CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METHOMYL

Chemical Code # 383**, Document Processing Number (DPN)** # 00253
SB 950 # 169
Original date: August 8, 1986
Revised: 11/6/87, 6/15/88, 7/21/89, 1/10/90, 9/15/97, 5/2/98, 1/12/99, 9/28/07, 8/28/12, 3/12/14, 4/28/16

DATA GAP STATUS

Combined toxicity, rat:	No data gap, possible adverse effect (chronic, no tumors)
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no 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:	No data gap, possible adverse effect

Toxicology one-liners are attached.

All relevant DPR records on file as of April 28, 2016 have been evaluated (including record numbers through 265393, Document No. 253-0303). Several older record numbers evaluated are of the series 900,000+.

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: T160428
Revised by [redacted], 4/28/16.

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

253-0296; 264058; "The Metabolism of [1-^{14}C]Methomyl in Male Cynomolgus Monkeys"; (D.R. Hawkins, B.C. Mayo, A.D. Pollard, L.M. Haynes; Department of Chemical Metabolism and Radiosynthesis and Department of Non-Rodent Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. DPT 258/920494; 6/16/92); Four male cynomolgous monkeys were dosed orally by gavage with 5 mg/kg of [1-^{14}C]Methomyl (lot no. 2729-122, purity: 99.9%, radiochemical purity: >97%, specific activity: 44.8 µCi/mg). The final specific activity was adjusted to 15.1 µCi/mg with [1-^{13}C]Methomyl (lot no. 2565-151, chemical purity: 99.9%) and unlabeled methomyl (lot no. DPX-X1179-379, purity: 98.9%). Urine and feces were collected up to 168 hours post-dose. The most important route of excretion was via exhalation with 39% of the administered dose excreted within the first 48 hours. Another 32% was recovered in the urine (urine and cage wash). Only 3% of the label was recovered from the feces. At 168 hours post-dose, 4.76% of the label was still retained in the tissues. Only 79% of the administered dose was recovered. The reason for this low percentage of recovery was likely due to the fact that excretion via exhalation persisted beyond 48 hours post-dose when the collection of air samples was discontinued and the carcasses, in which additional radiolabel could have been recovered, were not analyzed. A significant fraction of radiolabel was ^{14}carbon dioxide which was not only exhaled but also incorporated into other chemicals through catabolic metabolism. This incorporation was evident in the high percentage of the administered dose which was recovered in the tissue after 168 hours and the relatively equal distribution of the radiolabel throughout the body. Due to the myriad of radiolabeled compounds recovered in the urine, identification of specific moieties was limited. Tentatively identified compounds included the mercapturic acid derivative of methomyl (0.8%), methomyl oxime sulfate (1.5%), acetonitrile (1.7%), acetate (0.4%) and acetamide (0.4%). **Study supplemental** (non-guideline study). ([redacted], 4/3/12)

253-0296; 264059; "The Metabolism of [1-^{14}C]Methomyl in Rats"; (D.R. Hawkins, B.C. Mayo, A.D. Pollard, L. Haynes; Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England, E.I. du Pont de Nemours & Co., Du Pont Agricultural Products, Research and Development Division, Experimental Station, Wilmington, DE; Report No. DPT 210/91311; 9/6/91); Five Sprague Dawley rats/sex were dosed orally by gavage with 5 mg/kg of [1-^{13}C/^{14}C]Methomyl ([1-^{14}C]Methomyl: lot no. 2449-040, radiochemical purity: >97%, specific activity: 66.9 µCi/mg; [1-^{13}C]Methomyl: lot no. 2565-151, chemical purity: 99.9%). Urine and feces were collected up to 168 hours post-dose. Expired air was recovered up to 120 hours post-dose. Approximately 53% of the administered dose was recovered in the urine. An important route of excretion was via exhalation with 34% to 36% of the administered dose being excreted by 120 hours post-dose. Only 2 to 3% of the label was recovered from the feces. At 168 hours post-dose, 8 to 9% of the administered label was still retained in the tissues. Predominant sites of the recovery were red blood cells and skin (1.5 to 1.9% and 2.4 to 2.5%, respectively). A significant fraction of radiolabel was ^{14}carbon dioxide and other low molecular compounds which were not only

exhaled but also incorporated into other chemicals through catabolic metabolism. This incorporation was evident in the high percentage of the administered dose which was recovered in the tissue after 168 hours and the relatively equal distribution of the radiolabel throughout the body (excluding the high levels in the red blood cells and skin). Due to the myriad of radiolabeled compounds recovered in the urine, identification of specific moieties was limited. Identified compounds included the mercapturic acid derivative of methomyl (17 to 18%), methomyl oxime sulfate and acetic acid (5.0 to 5.4%), acetonitrile (6%), acetate (1.4 to 2.0%) and acetamide (0.2 to 0.4%). **Study supplemental** (non-guideline study). [redacted] 4/4/12)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat **

