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

SUMMARY OF TOXICOLOGY DATA
GLYPHOSATE [N-(phosphonomethyl)glycine],
(commonly formulated as a salt, such as isopropylamine)
(frequently named CP67573 in older studies)

Chemical Code # 1855 †, Document Processing Number (DPN) # 00364 †
SB 950 # 241
December 2, 1986
Revised 12/14/87, 11/18/88, 11/03/92, and 8/27/2015

DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers for the above study types through 248122 (Document No. 364-0830) were examined. This includes all relevant studies indexed by DPR as of 6/26/2015.

† This Summary contains data provided under Chemical Code # 1855 and Document Processing Number (DPN) # 00364, as submitted under Monsanto. Another series of FIFRA studies was

submitted to support a trimesium salt (also called Sulfosate with a brand name Touchdown, now owned by Syngenta, Chemical Code 2327, DPN 51764). Sulfosate products were registered in California between 1996 and 2003, but none of those products are currently registered in this state. Sulfosate is currently registered with U.S. EPA, and has international registrations. There are several other active ingredients containing glyphosate that have been or are currently registered at DPR search for "glyphosate," but their databases do not contain data other than the common acute studies (Chem Codes 2997, 5810, 5972, 2301, 5820, and 2275). [redacted], 8/20/15.

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

File name: t20150827
Current revision by [redacted], 8/27/15

NOTE: The following symbols may be used in the **Table of Contents** which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
(N/A) = study type not currently required

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

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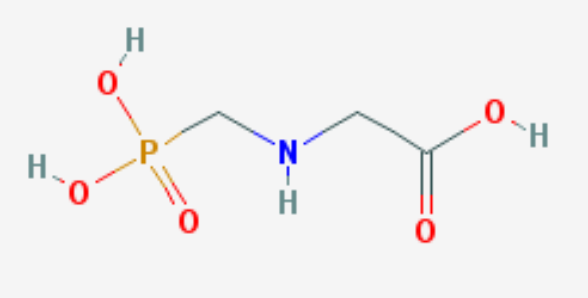
METABOLISM AND PHARMACOKINETICS



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00364-0005 937447 Colvin, L. B., J. A. Miller, and J. T. Marvel, "CP 67573 residue and metabolism, Part 8: The gross metabolism of N-phosphonomethylglycine-^{14}C (CP 67573-^{14}C) in the laboratory rat following a single dose," Monsanto Agricultural Division Research Department, 6/15/73. Agricultural Research Report # 297. Wistar rats were dosed by gavage with glyphosate of unspecified purity, (6.7 mg/kg, 8 to 10 mCi/mmole). Typically there were 2-3 males or 1-2 females treated with ^{14}C radiolabel in each of the following locations: N-phosphonomethyl methylene, glycine component carboxyl, or on glycine methylene carbon α to the carboxyl. Also, intraperitoneal (ip) dosing was done only in males (2-3 rats per label position). Gavage treatment of extracts, mainly from roots of soybeans grown hydroponically with glyphosate labeled on either of the 3 label loci, was done in 2 males for each label location. Male rats administered gavage doses of glyphosate excreted 81-85% of recovered label in feces, and 14-16% in urine, regardless of placement of radiolabel. Most label was cleared by 48 hours. Females excreted 35-43% of recovered dose in urine and 49-55% in feces, suggesting greater absorption by oral route than males. In both sexes, CO_2 derived from carbons on the glycine portion of the molecule (sometimes approaching 1% of administered label) suggest a modest assimilation of such residues into the carbon pool. By contrast, CO_2 derived from the N-phosphonomethyl carbon accounted for only 0.02% of administered dose in males, and 0.2% in females. This suggests that the aminomethyl-phosphonic acid portion of the molecule remains intact (see also Record No. 937690 in this volume). After ip injection of glyphosate, urinary residues were comprised 82% of administered N-phosphonomethyl label, and 88% to 90% of urinary residues recovered from dosing in the two glycine label positions. Fecal elimination was 14% associated with the N-phosphonomethyl label, and 6-8% following treatment with label in the glycine carbons. As in the case of gavage administration, CO_2 residues were tiny after treatment with N-phosphonomethyl label (0.05% of administered dose), and more substantial if the label was on one of the glycine carbons (0.70% and 0.83% of administered dose). In all cases following ip exposure, 76% to 88% of residues were cleared within the first 12 hours by combined routes. A minor component of this study addressed excretion patterns and tissue residues in rats which had consumed soybean root extracts (the plants having been exposed to glyphosate labeled in the three above loci). Residues in tissues 120 hours following exposure were uniformly low in the N-phosphonomethyl methylene and carbonyl label groups, whereas tissues of rats administered label α to the carboxyl had residues several-fold higher than the former two. This suggests that the α carbon had, to a small extent, entered into the carbon pool. Biliary excretion was evident, despite the small size of the molecule. Three figures show biliary excretion following N-phosphonomethyl methylene label dosing via "rapid gastric infusion," ip administration, and iv injection. Available information in the text or in the tables does not reveal details of this phase of the study, nor of the percent of total dose collected in bile. This study is not acceptable and is not upgradeable, due to several features, including a non-guideline design, and not providing sufficient detail to properly evaluate results. The study lacked QA oversight and pre-dated modern GLP standards. The study provided some useful information, which can be assessed along with other studies of glyphosate disposition. [redacted], 8/17/15.

00364-0005 937689 Colvin, L. B., J. A. Miller, and J. T. Marvel, "CP 67573 residue and metabolism, Part 9: The gross metabolism of N-phosphonomethylglycine-^{14}C (CP 67573-^{14}C) in the rabbit," Monsanto Agricultural Division Research Department, 6/15/73. Agricultural

Research Report # 298. As summarized results of this study were comparable to those of the rat, above, this study on rabbits was not reviewed by DPR. [redacted], 7/13/15.

00364-0013 937533 Colvin, L. B., J. A. Miller, and J. T. Marvel, "CP 67573 residue and metabolism, Part 13: The dynamics of accumulation and depletion of orally ingested N-phosphonomethylglycine-^{14}C," Monsanto Agricultural Division Research Department, completed Sept. to Oct., 1973. Agricultural Research Report #: No. 309. Wistar rats were dosed in diet with CP 67573 of unspecified purity, labeled with ^{14}C at unspecified locus or loci and at unspecified radiopurity. Since other studies show that most of glyphosate is excreted unchanged, these limitations do not entirely eliminate the utility of this study. There were two rats/sex per sacrifice time at 1, 10, and 100 ppm. Sacrifice times were after 2, 6, 10, or 14 days of treatment, or 1, 3, 6, or 10 days post-dosing. There were no apparent treatment effects on body weights over time or on organ weights over time. Gut (with ingesta) maintained a very high and reasonably steady concentration range throughout the treatment period, with a precipitous decline after cessation of dosing. Of other tissues assessed during the treatment period, kidneys typically had the highest concentrations in either sex, with spleen, ovaries, and fat at slightly lower concentrations. Concentrations in other tissues were typically less than 50% of kidney concentrations. Lowest concentrations were observed in whole blood and in muscle. Examination of tissue label across dose levels and sexes indicates little or no evidence of systematic increases in tissue levels over time after the day 2 sampling. Tissue concentrations appeared to be proportional to treatment level in all treatment groups. Tissues (other than gut with ingesta) showed only gradually diminished label concentrations at 1 or 3 days post-treatment compared to concentrations during the treatment period, suggesting that residues resulted largely from incorporation of label into natural cellular constituents. This study is not acceptable, and is not upgradeable, due to several features, including a non-guideline design, and not providing sufficient detail to properly evaluate results. The study lacked QA oversight, and pre-dated modern GLP standards. The study provided some useful information, which can be assessed along with other studies of glyphosate disposition. [redacted], 8/25/15.

