABLE. (H. Green & M. Silva, 8/27/90).

317-0094 186215 Kumaroo, P. V., "Propyzamide: RH-7988 - Test for chemical induction of chromosome aberration using monolayer cultures of Chinese hamster ovary (CHO) cells with and without metabolic activation," 2/26/87. SITEK Study No. 0046-3100. This report was submitted to DPR by Dow AgroSciences, which did not commission the original study. Submission was in response to a DPR request for SITEK Study No. 0046-3100. The test article was evidently RH-7988, a Rohm and Haas product that is neither structurally nor functionally related to propyzamide. This report [SITEK Study No. 0046-3100] was reviewed as an RH-7988 (Triazamate) study, and was accepted and negative in any case. The DPR review for this study is found in the Triazamate files as DPR Document No. 52610-062, Record No. 170848. No further action is needed. Aldous, 3/25/16.

REPRODUCTIVE TOXICITY, RAT **

** 317-059, -072, -081 091887, 118046, 131699 "Pronamide: Two-Generation Reproduction Study in Rats", (H.M. Solomon & W.R. Brown, Rohm & Haas Company, Toxicology Dept., Report No. 88R-257, 6/14/90). "Additional Data to Two Generation Reproduction Study in Rats," (O'Hara, G.P., Rohm & Haas Company, no date). "Pronamide: Two Generation

Reproduction Study in Rats (88R-257): California Review of Final Report and Supplemental Data." Pronamide/propyzamide (Kerb* Technical, purity = 93.1%) was incorporated in the feed at concentrations of 0, 40, 200 or 1500 ppm and fed to 25 mated female Charles River Crl: CD*BR P1 and P2 rats/group (20 females in the P2 generation in the 40 ppm group). P1 rats received treated feed when approximately 42 days old and throughout premating (minimum of 10 weeks), mating, gestation and lactation. P2 rats received treated food after weaning (minimum of 15 weeks), throughout mating, gestation, and lactation. Reproductive NOEL > 1500 ppm (No reproductive effects observed at any dose). Parental NOEL = 200 ppm (Both generations showed decreased body weights and food consumption during premating--both sexes, as well as during gestation and lactation--females at 1500 ppm. Both sexes of both generations showed an increase in hypertrophy of centrilobular hepatocytes, follicular cell hypertrophy in thyroid and hypertrophy of zona glomerulosa cells in the adrenal gland at 1500 ppm.) Pup NOEL = 200 ppm (F1 pups showed a significant decrease in body weight on day 1 post-partum.) Originally unacceptable (Silva, 3/6/92 & 2/22/94), however, after submission and review of the requested data, the study is now acceptable. M. Silva, 5/30/95.

028 036800, "Three Generation Reproduction Study on Rats Receiving RH-315 in Their Diet", (Depart. of Pharmacology, Medical College of Virginia, 4/10/70), RH-315 97% purity, lot no. SW-68-0261; 20/sex/group were fed in the diet 0, 30, 100, or 300 ppm over 3 generations, 2 litters/generation. No adverse effects are reported. NOEL > 300 ppm. UNACCEPTABLE and not upgradable (no analysis of diet for actual amount, no food consumption data, no justification of dose, incomplete histopathology, no MTD, fewer than 20 pregnant animals per group, no clinical observations). (Van Way, Remsen (Gee) 1/10/86).

034 051356, Additional information and/or explanations to support 028 036800, including test article characterization, individual animal data and dose selection criteria in response to deficiencies found in the initial review by J. Gee 1/10/86. Re-reviewed by J. Carlisle, 7/14/87. The Additional information led to no change in status.

011 961155, This is an abbreviated version of 036800 (Oshita, Wong 4/18/85).

DEVELOPMENTAL TOXICITY

Rat **

** 317-0052 075559, "Kerb* Herbicide: Oral (Gavage) Developmental Toxicity Study in Rats", (Solomon, H.M. and Holtz, J.W., Jr., Rohm and Haas Company, Toxicology Department, Spring House, PA., report # 87R-003, 7/10/87). Kerb* (propyzamide, 94.2% pure, lot 4859) was administered on days 6 through 15 of gestation (day 0 = detection of sperm plug) by gavage at 0 (vehicle = aqueous methylcellulose), 5, 20, 80, and 160 mg/kg/day to mated Crl:CD*BR female rats (25/group). No adverse effect. Maternal NOEL = 20 mg/kg/day (A reduced maternal body weight gain was reported at 80 and 160 mg/kg/day). Developmental NOEL $\geq$ 160 mg/kg/day (no effects were observed at any dose). ACCEPTABLE. (H. Green & M. Silva, 8/29/90).