**253-199; 113701; Acute Oral Toxicity; 811; Rat; Haskell Laboratory, Newark, DE; Study No. 661-91; 12/9/91; Methomyl technical (98.35%); 10/sex/dose; 20, 40, 80 mg/kg; mortalities- males: 2/10, 5/10, 10/10; females: 1/10, 8/10, 10,10, respectively; observations- clinical signs of toxicity (tremors, low posture, or salivation) apparent within 1 hour of dosing at 20 or 40 mg/kg in both sexes; all deaths occurred within 1 day of dosing; surviving animals underwent increases in body weight after day 2; convulsions and death in all rats receiving 80 mg/kg within 1 day of dosing; necropsies did not indicate target organ(s); NOEL<20 mg/kg (LDT); LD50, (M)=34 mg/kg; (F)=30 mg/kg; combined=32 mg/kg; Category I; Acceptable. ([redacted] 4/13/92)

253-0292; 259716; Acute Oral Toxicity; 811; rat; J. O. Kuhn, “Acute Oral Toxicity Study in Rats”; Stillmeadow, Inc., Sugar Land, TX; Project #: not specified; Laboratory Study #: 2918-96; 09/05/96; Methomyl 90% SP; Batch #: not specified; composition: a.i., 90% Rotam; 5.0, 6.5, 8.0, 10.0, 17.0, 24.0, and 25.0 mg/kg (neat); single, oral-gavage dose, with a 14-day observation period; 5 male or female test subjects/dose level; mortality: (5.0 and 8.0 mg/kg) none; (6.5 mg/kg) 1/5 F; (10.0 mg/kg) 5/5 F; (17.0 mg/kg) 4/5 M; (24.0 mg/kg) 5/5 F; (25 mg/kg) 5/5 M; clinical signs: (5.0 mg/kg) muzzle stained red (5/5 F), piloerection (5/5 F), salivation (3/5 F), body tremors (3/5 F), sensitivity to sound (3/5 F), rapid breathing (2/5 F), gasping (1/5 F), and polyuria (1/5 F); (6.5 mg/kg) piloerection (5/5 F), body tremors (5/5 F), diarrhea (4/5 F), and salivation (1/5 F); (8.0 mg/kg) piloerection (5/5 M), hypoactivity (5/5 M), salivation (5/5 M), rapid breathing (3/5 M), body tremors (2/5 M), ptosis (1/5 M), red-stained muzzle (1/5 M), and clear, nasal discharge (1/5 M); (10.0 mg/kg) none reported; (17.0 mg/kg) piloerection (1/5 M), gasping (1/5 M), salivation (1/5 M), rapid breathing (1/5 M), body tremors (1/5 M), hypoactivity (1/5 M), red-stained muzzle (1/5 M), red crust around nose (1/5 M), and eyes (1/5 M); (24 and 25 mg/kg) none reported; body-weight gain was positive in all throughout, except 1/5 F at the 5.0 mg/kg dose level from Day 7 to 14; necropsy: (5.0 and 8.0 mg/kg) no gross abnormalities reported; (6.5 and 10.0 mg/kg) (decedent[s]) chin hair matted and clear liquid in stomach in 1/5 F at 6.5 mg/kg and 5/5 F at 10.0 mg/kg; (17.0 mg/kg) muzzle hair matted, clear liquid in stomach, orange gel in small intestine, green paste in large intestine in 4/5 M; (24 mg/kg) chin hair matted (3/5 F); clear liquid in stomach (4/5 F); orange gel in small intestine (5/5 F), and green paste in large intestine (5/5 F); (25 mg/kg) muzzle and chin hair matted (5/5 F); gas and clear liquid in stomach (5/5 F); orange gel in small intestine (5/5 F), and green paste in large intestine (5/5 F); reported LD_{50} (M) = 14.2 (11.0 - 18.4) mg/kg; reported LD_{50} (F) = 7.14 (6.22 - 8.19) mg/kg; Toxicity Category I; **Acceptable. ([redacted], 09/27/11)