00364-0005 937691 Moran, S. J. and L. B. Colvin, "CP 67573 residue and metabolism, Part 12: The isolation and identification of the metabolites of CP 67573-^{14}C excreted by the laboratory rat," Monsanto Agricultural Division Research Department, Aug., 1973. Agricultural Research Report # 306. This report focused on analysis of extracts from rat urine and feces taken from other studies. Test article was CP 67573-^{14}C (glyphosate), purity unspecified. Label was apparently on the phosphonomethyl carbon. Investigators indicated that the labeled test article contained 5.6% aminomethylphosphonic acid-^{14}C (CP 50435-^{14}C). Extracts of urinary and fecal samples subjected to 2-dimensional thin-layer chromatography (TLC) yielded only one major spot, consistent with CP 67573. Nuclear magnetic resonance (NMR) spectral data for the two methylene groups are consistent with coupling of a glyphosate standard. Column chromatography with radiometric analysis employing three different stationary phases yielded 84%, 98%, and 97% of recovered label as CP 67573 (assuming no interfering peaks). This is the strongest case offered for parent CP 67573 as the clearly dominant residue. Mass spectrometric (MS) spectra showed characteristic m/e values of 220 and 247 for both CP 67573 standard and for urine sample extracts. Overall MS patterns were similar for standard and samples, again suggesting that CP 67573 was the dominant metabolite. Gas-liquid chromatographic (GLC) analyses (evidently using flame ionization detection) of urine from a gavage-treated female and

from a male following a "chronic" administration showed strong peaks corresponding to a CP 67573 standard in both cases. The single dose chromatogram appeared to show fewer additional strong peaks than the "chronic" dose chromatogram, suggesting that sustained exposure yields increased metabolites other than parent. The GLC data are not suited to assessing the percent of dose attributable to parent or to metabolites. This report was sometimes unclear and the study design was not as focused as current guideline studies, but provides some useful supplementary data. [redacted], 7/27/15.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

NOTE: There are many data sets for glyphosate (under Chemical Code 1855). This reviewer examined the most recent ten Product Registration Recommendation Sheets to obtain representative acute study results. After eliminating products with more than one active ingredient and removing cases in which multiple registration actions were bridged to the same product, there remained four data sets, which adequately characterize acute effects of glyphosate. Percent active ingredient in the studies below, which support these four registration actions, ranged from 51% to 62% ([redacted], 6/26/15).

Acute oral toxicity, rat ** (Toxicity Category IV in each study)

364-0471; 212674; Acute Oral Toxicity; 811; rat; Moore, G. E.; Product Safety Labs, Laboratory; Study #: 13033; 03/31/03; Nufarm NUP 3G 02 Herbicide; composition: a. i., not specified; 5.0 g/kg; single, oral-gavage dosage, with a 14-day observation period; 3 female test subjects/treatment level; mortality: none; clinical signs: although one animal had soft feces on Day 1, all three gained weight, appeared active, and healthy; necropsy: no gross abnormalities reported; reported LD_{50} (female) > 5.0 g/kg; Toxicity Category IV; **Acceptable**. ([redacted], 10/22/04)

364-330 170505; Acute oral toxicity; 811; Rat; Health & Environmental Research Laboratories, The Dow Chemical Co., Midland, Michigan; project #991048; 5/18/99; Glyphosate IPA (Isopropylamine) Salt (NAF-552); 5/sex, administered by gavage; 5000 mg/kg; no deaths; clinical observations: perineal urine soiling of three females on test day 2 only; necropsies: no dose-related alterations. LD50 (M/F) > 5000 mg/kg,; Toxicity Category IV; Acceptable. ([redacted], 11/4/99).

364-0749 215680; Acute oral toxicity; 811; Rat; Springborn Laboratories, Inc. (SLI), Spencerville, OH; SLI Study No. 3504.261; Dow Study No. 021117; 9/30/02; GF-887; 5/sex, administered by gavage; 5000 mg/kg; clinical observations: No mortality occurred during the test. In-life observations included transient occurrences of mucoid stools (9/10 animals), soft stools (10/10), few feces (7/10), hunched posture (6/10), palpebral closure- 50% to completely closed, (4/10 animals), dark material around the eyes (8/10), dark material around the nose (10/10), dark material around the mouth (10/10 animals), rough coat (7/10), thin appearance (4/5 females), dehydration (5/10), unkempt appearance (9/20), urogenital fecal staining (10/10 animals), urogenital urine staining (6/10), distended abdomen (5/10), labored breathing (2/5 females), abdomen fecal staining (5/5 females) and hair-loss around eyes (3/5 females), hair-loss around mouth (7/10 animals), hair-loss ventricle thoracic area (1/5 females), thin appearance (4/5 females), lacrimation (7/10 animals), decreased responsiveness to touch (2/5 females) and poor gait coordination (2/5 females); slight body weight loss was noted for one female rat during the

day 0-7; Body weight gain was noted for all animals during the test period; no significant gross internal observations were noted at necropsy on day 14; all female rats showed some external hair-loss and staining of the coat. One incidence of a ruptured liver was observed during gross necropsy on day 14, considered to be injury-related prior to necropsy and not test article related. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; Acceptable. ([redacted], 5/17/05).

364-374; 180189; "Glyphosate 62% Acute Oral Toxicity (Limit) Test in Rats" (Donald, E and Donald, L., Inveresk Research, Tranent, EH33 2NE, Scotland, Inveresk Report No.: 18422, 03/31/00). A dose of 5.0 g/kg of Glyphosate 62% (Batch No. 5, 62 % a.i.) was administered as undiluted test substance via oral gavage to 5 Sprague Dawley rats/sex. No mortality, body weight changes or adverse clinical signs of toxicity were reported. Necropsy revealed no abnormalities. LD50 (M/F) > 5.0 g/kg. Toxicity Category IV. **Acceptable.** ([redacted], 04/20/01).

Acute dermal toxicity ** (Toxicity Category Range: III to IV)

364 – 0471; 212675: Acute Dermal Toxicity; 812; rat; Moore, GE.; Product Safety Labs, Laboratory Study #: 13034; 03/31/03; Nufarm NUP 3G 02 Herbicide; composition: a. i., not specified; 2.0 g/kg; single, 24-hour, dermal exposure (intact dorsal skin), with covering and a 14-day observation period; 5 test subjects/sex/treatment level; mortality: none; clinical signs: none reported (no observable, treatment-related effects); reported LD_{50} (M/F) > 2.0 g/kg; Toxicity Category III; **Acceptable**. ([redacted], 10/25/04)

364-330 170506 Acute dermal toxicity; 812; Rabbit; Health & Environmental Research Laboratories, The Dow Chemical Co., Midland, Michigan; project # 991049; 5/18/99; Glyphosate IPA (Isopropylamine) Salt (NAF-552); 5 animals/sex; Dose: 5.0 g/kg, 24 hour exposure, occlusive wrap; No mortality; Clinical Observations: skin at the dermal test site was reddened in all rabbits; thickening of skin in 9 of 10 rabbits on test day 2; no abnormal clinical signs from day 6 onward. All rabbits lost weight over the first two days, but regained or surpassed their pre-study weight by day 14. Necropsy: no treatment-related lesions; LD50 (M/F) > 5.0 g/kg; Toxicity Category IV; Study acceptable. ([redacted], 11/4/99).

364-0749 215682; Acute dermal toxicity; 812; Rat; Springborn Laboratories, Inc. (SLI), Spencerville, OH; SLI Study No. 3504.262; Dow Study No. 021118; 9/30/02; GF-887; 5 animals/sex; Dose: 5.0 g/kg, 24 hour exposure, occlusive wrap; No mortality; Clinical Observations: dark material around the eyes (4/10 animals), nose (6/10) and mouth (3/10) and urogenital urine staining (2/5 females); test site was reddened in all rats; no abnormal clinical signs were seen at study termination (day 14) and all rats gained weight by day 14. Necropsy: no treatment-related lesions; LD50 (M/F) > 5.0 g/kg; Toxicity Category IV; Study acceptable. [redacted], 5/17/05).

364-374; 181190; "Glyphosate 62% Acute Dermal Toxicity (Limit) Test in Rats" (Donald, E. and Donald, L., Inveresk Research, Tranent, EH33 2NE, Scotland, Inveresk Report No.:18450, 03/31/00). Glyphosate 62% (Batch No. 5, 62 % a.i.) was applied undiluted to the shaved intact skin of 5 Sprague Dawley rats/sex at 5.0 g/kg body weight for 24 hours. No mortality, body weight changes or adverse clinical signs of toxicity were reported. Necropsy revealed no abnormalities. LD50 (M/F) > 5.0 g/kg. Toxicity Category: IV. **Acceptable.** ([redacted], 04/23/01).

Acute inhalation toxicity, rat ** (Toxicity Category Range: III to IV)

364–0471; 212676; Acute Inhalation Toxicity; 813, rat; Moore, G.E.; Product Safety Labs; Laboratory Project Identification #: 13035; 04/01/03; Nufarm NUP 3G 02 Herbicide; composition: a. i., not specified; mean gravimetric concentration: 2.09 mg/L, with a mean MMAD (plus or minus GSD) of 2.5 microns (plus or minus 1.82 microns) for 5 rats/sex and at 0.57 mg/L with a mean MMAD (± GSD) of 2.4 microns (plus or minus 1.84 microns) for 5 males, via a 4-hour, whole-body, inhalation exposure; mortality (M/F): 0.57 mg/L, 0/5, 0/5; 2.09 mg/mL, 2/5, 1/5 (within 3 days of exposure); clinical signs: animals in both exposure groups (0.57 mg/L and 2.09 mg/mL) exhibited ocular and nasal discharge, irregular respiration, hunched posture, and/or hypoactivity; 02.09 mg/mL, dyspnea and gasping was also exhibited; after exposure, all 0.57 mg/L males were active and healthy; the 2.09 mg/L group continued to exhibit signs observed during exposure (except ocular and nasal discharge) including rales, prone and/or reduced fecal volume to Day 5; all survivors appeared active, healthy, and gained body weight; necropsy: discolored lungs, liver and intestines along with rigor mortis in decedents; reported LC_{50} (M, F) > 0.57< 2.09 mg/L; Toxicity Category III; **Acceptable**. ([redacted], 10/25/04)

**364-330 170507; Acute Inhalation Toxicity Study; 813; Rat; Health & Environmental Research Laboratories, The Dow Chemical Co., Midland, Michigan; project# 991076; 5/24/99; Glyphosate IPA (Isopropylamine) Salt (NAF-552); 5 animals/sex; Exposure Concentration (gravimetric): 6.37 mg/l mean MMAD (GSD) 0.64 (3.69) um, 4 hour nose-only exposure; Mortality: none; Clinical Observations: all had slow respiration and three females were soiled during exposure; two males and all females were soiled on day 2 and one female had perinasal soiling on day 2; Necropsy: no dose-related changes; Acceptable; Toxicity Category IV. ([redacted], 11/4/99).