317-0029 036801, "Effects of RH315 on the Fetal Development in Rats", (Food and Drug Research Laboratories Inc., Maspeth, N.Y., # 0512, 10/22/71), Kerb Technical Ref. SW-0225, no purity stated; in corn oil administered by gavage to 26 pregnant females/group at 0, 150, or 300

ppm from day 6 through 16 of gestation; Caesarean sections performed on day 20. No maternal or developmental adverse effects reported. UNACCEPTABLE and not upgradable (only 2 dose levels, no individual fetal data, no necropsy or clinical findings given, no analysis of dosing suspension) (VanWay, Parker 12/9/85)

Rabbit **

Range finding Study:
317 - 030 036802 "Range finding Teratology Study with Kerb in Rabbits," (Costlow, R.D., Kane, W.W.; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report #: 83R-025; Protocol #: 83P-063; 5/24/85). Propyzamide (Kerb, 96.8% pure) was administered by oral gavage to artificially inseminated New Zealand White rabbits (6/dose) at 0 (0.5% methylcellulose), 10, 31.6, 100, 215, 464 and 1000 mg/kg (limit test) during days 7 - 19 of gestation. Maternal NOEL = 10 mg/kg (At 100 and 215 mg/kg, mottled/congested liver and reddened gastric mucosa were observed. Abortions were treatment-related, secondary to maternal toxicity but not a direct effect on the conceptus (though a concomitant primary embryotoxic effect cannot be discounted according to the report) at 100 and 215 mg/kg. Abortions were not increased at 464 and 1000 mg/kg, since high maternal toxicity killed does before they could abort. Does at ≥ 215 mg/kg, had increased clinical signs (irregular feces, urine stained fur, red urine, anuria, soiled anal area, passiveness, ataxia, lethargy/prostration, discharge from nose/eyes, diarrhea, salivation). Body weights were significantly decreased from day 11 - 29 at ≥100 mg/kg. At ≥ 100 mg/kg, does had an increased incidence in periportal to midzonal punctate vacuolization, individual hepatocellular necrosis, pigmentation of Kupffer cells, periportal - midzonal hypertrophy, increased eosinophilia and cloudy swelling of hepatocytes. One doe at 31.6 mg/kg had periportal punctate vacuolization.) Developmental NOEL = 31.6 mg/kg (**Possible adverse effect:** There was an increased incidence in resorptions at ≥ 100 mg/kg. The report considered propyzamide to be embryo-fetotoxic at ≥ 100 mg/kg.) These data are supplemental. Parker, 12/10/85 and Silva, 11/8/01.

Definitive Study:
** 317 - 030 036803 "Teratology Study with Kerb Technical (No Clay) in Rabbits," (Costlow, R.D., Kane, W.W.; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report #: 83R-026; Protocol #: 83P-064; 6/4/85). Propyzamide (Kerb, 96.8% pure) was administered by oral gavage to artificially inseminated New Zealand White rabbits (18/dose) at 0 (0.5% methylcellulose), 5, 20 and 80 mg/kg during days 7 - 19 of gestation. The study was previously reviewed (Parker, 12/10/85) with a Maternal NOEL = 5 mg/kg and a Developmental NOEL > 80 mg/kg. Upon re-evaluation of developmental effects, the maternal NOEL remains at 5 mg/kg (At ≥ 20 mg/kg there was an increase in irregular feces, anorexia, red or white precipitate in the urine, blood and/or aborted material in the drop pan and hunched appearance. The drop in soiled anal area at 80 mg/kg was attributed to anorexia. Maternal body weights (days 11 - 20) and body weight gains (day 7 - 20) were significantly decreased at 80 mg/kg. Absolute and relative liver weights were increased at 80 mg/kg. There was an increased incidence in late resorptions that went along with abortions at 80 mg/kg. At 80 mg/kg increased incidence in punctate vacuolated hepatocytes, swollen hepatocytes, hepatocellular necrosis, pigmentation of Kupffer cells and hepatocytes and eosinophilic hepatocytes occurred. At 80 mg/kg does with liver lesions were generally those that died prior to day 29 or those that aborted