Acute dermal toxicity **

253-199; 113702; Acute Dermal Toxicity; 812; Rabbit; Haskell Laboratory, Newark, DE; Study No. 455-91; 8/7/91; Methomyl technical (98.35%); 5/sex; 2000 mg/kg; 24 hours; no deaths; slight loss in body weight (up to 3%) in some animals 1 day after treatment with recovery by 7

days; slight erythema in 2 animals 1 day after treatment which resolved itself by 2 days; Toxicity Category III; Acceptable. ([redacted], 4/13/92)

253-0292; 259717; Acute Dermal Toxicity; 812; rabbit; J. O. Kuhn; "Acute Dermal Toxicity Study in Rats"; Stillmeadow, Inc., Sugar Land, TX; Project #: not specified; Laboratory Study #: 2919-96; 08/22/96; Methomyl 90% SP; Batch #: not specified; composition: a.i., 90% Rotam; 5.05 g/kg (neat); single, 24-hour, dermal exposure, with a semi-permeable wrap and a 14-day observation period; 5 test subjects/sex; mortality: none; clinical signs: rapid breathing (2/5 M, 2/5 F) at 1 hour; erythema, grade 1 in 5/5 M and 5/5 F at 24 hours, decreasing to grade 1 in 2/5 M by Day 4, with complete clearing by Day 7; edema, none reported; body-weight gain was positive in all throughout, except 1/5 M during the Day 7 to 14 period where it was unchanged and 1/5 F during the same time period where it was decreased; necropsy: no gross abnormalities reported; reported LD_{50} (M/F) > 5.05 g/kg; Toxicity Category IV; **Acceptable. [redacted], 09/27/11)

Acute inhalation toxicity, rat **

253-199; 113703; Acute Inhalation Toxicity; 813; Rat; Haskell Laboratory, Newark, DE; Study No. 678-91; 11/1/91; Methomyl technical (97.7%); 5/sex/dose; doses (mean gravimetric concentrations)-0.137, 0.181, 0.182, 0.232, 0.326 mg/L; MMAD=1.3-3.8 mm; 4 hr exposure (nose only); mortalities-males: 0/5, 0/5, 0/5, 3/5, 3/5; females: 0/5, 0/5, 1/5, 3/5, 4/5, respectively; observations-nasal discharge and salivation during exposure; diarrhea, lethargy, and ocular and/or nasal discharge after exposure; concentrations high enough to cause death also caused transient abnormal gait, tremors, hyperactivity, hyperreactivity, muscle fasciculations, and hunched and/or low posture in surviving animals; survivors gained weight during the 14-day observation period despite slight losses on the first post-exposure day; deaths occurred within one day of treatment; necropsy-no apparent compound-related abnormalities; LC50, (M)=0.273 mg/L, (F)=0.243 mg/L, combined=0.258 mg/L; Category II; Acceptable. [redacted] 4/14/92) (Record No. 116109 in Document No. 253-199 is a duplicate of Record No. 113703).