364-374; 180191; "Glyphosate 62% Acute Inhalation Toxicity Study in Rats" (Anderson, B.T.; Inveresk Research, Tranent, EH33 2NE, Scotland., Inveresk Report No.: 18439, 04/03/00). Glyphosate 62% (Batch No. 5, 62 % a.i.) was administered to 5 Sprague-Dawley rats/sex via nose-only inhalation exposure as an aerosol at 7.03 mg/L (mean gravimetric exposure concentration, MMAD = 3.09 um; and GSD = 2.45) for 4 hours. No mortality, effects on body weight, or clinical signs were observed throughout the study. Common procedural observations such as labored respiration during exposure, and unkempt appearance, staining of test material on snout and eyes ca. 1-2 h post-exposure, were noted. There were no necropsy findings considered related to treatment. Effects on lung to bodyweight ratio after exposure was not observed. LC50 (M/F) > 7.03 mg/L. Toxicity Category IV, **Acceptable. ([redacted], 04/24/01).

**364-058; 937621; Acute Inhalation; 813; rat; Monsanto Company, Environmental Health Laboratory, St. Louis, MO; Lab Study No. 810093; 3/17/82; ROUNDUP, Lot Nos. LBRP-06110 (41.01% purity) and LBR-07-140 (41.36% purity), used neat; 0 (air only) (15M/15F), 1.10 (5M/5F), 1.99 (5M/5F), 2.39 (5M/5F), 2.46 (10M/10F), 2.56 (5M/5F), 2.96 (5M/5F), 3.42 (max. attainable concentration) (5M/5F) mg/l (analytical); liquid aerosol/vapor inhalation, whole-body, 4-h exposure; MMADs ranged 1.96 to 2.72 (GSDs ranged 1.86 to 2.00) w/cascade impactor; Mortality- male: 0/15, 0/5, 0/5, 1/5, 1/10, 0/5, 2/5, 4/5, female: 0/15, 0/5, 0/5, 0/5, 1/10, 0/5, 1/5, 2/5; Clinical Observations- included chromorhinorrhea; gasping/breathing difficulty; conjunctival edema; hypoactivity; piloerection; Necropsy- included lungs congested with blood;

LC50 (M) = 3.05, (F) = 3.62, (M/F) = 3.28 mg/l; Toxicity Category III; Acceptable. ([redacted], 9/12/90).

Primary eye irritation, rabbit ** (Toxicity Category Range: III to IV)

364-0872; 271444; Primary Eye Irritation; 814; rabbit; J. Durando; "Primary Eye Irritation Study in Rabbits"; Eurofins, Product Safety Laboratories, Dayton, NJ; Laboratory Study #: 29575; 04/21/10; NUP-09158; Lot #: EDS-05-21D; composition: a. i., 38.3% glyphosate; 0.1 mL/eye; single, ocular instillation, with a 72-hour observation period; 3 male test subjects/treatment level; mortality: none; clinical signs: no systemic effects reported; corneal opacity, grade 1 in 3/3 at 1 hour, with complete clearing at 24 hours; iritis, grade 1 in 3/3 from 1 through 24 hours, with complete clearing by 48 hours; conjunctivae, redness - grade 2 in 3/3 from 1 through 24 hours, decreasing to grade 1 in 3/3 at 48 hours, with complete clearing by 72 hours; chemosis - grade 1 in 3/3 from 1 hour through 24 hours, with complete clearing by 48 hours; discharge - grade 2 in 3/3 at 1 hour, decreasing to grade 2 in 1/3 at 24 hours (grade 1 in 2/3) and grade 1 in 2/3 by 48 hours, with complete clearing by 72 hours; body-weights not reported; reported Maximum Mean Total Score = 13.7 (at 24 hours); Toxicity Category III; **Acceptable**. ([redacted], 08/13/13)

364-0872; 271445; Primary Eye Irritation; 814; rabbit; S. Dana Oley; "Primary Eye Irritation Study in Rabbits"; Eurofins, Product Safety Laboratories, Dayton, NJ; Laboratory Study #: 29576; 06/18/10; NUP-07144; Lot #: EDS-05-21B; composition: a. i., 38.3% glyphosate; 0.1 mL/eye; single, ocular instillation, with a 72-hour observation period; 3 male test subjects/treatment level; mortality: none; clinical signs: no systemic effects reported; corneal opacity, grade 1 in 3/3 from 1 through 24 hours, decreasing to grade 1 in 2/3 at 48 hours, with complete clearing at 72 hours; iritis, grade 1 in 3/3 from 1 through 48 hours, with complete clearing by 72 hours; conjunctivae, redness - grade 2 in 3/3 from 1 through 24 hours, decreasing to grade 2 in 1/3 at 48 hours (grade 1 in 2/3), with complete clearing by 72 hours; chemosis - grade 1 in 3/3 from 1 through 24 hours, with complete clearing by 48 hours; discharge - grade 3 in 1/3 at 1 hour (grade 2 in 2/3), decreasing to grade 2 in 1/3 by 24 hours (grade 1 in 2/3), grade 1 in 3/3 at 48 hours, with complete clearing by 72 hours; body-weights not reported; reported Maximum Mean Total Score = 18.7 (at 24 hours); Toxicity Category III; Acceptable. ([redacted], 08/16/13)

364-330 170509; Primary Eye Irritation Study; 814; Rabbit; Health & Environmental Research Laboratories, The Dow Chemical Co., Midland, Michigan; project # 991052; 5/18/99; Glyphosate IPA (Isopropylamine) Salt (NAF-552); 3 rabbits; Dose: 0.1 ml in the right eye; Observations: no corneal opacity or iritis seen, Conjunctiva-redness (score 1) in 1/3 rabbits at 24 hours and none at 48 hours, no chemosis or discharge reported at 24 hours; Toxicity Category IV; Study acceptable. ([redacted], 11/5/99).

364-0751 215642; Primary Eye Irritation Study; 814; Rabbit; Product Safety Labs, Dayton, NJ; PSL Study# 14373; Dow Study# 030127; 9/30/01; GF-1279; 3 female rabbits; Dose: 0.1 ml in the right eye; Observations: neither corneal opacity nor iritis was seen at 24 hours or up to day 7; conjunctival irritation (redness), score 1 in 3/3 rabbits was noted at 24 and 48 hours, with persistence in one rabbit to 72 hours and another to day 4; clearing in all was seen by day 7; conjunctival chemosis (score 1) was seen in 2/3 rabbits at 24 and 48 hours with persistence in one rabbit up to day 4 and clearing by day 7; Toxicity Category IV; Study acceptable. ([redacted], 5/18/05).

364-374; 180192; "Glyphosate 62% Acute Eye Irritation Test in Rabbits" (Donald, E. and Donald L., Inveresk Research, Tranent, EH33 2NE, Scotland, Inveresk Report No.: 18411, 03/31/00). Glyphosate 62% (Batch No. 5; 62% a.i) 0.1 mL was introduced, undiluted, into the lower conjunctival sac of the right eye of 3 male New Zealand White rabbits. The untreated eye served as the control. No mortality or clinical signs of systemic toxicity were reported. No corneal, or iridial responses were observed. Conjunctival redness and chemosis were noted in all animals at 1 h or 1 and 24 h after instillation of the test material. Conjunctival redness score was positive in all 3 animals 1 h after administration. Slight discharging was noted in all animals 1 h after instillation. Reaction to treatment immediately after instillation such as vocalization, jumping, and shutting or blinking of the treated eyes were observed. Toxicity Category IV. **Acceptable.** ([redacted], 04/24/01).