and were killed prior to day 29. Grossly mottled or dark liver corresponded to moderate or severe liver lesions in 5/5 cases at 80 mg/kg. In 3/13 livers which were grossly normal there were moderate or severe liver lesions.) The developmental NOEL, depending on how abortions and resorptions are interpreted may be considered to be 20 mg/kg (There was an increased incidence in late resorptions that went along with abortions at 80 mg/kg. There is no evidence to show that these effects are due to maternal toxicity or to direct embryo/fetotoxicity.) The study remains acceptable. Parker, 12/10/85 and Silva, 11/9/01

NEUROTOXICITY

Acute neurotoxicity, rat **

**317-0133 273313, "Pronamide: Acute Neurotoxicity Study in F344/DuCrl Rats," (A. K. Andrus and R. R. Hukkanen, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI., Study ID: 101164, 7 September 2011). Ten F344/DuCrl rats per sex per group received a single oral gavage dose of KERB™ Technical (96.2% pronamide) at 0 (0.5% aqueous METHOCEL™), 40, 200, and 600 mg/kg followed by a 14-day observation period. One 600 mg/kg female was found moribund on study day 2 and euthanized. Necropsy results included congestion in the left lung lobe and hemolyzed blood in the stomach, but the cause of morbidity was not determined. Treatment-related clinical signs noted at 600 mg/kg on study day 2 included decreased activity (5/10 males and 9/10 females), decreased or absent feces (1/10 males and 5/10 females), incoordinated gait (3/10 males and 6/10 females), red periocular soiling (2/10 males and 3/10 females), slow or labored respiration (5/10 females), and cold to touch (2/10 females). All clinical signs were resolved by study day 4 except for red periocular soiling in 1 male. Slight decreases in group mean bodyweight were noted for high dose males and females at study days 8 (-7%) and 15 (-3 to -4%) vs controls and for mid-dose females (-5% on day 8 and -2% on day 15). Treatment-related FOB observations were present only on study day 1 in males and females treated at 200 and 600 mg/kg. Males and females treated at 200 and/or 600 mg/kg showed significant decreases in resistance to removal from the home cage, muscle tone, reactivity to handling, level of activity in the open-field, response to sharp noise, response to touch, response to tail pinch, gait coordination (5/10 high dose females were unable to walk). Also, females of the 200 and/or 600 mg/kg group exhibited increased pupil size, salivation, and extensor thrust response. Females were generally more affected than males. Group mean rectal temperatures for males and females treated at 200 and 600 mg/kg were significantly reduced vs controls on study day 1 (values for days 8 and 15 were comparable to controls). Significantly decreased group mean hind- and forelimb performance was noted for females treated at 200 and 600 mg/kg vs controls on study day 1 while values for days 8 and 15 were comparable to controls. Group mean landing foot splay values were significantly increased for males at 200 and 600 mg/kg and for females at 40 and 200 mg/kg (600 mg/kg females were excluded from calculations due to the inability to walk) vs controls on study day 1 (values for days 8 and 15 were comparable to controls). Group mean values for motor activity (MA) were significantly decreased for males and females at 200 and 600 mg/kg and for males at 40 mg/kg vs controls on study day 1, and values were comparable to controls on days 8 and 15. Gross pathology was unremarkable. Treatment-related neuropathology was not indicated. Systemic NOEL < 40 mg/kg (based on increased landing foot splay, decreased motor activity). No adverse effect. Acceptable. (Green, 11/15/13).