253-0310 276172 Weinberg, J. T., "A nose-only inhalation study to determine the effect of Methomyl (DPX-X1179) Technical on red blood cell and brain cholinesterase activity in Sprague-Dawley rats," WIL Research, Ashland, OH, Jan. 7, 2014. Sponsor Project ID: DuPont-34303. This supplementary study assayed acetylcholinesterase (AChE) levels in rat RBC and brain following 6-hr inhalation exposure to DPX-X1179-616, [methomyl, Lot No. NOV11LP048, purity 99.4%, (MMAD 1.3 to 1.8, GSD 1.69 to 2.02)]. Study assessed time dependence of inhibition and recovery in 3 phases. Phase I evaluated doses of 100-195 mg/m^3 in both sexes. Generally 100 to 195 mg/m^3 elicited salivation, lacrimation, tremors, findings of body or extremities "cool to touch," plus numerous occasions of "wet clear material" on the head and facial areas, dried material (typically red) on head and facial areas, and dried material (typically yellow) on most other body areas. Phase II found that a fixed dose of 136 mg/m^3 achieved maximal brain and RBC AChE inhibition by one hour of exposure, with no subsequent change over the 6-hour exposure period (65% to 69% inhibition in brain, 73% to 84% inhibition in RBC's in either sex). Inhibition was clearly diminishing within 1-2 hours after cessation of exposure in brain and RBC's. By 4 hours post-exposure, inhibition was reduced to about 20% for males or females in brain or RBC. Having established that there were no apparent differences between sexes, and determining that full AChE inhibition was achieved for both brain and RBC's within 3 hours, Phase III evaluated dose-response for males over a large dosage range following 3 hours of exposure. Brain AChE inhibition varied from 13% at 5.6 mg/m^3 to 66% at 105 mg/m^3. RBC AChE inhibition varied from 16% at 5.6 mg/m^3 to 93% at 105 mg/m^3 in Phase III tests. This is a valid supplementary study. [redacted], March 12, 2014.

253-0292; 259721; Acute Inhalation Toxicity; 813; rat; J. Bennick; "Acute Inhalation Toxicity Study in Rats"; Stillmeadow, Inc., Sugar Land, TX; Project #: not specified; Laboratory Study #: 2920-96; 08/20/96; Methomyl 90% SP; Batch #: not specified; composition: a.i., 90% Rotam; gravimetric concentration: 0.114 and 0.299 mg/L; MMAD (GSD): 1.175 (4.4) and 3.224 (4.373) microns, respectively; nominal concentration: 0.272 and 0.806 mg/L, respectively; single, 4-hour, nose-only inhalation exposure, with a 14-day observation period; 5 test subjects/sex/exposure; mortality (M/F): (0.114 mg/L) 0/5, 0/5; (0.299 gm/L) 5/5, 5/5; clinical signs: (in-chamber) none reported; (post-exposure) (0.114 mg/L) polyuria (5/5 M, 5/5 F), hypoactivity (5/5 M, 5/5 F), piloerection (5/5 M, 5/5 F), body tremors (5/5 M, 5/5 F), unsteady gait (5/5 M, 5/5 F), fur coat with feces/urine (5/5 M, 5/5 F), withdrawn testes (5/5 M), red ocular discharge (3/5 M), nasal discharge (3/5 M), and crusty material around eyes (3/5 M), ptosis (2/5 F), and lacrimation (3/5 F); (0.299 mg/L), piloerection (1/5 F), body tremors (1/5 F), and polyuria (1/5 F); body-weight gain was positive in all survivors throughout; necropsy: (0.114 mg/L) no gross abnormalities reported; (0.299 mg/L) red, matted hair around the mouth and nose (1/5 M), red, matted eyes (4/5 M, 5/5 F), tip of tongue purple and lacerated (5/5 M, 5/5 F), matted ventral hair (5/5 M, 5/5 F), lungs red and swollen to double normal size (5/5 M, 5/5 F), hair around mouth and nose matted and foamy (4/5 M, 5/5 F), urinary bladder full of clear liquid (1/5 M), and matted genital hair (1/5 M); reported LC_{50} (M/F) > 0.114 and < 0.299 mg/L; Toxicity Category II; **Acceptable. [redacted], 09/28/11)

Primary eye irritation, rabbit **

253-199; 113706; Primary Eye Irritation; 814; Rabbit; Haskell Laboratory, Newark, DE; Study No. 280-91; 7/18/91; Lannate (90% methomyl); 6 males/dose; dose-10 mg in .017 ml; observations-15 mg lethal in range-finding assay; animals dosed with 10 mg showed severe symptoms of systemic toxicity; mild ocular irritation (1 on Draize scale except where indicated); corneal opacity in 1 of 6 animals at 1 hr but reversed at 24 hr; iritis in 4 of 6 animals at 1 hr, reversed by 24 hr; conjunctival redness, noted in all 6 rabbits at 1 and 24 hr, persisted for 72 hr in 3 animals, but had resolved by 7 days; conjunctival chemosis in 6 of 6 animals at 24 hr, resolved by 48 hr; conjunctival discharge with positive indication of occult blood in 2 animals, one of which registered 2 on Draize scale, at 1 hr and 1 animal (2 on Draize scale) at 24 hr, resolved by 48 hr; Toxicity category cannot be determined due to lethality of required dose; Supplemental. ([redacted] 4/16/92)

253-0290 252480 May 19, 2010 Adverse Effects Disclosure memo by Medical Toxicology Branch relating to observed lethality in Record No. 113706, above.