Primary dermal irritation ** (Toxicity Category IV)

364–0471; 212678; Primary Dermal Irritation; 815; rabbit; Moore, G.E.; Product Safety Labs; Laboratory Study #: 13036; 03/31/03; NUP 3G 02 Herbicide; composition: a. i., not specified; 0.5 mL/site; single, 4-hour, dermal exposure (to dorsal area and trunk of intact skin), with a semi-occlusive dressing and an observation period; 2 male/1 female New Zealand rabbits; mortality: none; clinical signs: erythema, score 1 in 3/3 at 1 hour, increasing to score 2 in 3/3 at 24 hours, and decreasing to score 1 in 2/3 by 48 hours; edema, none reported; Toxicity Category IV; **Acceptable**. ([redacted], 10/25/04)

364-330 170508; Primary Dermal Irritation Study; 815; Rabbit; Health & Environmental Research Laboratories, The Dow Chemical Co., Midland, Michigan; project # 991051; 5/18/99; Glyphosate IPA (Isopropylamine) Salt (NAF-552); 3 animals; Dose: 0.5 ml/site, one site/animal, 4 hour exposure, semi-occlusive wrap; Observations: no erythema or edema was noted at observation periods up to test day 4; Toxicity Category IV; Study acceptable. ([redacted], 11/5/99)

364-0750 215685; Primary Dermal Irritation Study; 815; Rabbit; Springborn Laboratories, Inc. (SLI), Spencerville, OH; SLI Study No. 3504.264, Dow Study No. 021120; 10/25/02; GF-887; 3 animals; Dose: 0.5 ml/site, one site/animal, 4 hour exposure, semi-occlusive wrap; Observations: erythema (score 1) was seen in 3/3 rabbits at 24 hours and in one rabbit at 48 hours, with clearing in all by 72 hours; no edema was reported up to study termination (72 hours); Toxicity Category IV; Study acceptable. ([redacted], 5/17/05)

364-374; 180193; "Glyphosate 62% Acute Dermal Irritation Test in Rabbits" (Donald, E. and Donald, L., Inveresk Research, Tranent, EH33 2NE, Scotland, Inveresk Report No. 18410, 03/31/00). Glyphosate 62% (Batch No. 5, 62 % a.i) undiluted test substance 0.5 mL was applied topically to the shaved intact test site of 3 female New Zealand White rabbit for 4 hours under semi-occluded conditions. Very slight erythema was noted 1 h after patch removal in one animal. No edema was noted in any animals. No mortality was reported during the study. Toxicity Category IV. **Acceptable.** ([redacted], 04/25/01).

Dermal sensitization ** (Not a sensitizer)

364–0471; 212679; Skin Sensitization; 816; guinea pig; Moore, G.E.; Product Safety Labs; Laboratory Study #: 13037; 09/14/98; Nufarm NUP 3G 02 Herbicide; composition: a. i., not specified; induction: 0.4 mL/site applied at induction for a single, 6-hour, dermal exposure, using

an occlusive, 25-mm, Hill Top Chamber® once per week for 3 consecutive weeks to an intact skin site on the left side of each of 20 male Hartley albino test guinea pig subjects; challenge: a single challenge treatment of 0.4 mL/site was applied 27 days after the 1st induction treatment to the right side of each subject; naïve challenge an additional 10 male subjects were similarly treated with 0.4 mL/site of the test article during challenge period and served as the naïve, challenge-control subjects; treated sites of some test subjects exhibited erythema (score 0.5) during the induction phase; during challenge phase, erythema (very faint/score 0.5) was present only at 24 hours in 5/20 test subjects and 2/10 naïve-control subjects; positive-control treatments confirmed the validity of the test; Toxicity Category: **Not a sensitizer**; **Acceptable**. (10/26/04)

364-330 170510 "Glyphosate IPA Salt (NAF-552): Dermal Sensitization potential study in Hartley Albino Guinea Pigs." DPR review indicated that the subject product was negative for delayed contact hypersensitivity when tested by the method of Buehler, with modifications. See Worker Health & Safety memo, dated 2/17/00.

364-0750 215686; Skin Sensitization Study; 816; Guinea Pigs; Springborn Laboratories, Inc. (SLI), Spencerville, OH; Dow Study No. 021119; SLI Study# 3504.265; 10/9/02; GF-887; Guinea Pigs (10/sex test chemical induced plus 5/sex naive controls); Method of Buehler (1965) with modifications; Dermal application was achieved by placing 0.3 ml of test substance onto a 25 mm "Hilltop Chamber" backed by adhesive tape (occlusive patch) and applying this to the exposed skin; Induction phase: three applications (7 days between each exposure) of 0.3 ml of undiluted test substance were applied to same site under occlusion for at least 6 hours per exposure; Two weeks after the last induction dose, the challenge phase consisted of a single 0.3 ml dose applied to a second exposed area for a 6 hour exposure; scoring for irritation was performed at 24 and 48 hours post application; after challenge, dermal scores of 0 were noted in all test chemical-induced and naive control animals at 24 and 48 hours; Toxicity Category: Not a Contact Sensitizer. Study Acceptable. (, 5/18/05).

364-374; 180194; "Glyphosate 62% Magnusson Kligman Maximization Test in Guinea Pigs" (Donald, E., and Donald, L., Inveresk Research, Tranent, EH33 2NE, Scotland., Inveresk Report No.: 18485, 03/31/00). Glyphosate 62% (Batch No. 5; 62 % a.i) 10% w/v was injected intradermally into the dorsal scapular region of the shaved intact test site of 20 female guinea pigs. Six days after injection, the intact skin site was pre-treated with 0.5 mL of 10% w/w sodium lauryl sulfate in water, followed by a placement of a Webril patch with ca. 0.5 mL of Glyphosate 62% for 48h. Thirteen-days after topical induction, the control and test animals were challenged topically with Glyphosate 62%. Ten control guinea pigs were used for this study. Glyphosate 62% did not produce evidence of skin sensitization (delayed contact hypersensitivity) in any of the test animals. Toxicity Category: not a sensitizer. **Acceptable.** (, 04/24/01).

364-0090 937649 Auletta, C. A., "A dermal sensitization study in Guinea pigs with Glyphosate, Bio/dynamics, Inc., Study No. BD-83-008. This is a negative study for which there is no Human Health Assessment Branch or Medical Toxicology Branch worksheet. Since there are reviewed and accepted studies for this study type, no review of this report is needed at this time. , 8/18/15.

SUBCHRONIC STUDIES

Oral toxicity, rat:

364-0002 49101 "90-day subacute oral toxicity study with CP 67573 (Glyphosate) in albino rats," INDUSTRIAL BIO-TEST LABORATORIES INC. NORTHBROOK, IL, 06/01/1972. IBT No. B1020 (ruled "invalid" by U.S. EPA - no DPR review needed).

Oral toxicity, non-rodent:

00364-0001 056346 Burtner, B. R. and D. C. Lindberg, "Ninety-day subacute oral toxicity study with CP 67573 in beagle dogs," IBT, 6/19/1972. IBT No. C1021. U.S. EPA validation status for this IBT study is "valid." Four beagles/group were dosed in diet with glyphosate [CP 67573] of unspecified purity at 0, 200, 600, and 2000 ppm. No treatment effects were observed. This study had weaknesses such as lack of internal QA oversight, lack of dietary analyses, sparse information on husbandry conditions, and an apparently high background of disease processes (intestinal roundworms, chronic pneumonitis) compared to modern studies. Thus, although EPA-valid, this study should be designated as supplementary data. Apparent NOEL is 2000 ppm. Given that there is an accepted dog chronic study with a challenging treatment range, there is no need for a replacement subchronic study at this time. [redacted], 7/17/15 (no DPR worksheet).

Dermal toxicity, 21/28-day or 90-day: (supplementary data)

364-0058 937603 Johnson, D. E., "Glyphosate Technical: 21-day dermal toxicity study in rabbits," IRDC, March 10, 1982. Monsanto Study # IR-81-195. Five NZW rabbits/sex/group were dosed with Glyphosate Technical (technical powder rendered as a paste with saline vehicle) at 0, 100, 1000, or 5000 mg/kg/day (6 hrs/day under secured gauze dressing, 5 days/week, for 15 exposures in 21 days). An additional 5/sex/group were treated the same, but with skin gently abraded. Investigators assessed effects on body weight, clinical signs, food consumption (qualitative), gross and microscopic pathology, and organ weights. Importantly, investigators performed graded assessments of exposure site for responses of the skin. NOEL for systemic effects is 5000 mg/kg/day (highest dose tested). NOEL for application site skin response is 1000 mg/kg/day, based on low grade erythema and edema in both sexes, regardless of whether skin was intact or abraded. Study is not acceptable, but useful enough that no additional information is needed at this time. No adverse effects are indicated. [redacted], 8/25/15.

Inhalation toxicity, 21/28-day or 90-day: (acceptable 4-week rat study)

364-0100 17465 (review gives ID or Record No. 15357), Velasquez, D. J., "Four-week study of 33-1/3% use-dilution of Roundup in water administered to male and female Sprague-Dawley rats by inhalation," (Part 1 tab in volume), Monsanto Environmental Health Lab Study No. 830025, 12/21/83. A 33.3% use dilution of Roundup was tested at 0.05, 0.16, and 0.36 mg/l. The latter dose was the highest possible concentration which could be generated. Exposure was 6 hrs/day, 5 days/week, for 4 weeks. There were no treatment-related effects noted. NOEL = 0.36 mg/L. Study is complete (reviewer considered study to be valid for a 4-week study, but study was not considered to fill the data requirements for a 90-day study. V. de Vlaming, 2/19/86. (Handwritten review in volume).