90-day neurotoxicity, rat **

**317-0135 273315, "Pronamide: 90-Day Dietary Subchronic Neurotoxicity Study in F344/DuCrl Rats," (M. S. Marty, *et al*., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI., Study ID: 111003, September 8, 2011). Ten F344/DuCrl rats per sex per group received KERB™ Technical (96.2% pronamide) in the diet at 0 (basal diet), 40, 200, and 1000 ppm for 90 days. All animals survived to the end of the treatment period. Group mean time-weighted daily intake of KERB™ Technical was 2.4, 11.8, and 59.5 mg/kg/day for males and 2.7, 13.3, and 65.2 mg/kg/day for females at 40, 200, and 1000 ppm, respectively. At the end of the treatment period, group mean bodyweights and bodyweight gains were significantly reduced for males and females at 200 and 1000 ppm vs controls. At 200 ppm, bodyweight reductions were 13% for males and 4% for females and bodyweight gain reductions were 22% for males and 10% for females vs controls. At 1000 ppm, reductions in bodyweight were 15% for males and 9% for female and bodyweight gain reductions were 28% for males and 23% for females vs controls. Group mean food consumption was significantly reduced for males and females at 1000 ppm and for males at 200 ppm vs controls. Additionally, at 40 ppm, slight but significant intermittent reductions in food consumption were noted for males vs controls. No treatment-related effects were noted for clinical signs, FOB observations, grip performance, rectal temperature, landing foot splay, motor activity, ophthalmology, necropsy results, or neural histology. Systemic NOEL = 40 ppm (2.4 mg/kg/day for males and 2.7 mg/kg/day for females) based on reduced bodyweight and bodyweight gain. Neurotoxicity NOEL = 1000 ppm (59.5 mg/kg/day for males and 65.2 mg/kg/day for females). No adverse effect. Acceptable. (Green, 12/4/13).

Developmental neurotoxicity, rat

No study on file.

Delayed neurotoxicity, hen

No required at this time.

IMMUNOTOXICITY **

**317-0132 271019, "Pronamide - A 28-Day Dietary Immunotoxicity Study in Male CD-1 Mice," (P.L. Crittenden, WIL Research Laboratories, LLC, Ashland, OH., Study No. WIL-410031, December 16, 2010). Ten male Crl:CD-1 mice per group received pronamide (96.2%) in the diet at 0 (basal diet), 15, 75, and 250 mg/kg/day for 28 days. All animals survived to terminal sacrifice. Group mean absolute and relative liver weights were significantly increased at 75 and 250 mg/kg/day compared to controls. No treatment-related effects were noted for clinical observations, bodyweight, food consumption, hematology, or gross pathology. Group mean spleen and thymus weights for males at 15, 75, and 250 mg/kg/day were comparable to controls, and there was no treatment-related reduction in anti-SRBC IgM at any dose level. Positive controls were functional. Immunotoxicity NOEL (M) = 250 mg/kg/day. Systemic NOEL (M) = 15 mg/kg/day based on liver weights. Acceptable. (Green, 9/23/14).

ENDOCRINE DISRUPTOR STUDIES †

075 128086 "Pronamide (Kerb Herbicide): Effect of Endocrine Regulation on Rat Testes," (Hazelton, G.A., DiDonato, L.J., Kaminski, E.J. and Lomax, L.G., Rohm & Haas Company, PA,

9/24/93; Protocol #: 92P-053, Report #: 92R-053). Propyzamide technical (96.8% pure) was fed in diet to Crl:CD BR male rats at 0 (acetone), 40, 1000, and 4000 ppm for 4 or 17 weeks. Another group was treated at 4000 ppm for 4 weeks, followed by a 13 week recovery (30 rats). At 0 & 4000 ppm, there were 60 rats/dose (30 for a 4 & 30 for a 17 week treatment). At 40 & 1000 ppm there were 40 rats/dose (20 for a 4 & 20 for a 17 week treatment). NOEL = 40 ppm (There was a significant decrease in body weight gain at ≥ 1000 ppm. LH, FSH and estrone were significantly increased at 4000 ppm. Testes, pituitary and liver weights were significantly increased at ≥ 1000 ppm & 4000 ppm. Vacuolation, hypertrophy, and increased LH & FSH activity occurred in the pars distalis of the pituitary. Interstitial cell hypertrophy was observed at 4000 ppm, as was an increase in labeled cells at 17 weeks.) **Possible adverse effect indicated** (interruption in the pituitary-testis endocrine axis occurred at ≥ 1000 ppm.) These data are supplemental. M. Silva, 5/6/94.