253-0292; 259718; Primary Eye Irritation; 814; rabbit; J. O. Kuhn; "Primary Eye Irritation Study in Rabbits"; Stillmeadow, Inc., Sugar land, TX; Project #: not specified; Laboratory Study #: 2921-96; Methomyl 90% SP; Batch #: not specified; composition: a.i., 90% Rotam; 0.05 mL (22.4 mg); single, ocular instillation, with a 72-hour observation period; 3 male/3 female test subjects/treatment level; mortality: none; clinical signs: no systemic toxicity reported; corneal opacity, grade 1 in 4/6 at 24 hours, with complete clearing by 48 hours; iritis, none reported from 24 hours onward; conjunctivae, redness - grade 1 in 6/6 at 24 hours, decreasing to grade 1 in 1/6 from 48 hours, with complete clearing by 72 hours; chemosis - none reported; discharge - none reported; necrosis or ulceration - none reported; constricted pupil in 3/6 at 1 hours post instillation; body-weight gain not reported; reported Maximum Mean Total Score = 6.2 (24 hours); Toxicity Category III; **Acceptable. [redacted], 09/27/11)

Primary dermal irritation **

**253-0292; 259719; Primary Dermal Irritation; 815; rabbit; J. O. Kuhn, "Primary Dermal Irritation Study in Rabbits"; Stillmeadow, Inc., Sugar land, TX; Project #: not specified;

Laboratory Study #: 2922-96; 08/15/96; Methomyl 90% SP; Batch #: not specified; composition: a.i., 90% Rotam; 0.5 mL/site (neat); single, 4-hour, dermal exposure, with a semi-occlusive wrap and a 7-day observation period; 3 male/3 female test subjects; mortality: none; clinical signs: no systemic toxicity reported; erythema, grade 2 in 1/6 from 24 through 48 hours (grade 1 in 2/6), decreasing to grade 1 in 1/6 by 72 hours; edema, none reported; reported Primary Dermal Irritation Index (PDII) = 0.6; Toxicity Category IV; **Acceptable**. [redacted], 09/28/11)

**253-219; 126287; Primary Dermal Irritation; 815; Rabbit; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Report No. 563-93, 8/20/93; Methomyl Technical (DPX-X1179-394) (98.35% a.i.); 6 animals; 0.5 g (moistened with deionized water)/animal; 4 hr exposure, covered; observations- no erythema or edema in any test animal; Category IV; Acceptable. [redacted], 10/12/93)

**253-219; 126285; Primary Dermal Irritation; 815; Rabbit; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Report No. 562-93, 8/23/93; Methomyl Composition (DPX-X1179-425) (92.4% a.i.); 6 animals; 0.5 g (moistened with deionized water)/animal; 4 hr exposure, covered; observations- no erythema or edema in any test animal; Category IV; Acceptable. ([redacted] 10/8/93)

253-199; 113704; Primary Dermal Irritation; 815; Rabbit; Haskell Laboratory, Newark, DE; Study No. 165-91; 5/9/91; Methomyl technical (98.35%); 6 males/dose; dose-0.5 grams; 4 hr exposure; no deaths; observations-no erythema and eschar or edema noted at 1, 24, 48, or 72 hr post-exposure; Toxicity Category IV; Unacceptable and not upgradeable since recent information submitted in document 253-219 revealed that test animals had been tested concurrently with multiple chemicals. ([redacted] 4/15/92; revised, [redacted] 10/12/93)