CHRONIC STUDIES

Combined (all rat chronic and/or oncogenicity studies) ** †

****364-207 091579** "Chronic study of glyphosate administered in feed to albino rats", (L.D. Stout and F.A. Ruecker, Monsanto Agricultural Co., Environmental Health Laboratory, St. Louis, MO. Laboratory Project No. MSL-10495, 9/26/90). Glyphosate (Lot XLH-264); 96.5% pure, was administered at concentrations of 0, 2,000, 8,000, or 20,000 ppm in diets of 50 Sprague Dawley rats/sex/group for 24 months. An additional 10 rats/sex/group were designated for 1-year interim sacrifice. NOEL = 8,000 ppm (b.w. decrement in females, basophilic degeneration of the posterior subcapsular lens fibers in males, and increased liver weights in males). In addition, a modest incidence of relatively uncommon tumor type (adrenal cortical carcinomas) was found only in 20000 ppm females (3/50, vs none in other groups of either sex), and is considered a "**possible adverse effect**". [No NOEL is presumed for neoplasia, since no threshold has been established]. The lack of notable findings up to and including 8000 ppm and the marginal evidence of tumor effects suggest minimal health concerns. **Acceptable**. Additional Record #'s 117131-117133 in Document No. 51834-002 were considered in this review. [redacted] and [redacted], 11/03/92.

51834-002 117131 Monsanto in-house (EHL) historical control data in support of Record No. 091579, above.

51834-002 117132 Bio/dynamics, Inc. historical control data in support of Record No. 091579, above.

51834-002 117133 Charles River Laboratories historical control data in support of Record No. 091579, above.

086/122 937682 "A Lifetime Feeding Study of Glyphosate (ROUNDUP Technical) in Rats"; Project No. 77-2062; Bio/dynamics Inc., East Millstone, N.J., 9/18/81. Glyphosate (98.7%) at 0, 3.05, 10.3 & 31.5 mg/kg (30, 100 & 300 ppm) to 50 Sprague-Dawley rats/sex/group for 24 months. **No adverse effects indicated** (J. Christopher had requested additional information on possible increase in interstitial cell (ISC) tumors in high dose males, but did not consider data to indicate an adverse effect. Historical data in 162 048774 indicate that ISC tumors were incidental). Report complete, but **unacceptable and not upgradeable** (inadequate doses, no toxicity seen at any dose). [redacted] 7/15/85 & 12/3/85. Subsequent review and rebuttal response (to 162 048774) by [redacted], 11/12/86.
NOTE: U.S. EPA required a more rigorous study to supersede this one, which has now been reviewed as Document No. 364-207 (p. 2 of this Summary).

087/123 937681 9/18/81, Pathology Report (Pathology Summary, Summary Incidence Tables, Neoplasm Summary Incidence Tables, Histopathology Incidence Tables, Males (Vol. 2 of 5); Part of 086 937682.

088/124 937680 7/17/81, Histopathology Incidence Tables, Females (vol. 3 of 5); Part of 086 937682. Note: Volume 124 is missing pages 3-117 to 3-183.

125 035836 9/18/81 [redacted] 12/3/85; Individual Body Weights, Food Consumption & Test Substance Intake Values - Males (Vol. 4 of 5); Part of 086 937682.

126 035837 9/18/81 [redacted] 12/3/85; Individual Body Weights, Food Consumption & Test Substance Intake Values - Females (Vol. 5 of 5); Part of 086 937682.

127/089 035838 11/9/82 & 11/18/82 [redacted] 12/3/85; Letters from 2 pathologists regarding increased incidence of thyroid tumors; Supplemental information to 086 937682.

058 937657 9/18/81, Study Summary (11 pages) and 19 pages of text; Partial duplicate of 086 937682.

364-0830 248122 [The first 15 pages apply to rat combined study, followed by 6 pages summarizing a chronic dog study. Only the **rat** study is covered by the present DPR worksheet.] No authors are listed. "Two-year repeated oral dose toxicity and carcinogenicity study." Study was conducted by Nippon Experimental Medical Research Institute Co., Ltd. in 1999 for an unspecified sponsor. Fifty F-344 rats/sex/group were treated in diet for 104 weeks in the main study at 0, 500, 4000, or 32000 ppm of (apparently) glyphosate, isopropylamine salt (97.5%). An additional 14/sex were assigned to satellite groups, designated for wk 79 sacrifice. Achieved doses were 25.0, 201, and 1750 mg/kg/day in males, and 29.7, 239, and 2000 mg/kg/day in females. There is too little information in this synopsis to make definitive conclusions, hence study is **unacceptable**. Apparent NOEL = 500 ppm. For males, this was based on transitory body weight decrements during the last quarter of the study, and to slightly reduced RBC count and HCT at 1-yr hematology at 4000 ppm. For females, slightly reduced RBC count at 26 weeks was attributed by investigators to treatment at 4000 ppm. At 32000 ppm, both sexes showed marked body weight decrements, diarrhea or loose stools, and distention of the bowel lumen. Kidney eosinophilic granules or hyaline droplets were significantly elevated in 32000 ppm males and females. Both sexes also indicated modest but consistent reductions in RBC count, HCT, and Hb. No oncogenicity was indicated. The full report is requested. [redacted], 8/26/15.

002 937658 "Two-Year Chronic Oral Toxicity Study With CP67573 In Albino Rats," IBT 1/14/74, IBT Study No. B564; [redacted] 7/8/85, Dose levels of 0, 30, 100 or 300 ppm: Invalid.

022/043 025282 IBT Summary, Duplicate information of 002 937658.

Chronic, dog **

** 131 037076 "Twelve Month Study of Glyphosate Administered by Gelatin Capsule to Beagle Dogs" (831); Project No. ML-83-137; Monsanto, St. Louis, MO, 11/1/85. Glyphosate technical (96%) given by capsule at 0, 20, 100 or 500 mg/kg/day; 6/sex/group; **No adverse effect** identified; NOEL greater than 500 mg/kg. **Acceptable**. [redacted], 7/24/86.

364-0830 248122 [The first 15 pages apply to rat combined study, followed by 6 pages summarizing a chronic dog study. Only the **dog** study is covered in this DPR worksheet.] No authors are listed. "One-year repeated oral toxicity by forced oral administration to dogs." Study was conducted by Nippon Experimental Medical Research Institute Co., Ltd. in 1998 for an

unspecified sponsor. Four beagles/sex/group were dosed daily by capsule at 0, 30, 100, or 300 mg/kg/day for one year. There is too little information in this 6-page synopsis to make definitive conclusions, hence study is unacceptable. Apparent NOEL = 30 mg/kg/day, based on loose stool, diarrhea, watery diarrhea, and mucous stool at 100 to 300 mg/kg/day. No adverse effects are indicated. [redacted], July 7, 2015.

002 937659 "Two-Year Chronic Oral Toxicity Study With CP 67573 in Beagle Dogs". IBT No. 651-00565 (same as J-565, ruled "valid but unacceptable" by EPA); IBT, Northbrook, Illinois, 11/30/73; CP 67573 (Glyphosate) at 0, 30, 100 & 300 ppm in 4 dogs/sex/group; **Insufficient information for adverse effect assessment; Unacceptable** (No pathology summary report; no means or standard deviations presented for summary data; no statistical analysis). [redacted], 7/8/85.

022/043 025281 IBT Summary, Duplicate information of 002 937659.

Oncogenicity, mouse ** †

** **076 937660** "A Chronic Feeding Study of Glyphosate (ROUNDUP Technical) in Mice" (832); Project No. 77-2061; Bio/dynamics Inc., Monsanto, St. Louis, Missouri, 7/21/83. Glyphosate technical (99.7%); Dosages of 0, 1000, 5000 & 30000 ppm in diets of CD-1 mice. **Possible oncogenic effect** [equivocal effect on renal tubular epithelial adenomas plus carcinomas (relatively uncommon tumors) in males: incidence of adenomas plus carcinomas = 1, 0, 1 and 3 in 0, 1000, 5000 & 30000 ppm groups, respectively]. General systemic toxicity NOEL = 5000 ppm (effects at 30000 ppm included central lobular hepatocyte hypertrophy in males, central lobular hepatocyte necrosis in males, chronic interstitial nephritis in males, and proximal tubule epithelial basophilia and hypertrophy in females). CDFA/DPR reviews and history of disposition of study: [redacted], 7/19/85 (unacceptable, possible adverse effect indicated); [redacted], 5/1/86 (unacceptable, possible adverse effect indicated); [redacted] 11/17/86 and 12/14/87 (Report **acceptable with possible adverse effect** - both reviews). **NOTE: EPA had been requiring a repeat mouse oncogenicity study, but this requirement appears to have been waived on or before the time of the Federal Register document of 3/12/92 (**found in Appendix 3, at the end of Document No. 51834-002). See EPA publication, "Guidance for the reregistration of pesticide products containing glyphosate as the active ingredient" (June, 1986).