069 115339, "Pronamide (Kerb* Herbicide): Thyroid Function and Hepatic Clearance of Thyroxine in Male Rats", (G.A. Hazelton, L.J. DiDonato, K.F. Donofrio and B.A. Kulwich, Rohm and Hass Toxicology Department, Report No. 90R-178, 10/9/91). Pronamide (purity = 96.4%) admixed with the feed at concentrations of 0 (acetone mixed with feed), 40, 1000 or 4000 ppm was fed to Crl: CD*BR male rats (20-40/group). Treatment was 4 weeks for half the rats and 15 weeks for those remaining (per group). Also included was a "recovery group" consisting of 20 male rats fed 4000 ppm for 4 weeks and control diet for 11 weeks. NOEL = 40 ppm (Food consumption and body weight were significantly decreased at ≥ 1000 ppm. Absolute and relative liver and thyroid weights were increased at ≥ 1000 ppm and absolute pituitary weights were decreased at 4000 ppm. Thyroid and pituitary (pars distalis) hypertrophy/hyperplasia were increased at ≥ 1000 ppm. T4 (L-thyroxine) was significantly decreased at 4000 ppm. Biliary levels (bile to plasma ratios, bile flow and bile clearance) were increased at 4000 ppm. Percent dose excreted as T4-glucuronide was increased at 4000 ppm. Hepatic UDP-glucuronosyltransferase activity with L-thyronine treatment was increased/mg protein and increased/gram of liver and per whole liver at 4000 ppm. Effects were shown to be reversible (body weights, food consumption, gross liver pathology, liver and thyroid weights and histopathology in pituitary and thyroid) in the "recovery" group. Hormone, enzyme and biliary excretion of 125-I label were generally decreased over control in this group.) These data are supplemental to 060-061/091888-091889. (Silva & Kishiyama, 9/13/93).

070 115340, "Pronamide (Kerb* Herbicide): Effects of Endocrine Regulation of the Testis in Rats - Pilot Study", (G.A. Hazelton, L.J. DiDonato, K.F. Donofrio and B.A. Kulwich, Rohm and Haas Toxicology Department, Report No. 90R-179, 12/6/91). Pronamide (purity = 96.4%) in diet was fed to male Crl: CD*BR rats (20/group) at 0 (acetone mixed with feed) or 4000 ppm for 13 weeks. Alterations that may influence hormonal regulation of the testes occurred with increases in the following: serum concentrations (luteinizing hormone, follicle stimulating hormone and estradiol); testosterone oxidation capacity in liver microsomes; total p450 and cytochrome b5 content & activity of NADPH-cytochrome c reductase in the whole liver. The severity and incidence of hypertrophy/hyperplasia in the pituitary and the numbers of interstitial cells of the testes were also increased. **Possible adverse effect indicated: Hormone balance for testicular regulation is negatively affected. NOTE: These data are supplemental to study 060-061/091888-091889.** (Kishiyama & Silva, 9/15/93).