142 045712 7/21/83; [redacted] 11/21/86: Toxicology Report (Individual Body weight, Body weight gain, Food consumption, Feed efficiency & Test Substance Intake Values in Male Mice); Volume 2 of 8; Part of 076 937660.

143 045713 7/21/83; [redacted] 11/21/86: Toxicology Report (Individual Body weight, Body weight gain, Food consumption, Feed efficiency & Test Substance Intake Values in Female Mice; Volume 3 of 8; Part of 076 937660.

144 045714 7/21/83; [redacted] 11/21/86: Toxicology Report (Physical observations by group; Individual Water Consumption & Hematology Values, Total & Differential Leukocytes, Organ Weights & ratios; Volume 4 of 8; Part of 076 937660.

145 045715 7/21/83; [redacted] 11/21/86: Pathology Report (Individual Data in male mice killed by design: gross & microscopic findings; Volume 5 of 8; Part of 076 937660.

146 045716 7/21/83; [redacted] 11/21/86: Pathology Report (Individual data in male mice killed in extremis or found dead (unscheduled deaths)--gross & microscopic findings; Volume 6 of 8; Part of 076 937660.

147 045717 7/21/83; [redacted] 11/21/86: Pathology Report (Individual data in female mice killed by design: gross & microscopic findings); Volume 7 of 8; Part of 076 937660.

148 045718 7/21/83; [redacted] 11/21/86: Pathology Report (Individual data in female mice found dead or killed in extremis: gross & microscopic findings; Lesion incidences & Individual fate data for male and female mice; QA Statement; Volume 8 of 8; Part of 076 937660.

128 036060 10/7/85. Examinations of 3 additional sections of each kidney of each male in the primary study 076 937660, by the pathologist who read the original slides. No new renal epithelial tubular tumors were found. [Between the time of the final report and this re-evaluation, a renal epithelial adenoma was found in a control male. This lesion was not observed in the additional sections taken from the same kidney in the present report]. [redacted], 5/1/86.

163 048775 "Response to SB950 Data Request For Glyphosate, Oncogenicity: Rodent" (8/26/86 Rebuttal). Provided clarifications relating to primary study 076 937660 and historical control data on kidney lesion incidence for CD-1 COBS mice at Bio dynamics. Incidence of tubular adenomas was very low and there were no tubular carcinomas listed, indicating that the finding of 3 such tumors in a group of 50 males was an unusual incidental finding. [redacted] 11/17/86.

178 063476 "Pathology working group report on glyphosate in CD-1 mice." Report prepared by R. M. Sauer, V.M.D., on 10/10/85. Blind re-reading of all sections of kidneys of all males from primary study 076 937660 by original pathologist and by three other pathologists. Consensus was that renal tubular cell adenoma and carcinoma incidence was 1, 0, 1 and 3 for groups: control, 1000, 5000 and 30000 ppm respectively. [redacted] 11/10/87.

178 056111 FIFRA Scientific Advisory Panel: "A set of scientific issues being considered by the agency in connection with the registration standard for Glyphosate." (Meeting date after 1/17/86). Panel noted that renal tumor incidence data is equivocal: age-adjusted tumor incidence data do not demonstrate a statistically significant increase in such tumors based on concurrent controls, nevertheless the incidence at 30000 ppm (the HTD) is quite significant when compared to historical controls. The Panel proposed classification as "Group D" (not classified) and proposed further tests in rats and/or mice to resolve the oncogenicity issue. This evaluation was considered by [redacted] in 11/10/87 review.

178 056112 "FAO plant and protection paper #77: Report of the joint meeting on pesticide residues." Rome, 9/29/86 - 10/8/86. Report states that glyphosate is of low order toxicity in the major toxicity studies and that "There is no evidence of carcinogenicity."

178 (no record numbers) Additional interpretations associated with the 4/3/87 Rebuttal document by Monsanto Agricultural Co. These were brief memoranda by 4 prominent scientists in tabs "Part 1" through "Part 4": of this volume, who cited statistical and biological evidence for the proposition that glyphosate is not an oncogen. These statements were undoubtedly made available for SAP consideration in 1986, and should be considered by CDFA, should glyphosate come under risk assessment in California.

002 937661 Title: "18-Month Carcinogenic Study With CP67573 in Swiss White Mice," IBT 9/19/73; IBT Study No. B569; [redacted] 7/8/85; Dose levels of 100 or 300 ppm: Invalid.

022/043 025280 IBT 9/19/73; Summary; Duplicate information of 002 937661.

GENOTOXICITY

Bacterial reverse mutation assay **

** 057 937684 "Microbial Mutagenicity Testing on CP67573 (Glyphosate)," Institute of Environmental Toxicology; 7/20/78; S. typhimurium (TA 1535, TA 1537, TA 1538, TA 98, TA 100), also E. coli WP2 hcr; Glyphosate (98.4%) at 0, 10, 50, 100, 1000 and 5000 µg/plate; 2 plates/group; No mutagenicity indicated; **Acceptable.** [redacted], 7/9/85 & 7/11/85.

057 025275, 025274 7/20/78 Summary, Duplicate information for 002 937684.

057 033911 "Final Report on Salmonella Mutagenicity Assay of Glyphosate," Test No. LF-78-161, Monsanto, EHL, St. Louis, MO, 6/16/78; Ames spot test, plate incorporation & toxicity test; S. typhimurium (TA 100, TA 98, TA 1535, TA 1537); Glyphosate (98.4%); Spot test, 10 to 1000 µg/plate; Plate incorporation, 0, 0.1, 0.4, 1, 2, 10, 30, 100 and 1000 µg/plate; Toxicity test, 0.03, 0.1, 1, 3, and 10 µg/plate; Levels tested both with and without activation; Insufficient information for adverse effects assessment; **Unacceptable**, **Upgradable** (Needs toxicity test data, clarification of statistical methods used, description of microbiological methods. There is no apparent need to upgrade this study, as other studies are on file which fill this data requirement.) [redacted] 7/11/85.

Mutagenicity: *In vitro* mammalian cell assay **

** 100 017462 "CHO/HGPRT Gene Mutation Assay with Glyphosate," Study No. ML-83-155, Monsanto, St. Louis, MO, 10/20/83; CHO cell line (K1BH4); Glyphosate (98.7%); Doses of 0, 2, 5, 10, 15, 20 and 25 mg/ml; No evidence of mutagenicity up to doses which cause greater than 50% cytotoxicity; **Acceptable**. [redacted], 7/18/85.

100 017463 "Glyphosate: Mutagenicity Studies, Over-all Assessment," no date (Justification of dose levels for 100 017462, 100 017461 and 100 017459).

Mutagenicity: *In vivo* cytogenetics **

** 100 017461 "In Vivo Bone Marrow Cytogenetics Study of Glyphosate in Sprague-Dawley Rats," DMEH Project. No. ML-83-236 (Monsanto 10/20/83). In vivo cytogenetics (843).

Glyphosate (98.7% purity) administered i.p. to 18/sex/dose at 0 or 1.0 g/kg, sacrificed at 6, 12, or 24 hours, bone marrow cells scored for chromosome aberrations. No mutagenicity observed. **Complete, Acceptable.** [redacted] 7/18/85 & [redacted] 11/24/86.

100 017460 10/21/83 QA Statement; Bone marrow cell viability data (summary & individual), Appendices 1 & 2; [redacted] 7/18/85; Part of 100 017461.

100 017458 8/26/86; "A Study of the Plasma and Bone Marrow Levels of Glyphosate Following Intraperitoneal Administration in the Rat,", DMEH Project No. ML-83-218; Supplemental to 100 017461.

169 048781 10/29/83 Response to CDFA review of 7/18/85 (100 017461), includes also Attachment 1 (EPA comments and Monsanto response). [redacted], 11/24/86.

058 937685 "Dominant Lethal Study in Mice," (IRDC, 4/16/80). Mouse dominant lethal (843). Glyphosate (98.7% purity) administered by oral gavage to 10 males/dose at 0, 200, 800, 2000 mg/kg, followed by sequential matings of 2 females/male/week for 8 weeks, a total of 160 females/dose. No mutagenicity observed upon sacrifice and examination of uteri. **Incomplete, Unacceptable.** Too few animals, individual data missing. [redacted], 7/11/85 & [redacted], 11/24/86.

169 048782 8/26/83; Response to CDFA review of 058 937685 on 7/11/85 (1 page, no data); [redacted] 11/24/86.

179 057543, Partial duplicate of 937685.

002 024951 Title: "Mutagenic Study With CP67573 in Albino mice" (Dominant Lethal), IBT No. E567; IBT, 1/24/72; J. Christopher 7/8/85; Dose levels 5 and 10 mg/kg: Ruled **invalid** by EPA.

022 025276 4/16/80 Summary, Duplicate information of 002 024951.

030 056909, 056910, Summary of 024951.

DNA Damage (study type is not required at this time) **

** 100 017459 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound JJN-1020 (Glyphosate) Using Rat Hepatocytes in Culture," Study No. AH-83-181; (Naylor Dana Institute for Disease Prevention 10/21/83). Glyphosate (98.7% purity) at doses from 1.25 X 10E-5 to 1.25 X 10E-1 mg/ml to primary rat hepatocyte cultures. UDS measured by autoradiography. **No adverse effect. Acceptable.** (Previously considered unacceptable by [redacted], 7/18/85, later by [redacted], 11/24/86. Data in 179 057544 permitted status change to **acceptable** in [redacted] review of 12/7/87).

179 057544 "Data Submitted in Response to SB950 for Glyphosate In Vitro Hepatocyte UDS Assay." Raw data and supplementary information which made the study **acceptable with no adverse effect.** [redacted], 12/7/87.

170 048784 8/26/86; Response to first review of 100 017459, discusses the adequacy of dose levels; [redacted], 11/24/86.

100 017463 "Glyphosate - Mutagenicity Studies, Over-all Assessment," no date (Justification of dose levels for 100 017462, 100 017461 and 100 017459).

057 033913 "Microbial Mutagenicity Testing on CP67573 (Glyphosate)" (Institute of Environmental Toxicology 7/20/78). DNA damage (844). Glyphosate (98.4% purity) at doses of 0, 20, 100, or 200 µg/disk to B. subtilis matched strains H17 (repair-competent) and M45 (repair-deficient) in a disk diffusion, growth inhibition assay. No DNA mutagenicity observed. **Incomplete and Unacceptable.** Only single plates per treatment, doses tested from 20 to 200 µg/disk but reported as 20 to 2000. Reviews by [redacted], 7/9/85 and [redacted], 11/24/86. Also examined by [redacted] as part of 12/7/87 rebuttal (no separate written review).

170 048783 8/26/86; Response to review of 057 033913 on 7/9/85; [redacted], 11/24/86.

REPRODUCTIVE TOXICITY, RAT **

364-206 095055 "Two generation reproduction feeding study with glyphosate in Sprague-Dawley rats". M.S. Reyna, Monsanto Agricultural Co., Environmental Health Laboratory, St. Louis, MO, 8/27/90. Study # 88038. Glyphosate, 97.67% purity, lot number XLI-203, fed in the diet continuously to two generations of Sprague-Dawley rats. F0 parents produced one litter and F1 parents produced two litters at 0, 2000, 10000, or 30000 ppm. There were 30 rats/sex/group. Parental NOEL = 10000 ppm (soft stools and reduced body weights at the high dose). Reproductive NOEL = 10000 ppm (reduced pup growth late in lactation). **No adverse effects. **Acceptable**. ([redacted] and [redacted], 7/31/92).

057 937677 "A Three Generation Reproduction Study In Rats With Glyphosate," Project No. 77-2063, BDN 77-417; Bio/dynamics Inc., 3/31/81. Glyphosate, lot XHJ-64, 98.7% was administered at 0, 3, 10, and 30 mg/kg/day in diets of CD* rats; Apparent reproductive effects NOEL > 30 mg/kg/day (No definitive evidence of systemic or reproductive effects at the doses tested). CDFA review dates: [redacted], 7/10/85; [redacted], 11/19/86 and 12/9/87. Changes in CDFA study status: 7/10/85 review indicated unacceptable study, possible reproductive effect (based on the data then available: volumes 57, 77 and 79): 11/19/86 review indicated unacceptable study, no adverse effects indicated (based on review of previous data plus new data and Monsanto Rebuttal comments of 8/26/86 and 9/30/86 in volumes 164-168). The 12/9/87 review considered the 5/18/87 Monsanto Rebuttal statement, from Doc. #364-179, and did not recommend change of status, which is: **Unacceptable study with no adverse effects indicated,** (no definitive LEL for reproductive effects).

164 048776 Rebuttal (5 pages); Appendix D, Pathology Report, Terminal Sacrifice (Individual gross & microscopic observations, Summary-incidence of microscopic findings); [redacted], 11/19/86; Part of 057 937677.

165 048777 Pup selection procedure; Day 21 mean pup weights: individual and mean tables; [redacted], 11/19/86; Part of 057 937677.

166 048778 Individual organ and body weights and organ/body and organ/brain weight ratios; [redacted], 11/19/86; Part of 057 937677.

167 048779 Individual body weights, body weight change, food consumption and test substance intake data; [redacted], 11/19/86; Part of 057 937677.

168 048780 Individual maternal body weight data, gestation and lactation periods; [redacted], 11/19/86; Part of 057 937677.

077 937679 8/15/83 (Relates to 057 937677). Addendum: Pathology Report (Summary incidence of microscopic findings, terminal sacrifice); Contains pages 131-169 of full report); Part of [redacted], 7/10/85 review.

079 937678 7/6/80; [redacted], 7/10/85; Addendum to Pathology Report (Histopathology data on kidneys of low & mid-dose F3B males; includes historical background data for chronic nephritis); Part of 057 937677.

002 937676 Title: "Three-Generation Reproduction Study With CP 67573 in Albino Rats," IBT No. B566; IBT 7/26/73; [redacted] 7/8/85 Glyphosate (no purity); Doses of 0, 30, 100, 300 ppm; Ruled valid but unacceptable by EPA.

022 025279 6/26/73 IBT Summary, Duplicate info. of 002 937676.

106 065474 Rebuttal containing the proposed protocol for: Two Generation Reproduction Study of Glyphosate in the Diet of Albino Rats. CDFA acknowledges the intent of Monsanto Company to repeat the rat reproduction study. [redacted], 11/18/88.

DEVELOPMENTAL TOXICITY

Rat **

** 121 035832 "Teratology Study in Rats", Study No. IR-79-016, IRDC, 3/21/80. Glyphosate, technical (98.7%); Doses of 0, 300, 1000 and 3500 mg/kg/day by gavage; Maternal NOEL = developmental toxicity NOEL = 1000 mg/kg/day. Developmental toxicity was seen only at dosages which cause substantial maternal toxicity. Reviews by J. Christopher 7/11/85 (judged unacceptable, with possible adverse effects); J. Parker 11/25/85 (judged the study unacceptable due to insufficient data, but not to indicate adverse effects, because developmental effects were observed only at the level which caused marked maternal toxicity. [redacted] 11/20/86 (**Acceptable with additional data in 173 048856. No adverse effects.)**

173 048856 Rebuttal review by [redacted] (11/20/86); Rebuttal (2 pages) plus Addendum (Individual antemortem observations, test article homogeneity & stability, protocol revision sheet, test article calculations, test material preparation records, Individual rat test material administration and observation records, Individual necropsy observations & summary); Part of 121 035832.

058 937672 IRDC Historical Control Data: Charles River COBS CD Rats (3 pages of tables); [redacted] 7/11/85; Supplemental information to 121 035832. Reviewer considered increased resorptions, decreased fetal body weight, and increased numbers of unossified sternebrae as a "fetotoxic" response. (See updates in later reviews).

058 937674 Partial duplicate of 121 035832 (14 pages duplicate text plus 2 pages duplicate tables); see also comments by EPA staff and response by Monsanto at front of Part C.

022 025277 3/21/80 Summary, Duplicate information of 121 035832.

Rabbit **

** 121 035831 "Teratology Study in Rabbits", Study No. IR-79-018, IRDC, 2/29/80; Glyphosate technical (98.7%); Doses of 0, 75, 175 and 350 mg/kg gestation days 6-27 by gavage to Dutch Belted rabbits; Maternal toxicity NOEL = 175 mg/kg/day (high mortality, misc. clinical signs at 350 mg/kg/day). Developmental toxicity NOEL = 175 mg/kg/day (highest dosage without excess maternal mortality). Reviews by [redacted] 7/8/85 (insufficient information for assessment), J. Parker, 11/24/85 (unacceptable, needed additional data; no adverse effects, developmental NOEL = 350 mg/kg/day). Rebuttal (and additional data) review by [redacted], 11/21/86: **No adverse effects:** Developmental effects NOEL set at 175 mg/kg/day, the highest dose with sufficient surviving litters to assess developmental toxicity, however review noted that there was no developmental toxicity observed in the 6 litters delivered of 350 mg/kg/day dams). **Acceptable** on the basis of additional data.

058 937673 12/01/80; [redacted] 7/8/85; IRDC Historical Control Data: Dutch Belted Rabbits (3 pages of tables); Supplemental to 121 035831.

172 048855 (9/30/86, Rebuttal/additional data to study, 121 035381); [redacted], 11/21/86: Rebuttal (2 pages); Attachment 1, (Individual maternal antemortem, necropsy & pathology observations, analytical methods, homogeneity & stability data, protocol revision sheet; Attachment 2, (Test article calculations, test material preparation records, individual rabbit test material administration and observation records).