SUPPLEMENTAL STUDIES

317-0130 271016, "Pronamide (Propyzamide): 28-Day Dietary Toxicity Study in CD-1 Mice," (K.E. Stebbins et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI., Study ID: 021076, December 19, 2002). Ten CD-1 mice per sex per group received pronamide (95.9%) in the diet at 0 (basal diet), 15, 75, 375, and 1000 mg/kg/day for 28 days. All mice survived to the end of the 28-day treatment period. Treatment-related cageside observations noted at 1000 mg/kg/day included decreased feces for all males and females on test days 3 and 4 and for 1 female on test day 6. Group mean bodyweight for high dose males was significantly reduced on test days 4 through 28 and was 18.5% lower at study termination compared to controls. High dose females had slight bodyweight loss (ns) on test day 4 and, subsequently, gained bodyweight at comparable levels to controls during the rest of the study. Group mean food consumption was significantly reduced for high dose males (during weeks 1, 3, and 4) and females (during study weeks 1 and 3) compared to controls. Bodyweight, bodyweight gain, and food consumption for the other treatment groups were comparable to controls. Treatment-related hematology changes included significant decreases in group mean hemoglobin and hematocrit for 375 mg/kg/day females and high dose males and females and in red blood cell count for high dose females (values for high dose males were also reduced (ns)) compared to controls. Group mean platelet counts were significantly increased for high dose males and females. Treatment-related serum chemistry included significant increases in group mean values for alanine aminotransferase activity, aspartate aminotransferase activity, and alkaline phosphatase activity (AP) for males and females at 375 and 1000 mg/kg/day compared to controls (except the AP increase for 375 mg/kg/day females was not statistically significant). Liver and kidneys were primary target organs. Group mean absolute and relative liver weights were significantly increased for males and females at 75, 375, and 1000 mg/kg/day compared to controls. Relative kidney weight at all treatment levels for both sexes was comparable to controls. Treatment-related histology in the liver included bile stasis, bile duct hyperplasia, hepatocellular hypertrophy, hepatocellular necrosis (with accompanying inflammation), and increased numbers of mitotic figures in hepatocytes in male and females at 375 and 1000 mg/kg/day. Centrilobular hepatocellular hypertrophy (very slight to slight) was noted in males and females at 75 mg/kg/day. The incidence and severity of the effects were generally increased at 1000 mg/kg/day (severity grades included very slight, slight, and moderate). Histology results for kidneys included very slight multifocal hyperplasia of the proximal tubules in high dose females, and very slight hypertrophy of intercalated cells occurring in 375 mg/kg/day males and in males and females at 1000 mg/kg/day. NOEL (M & F) = 15 mg/kg/day based on liver weight and histology. No adverse effect. Supplemental data. (Green, 9/15/14).

317-0145 This volume includes several published articles by Dow researchers, a U. S. EPA communication to Brian Brett of Dow AgroSciences on Pronamide (Propyzamide) "Cancer Classification Reassessment," and an "EDSP Weight of Evidence Conclusions" report. All of these citations are detailed below. The documents were requested by the Risk Assessment Group of HHAB. None of these studies have been assigned to HHAB Data Review Group as of this time. Citations for these documents follow. Aldous, 8/15/16.

317-0145 293510 Matthew J. LeBaron, Reza J. Rasoulpour, B. Bhaskar Gollapudi, Radhakrishna Sura, H. Lynn Kan, Melissa R. Schisler, Lynn H. Pottenger, Sabitha Papineni, and David L. Eisenbrandt: "Characterization of Nuclear Receptor-Mediated Murine

Hepatocarcinogenesis of the Herbicide Pronamide and Its Human Relevance," Toxicological Sciences, 142(1), 2014, 74–92

317-0145 293511 Sabitha Papineni, M. Sue Marty, Reza J. Rasoulpour, Matthew J. LeBaron, Lynn H. Pottenger, David L. Eisenbrandt, "Mode of action and human relevance of pronamide-induced rat thyroid tumors," Regulatory Toxicology and Pharmacology 71 (2015) 541–551.

317-0145 293512 Reza J. Rasoulpour, Amanda K. Andrus, M. Sue Marty, Fagen Zhang, Johnson Thomas, Matthew J. LeBaron, Sabitha Papineni, Lynn H. Pottenger, and David L. Eisenbrandt, Regulatory Toxicology and Pharmacology 72 (2015) 394–404.

317-0145 293513 Mary Sue Marty, Sabitha Papineni, Katherine K. Coady, Reza J. Rasoulpour, Lynn H. Pottenger, and David L. Eisenbrandt, "Pronamide: Weight of evidence for potential estrogen, androgen or thyroid effects," Regulatory Toxicology and Pharmacology 72 (2015) 405–422.

317-0145 293514 US EPA, Memorandum of Dec. 2, 2014: "Subject: Pronamide (Propyzamide): Report of the Cancer Assessment Review Committee," (from Jess Rowland, Chair of Cancer Assessment Review Committee, to Stephen Dapson and Wilhelmena Livingston).

317-0145 293515 US EPA, Memorandum of 6/29/2015: "SUBJECT: Propyzamide (Pronamide): Data Evaluation Records (DERs) for EDSP Tier 1 Assays," (from Greg Akerman through Jess Rowland to Jolene Trujillo).