058 937675 2/29/80 Partial duplicate of 121 035831 (16 pages duplicate text, 2 pages duplicate tables).

022 025278 2/29/80 Summary; Duplicate information of 121 035831.

002 937670 Title: "Teratogenic Study With CP 67573 In Albino Rabbits," 6/30/72. IBT Study No. J568; Dose levels of 10 or 30 mg/kg Days 6-18: Invalid.

NEUROTOXICITY

Acute neurotoxicity, rat

90-day neurotoxicity, rat

Developmental neurotoxicity, rat

Delayed neurotoxicity, hen (study type is not required at this time)

043/045 035918 Title: "Neurotoxicity Study with Chickens," IBT No. 8580-09117, IBT, 12/17/86. Initially reviewed by [redacted] (7/8/85). Rebuttal review by [redacted] (11/18/86). Invalid IBT study. **No adverse effect indicated and no replacement study required**: Test article is not in the class of compounds which require this test, and there are no indications from other tests suggesting that delayed neurotoxicity potential exists.

171 048785 Response to review on 7/8/85 of 043/045 035918.

022 025273 Summary; Duplicate information of 043/045 035918.

IMMUNOTOXICITY

ENDOCRINE DISRUPTOR STUDIES

SUPPLEMENTAL STUDIES

Studies on Glyphosate impurities

00364-0005 937690 Colvin, L. B., S. J. Moran, J. A. Miller, and J. T. Marvel, "CP 67573 residue and metabolism, Part 11: The metabolism of aminomethylphosphonic acid-^{14}C (CP 50435-^{14}C) in the laboratory rat," Monsanto Agricultural Division Research Department, 6/15/73. Agricultural Research Report # 303. Male Wistar rats were dosed once by gavage with aminomethylphosphonic acid-^{14}C (CP 50435-^{14}C). This is a key metabolite of Glyphosate (CP 67573). Dose was about 6.7 mg/kg, labeled on the methylene carbon at 8.9 mCi/mmol. Urine, feces, and expired air (CO_2 trap) were collected over 120 hours, with tissue collection at termination. Residues were 20% of administered dose in urine, 73% in feces, and 0.06% in expired CO_2. About 92% of recovered dose was collected within 48 hours. No tissues contained remarkable amounts of label. Urine samples were lyophilized and derivatized with trifluoroacetic acid/trifluoroacetic anhydride and with diazobutene for the principal gas-liquid

chromatography (GLC) quantification and mass spectrometric (MS) analysis. Three different radiochromatography systems found the dominant peak of urine samples to co-elute with 50435-^{14}C fortified samples. That peak comprised 93-99% of total radioactivity eluted. GLC analysis of derivatized urine samples found a major peak corresponding to that of 50435 standards, although a peak of similar magnitude was also evident. A dominant MS peak (m/e 208) that was quite characteristic of derivatized 50435 standards was also dominant in un-fortified urine samples. It is thus clear that most of urinary excreta from an oral dose of aminomethylphosphonic acid was excreted unmetabolized, however this study did not seek to identify and quantify minor metabolites. Feces were not evaluated for metabolic profile. This study is supplementary by design, as it addresses the fate of a metabolite as opposed to the active ingredient. Although the study has a non-guideline design, and lacked QA oversight, the study provided some useful information relevant to glyphosate disposition. [redacted], 8/27/15.

The following summaries are either located under the title, "Summary of Toxicology Studies Conducted with N-nitroso Glyphosate (NNG)" in volume 364-045 or under the title, "Toxicology and Safety Assessment for N-Nitrosoglyphosate", pp. 12-16 in volume 364-071. N-nitroso Glyphosate is a manufacturing impurity of glyphosate found at very low levels. The following summaries were reviewed by CDFA toxicologist, R. Wang, who concluded that "Roundup herbicide and its nitrosoglyphosate contaminant do not appear to pose unreasonable health hazards to users and consumers" (memo from the beginning pages of Volume 071). Of the studies which follow, most report clearly negative results. **CDFA requests a copy of the full report summarized as Record #35925 (IBT study BTL-76-32)**, which indicated an increase in resorptions and decrease in 24-hr survival of offspring in a rabbit teratogenicity/reproduction study. No worksheets have been generated by Medical Toxicology Branch on the following studies.

045/071 035923 "Mutagenicity Evaluation of CP76100;" Salmonella (5 strains) and Saccharomyces (strain D-4); Litton Bionetics; BIO-76-116; No report date; N-nitroso Glyphosate; No mutagenicity indicated; **Very brief summary**.

045/071 035924 "Dominant Lethal Study with CP76100 in Albino Mice," BTL-76-31; NNG at 5 or 10 mg/kg by i.p. injection; No lab or report date; **No adverse effect indicated; Very Brief Summary.**

045 035925 "Teratogenic Study with CP76100 in Albino Rabbits;" Lab and report date not stated; N-Nitrosoglyphosate (Glyphosate manufacturing impurity) at 0, 10 or 30 mg/kg days 6-18 of gestation by gavage; Increased resorptions, decreased numbers live young per 100 implantation sites and reduction in 24-hour survival at 30 mg/kg; **Very Brief Summary.**

071 No record #; 3-Generation Reproduction - Rat (834); BTL-76-34; Lab and report date not stated; NNG at 0, 3, 10 and 30 mg/kg by gavage; **No adverse effects indicated; Very Brief Summary**.

045/071 035926 "Eighteen Month Oral Toxicity Study in Hamster;" No lab or report date; Study actually run 12 months due to excessive non-treatment-related deaths in all groups; NNG at 0, 3, 10 or 30 mg/kg/day by gavage; **No adverse effect indicated; Very Brief Summary.**

NOTE: There are U.S. EPA DER's of additional studies on this impurity.

071 No record #; Chronic - Rat (831); BTL-76-35; Lab & report date not stated; NNG at 0, 3, 10 OR 30 mg/kg for 2 years by gavage; **No adverse effects indicated; Very Brief Summary**.

071 No record #; Chronic - Dog (831); BTL-76-33; Lab & report date not stated; NNG at 0, 3, 10 or 30 mg/kg/day by gelatin capsules for two years; **No adverse effects indicated; Very Brief Summary**.

071 No record #; Oncogenicity - Mice (832); IRD-77-223; IRDC; Report date not stated, but this summary based on an interim report (in-life effects data only); NNG at 0, 50, 150 and 500 mg/kg/day for 24 months by gavage; **No adverse effects indicated; Very Brief Summary.**

Miscellaneous IBT study summaries

The following summaries are located under the title, "Summary of Available Toxicity Data with Glyphosate & Roundup Herbicide: Mutagenicity/Reproduction/Teratogenicity" in volume 364-045 (1 & 1/2 pages). All these studies are either invalid or do not meet EPA guidelines.

045 035937 IBT No. 633-07507 ; Gene Mutation (842) Salmonella (5 strains) plus 1 strain Saccharomyces; No adverse effect indicated: Invalid.

045 No record #; IBT No. 633-07801; Rec-assay (844); B. subtilis and E. coli; No adverse effect indicated: Invalid.

045 035939 IBT No. 623-7508; Host-mediated assay with S. typhimurium and albino rats and mice (842); no mutagenicity indicated: Valid study.

045 035901 IBT No A2144: A testicular effects study in rabbits. Not a standard reproduction study. **No adverse effects indicated.** No additional information necessary. [redacted], 11/16/87. No written review.

364-0001 56345 IBT No. A1549 (21-day dermal rabbit) U.S. EPA Invalid
364-0001 937655 IBT No. A2144 (21-day dermal rabbit) U.S. EPA Invalid
364-0001 937656 IBT No. A2468 (21-day dermal rabbit) U.S. EPA Invalid

Not on U.S. EPA validation list for IBT studies, but not reviewed by DPR:
364-0001 123845 IBT No. A2277 (acute oral rabbit)

NOTE: Many short summaries of studies were submitted in DPR Document No. 364-0022. These included largely 1 to 3-page summaries of IBT studies. A high percentage of studies from that laboratory have been designated as "invalid" or "supplementary" data by U.S. EPA. At present there is no evidence of any reviewable studies in this series. Associated record numbers are: 57841, 25274, 25276, 25278, 937696, 25281, 57844, 25275, 25279, 57842, 25273, 25280, 25282, 57845, 56348, 57718, 937605, 57843, 25277, 937580, 937650, and 57846.

364-0274 137951 Glyphosate Mammalian Toxicology Summary prepared for European Union Re-registration (81pages). Source: Cheminova (A/S) Lemvig, Denmark, Study Date: 05/01/1995. There are no reviewable data in this summary. [redacted], 8/13/15.

364-0274 137952 Glyphosate: Tier 1 Toxicological Data Summary (ca.100 pages), Cheminova (A/S) Lemvig, Denmark, Study Date: 04/01/1995. There are no reviewable data in this summary. [redacted], 8/13/15.