Dermal sensitization **

253-0292; 259720; Skin Sensitization; 816; guinea pig; J. O. Kuhn; “Dermal Sensitization Study in Guinea Pigs”; Stillmeadow, Inc., Sugar Land, TX; Laboratory Study #: 2923-96; 08/30/96; Methomyl 90% SP, Batch #: not specified; composition: a.i., 90% Rotam; Buehler Sensitization Method; induction treatments 1 - 3: 0.4 g amount of test-article moistened with 0.2 mL of deionized water applied for 6 hours once per week for 3 weeks (5 test subjects/sex); challenge: 0.4 g amount of test-article moistened with 0.2 mL of deionized water applied for 6 hours, 14 days after the last induction treatment; naïve-challenge: 0.4 g amount of test-article moistened with 0.2 mL of deionized water applied for 6 hours applied at challenge only (5 subjects/sex); positive control: (5 subjects/sex); a positive-control, naïve-challenge treatment group was also included in the study with a 0.4 mL aliquot of 100% HCA being applied to each subject (5 test subjects/sex/treatment level); mortality: none; clinical signs: induction treatments 1, erythema, grade 0.5 in 3/10 at 24, decreasing to grade 0.5 in 1/10 at 48 hours; induction treatments 2, erythema, grade 0.5 in 1/10 at 24 hours; induction treatment 3, erythema, grade 0.5 in 1/10 at 24 hours; challenge, erythema, grade 0.5 in 1/10 at 24 and 48 hours; naïve challenge, erythema, grade 0.5 in 2/10 at 24 hours, decreasing to grade 0.5 in 1/10 at 48 hours; the positive control, DNCB, was positive for dermal sensitization indicating that the test system was effective with a known sensitizer; body-weight gain was positive in all throughout; **the test article was not a dermal sensitizer; Acceptable. [redacted], 09/28/11)

**253-0285; 219356; “Methomyl (DPX-X1179) Technical: Local Lymph Node Assay (LLNA) in Mice”; (D. Hoban; E.I. du Pont de Nemours and Co., Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Laboratory Project ID No. DuPont-17212; 7/11/05); The dorsal skin on the ears of 5 female CBA/JHsd mice/group was treated by topical application with 25 µl/ear/day of 0 (vehicle: N,N-dimethylformamide), 5, 25, 50 or 100% (100%=1 g/ml) of

Methomyl (DPX-X1179) Technical (batch no. DPX-X1179-512, purity: 98.8%) for 3 days. Additionally, 5 female mice/group were dosed in the same manner with 0 (vehicle: 4:1 acetone:olive oil) or 25% hexylcinnamaldehyde for 3 days. Three days later, 20 µCi of ^{3}H-thymidine was injected iv into the tail vein of each animal and 5 hours later each animal was euthanized. The draining auricular lymph nodes were removed and single cell suspensions prepared and incubated overnight. The following day the cell suspensions were counted using a beta counter and the DPM's calculated. A stimulus index (SI) was determined by dividing the mean dpm of each experimental group by the mean value for the vehicle control. An SI value which was greater than 3.0 was considered to a positive response. There was no indication of a proliferative response in any of the treatment groups. The positive control was functional. **Study acceptable.** [redacted] 10/19/05)

253-0199; 113705**;** Skin Sensitization; 816; the test article, DPX-X1179-394, was **negative for dermal sensitization** in the guinea pig model species tested; see the Worker Health and Safety memorandum dated December 18, 1996; study title: Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with DPX-X1179-394 in Guinea Pigs.

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

253-0303; 265391; "Three-Month Dietary Administration - Rats, Insecticide 1179"; (T. Kundzin, O. Paynter; Hazleton Laboratories, Falls Church, VA; Project No. 201-151 (MRO-848); 1/4/66); Ten (strain unidentified) rats/sex/group received 0, 10, 50 or 250 ppm of Insecticide 1179 (methomyl technical) (lot no. H 4217; purity: 100%) in the diet for 3 months. Another group of 10 animals/sex received 125 ppm of the test material for 9 weeks, followed by 500 ppm for another 4 weeks. Approximate compound intakes were as follows: (**M**) 0, (10) 0.5 to 1.4, (50) 2.4 to 6.8, (125) 9.5 to 19, (250) 14 to 30, (500) 23 to 33 mg/kg/day; (**F**) 0, (10) 0.6 to 1.4, (50) 3.0 to 6.8, (125) 11 to 17, (250) 16 to 30, (500) 31 to 32 mg/kg/day. No deaths resulted from the treatment. The mean body weights of both sexes in the 125 ppm groups and above were less than the control values. The hematology and urinalysis did not indicate any treatment-related effects. There was no apparent treatment-related effect upon RBC or plasma cholinesterase activity in the 125 ppm group after 2 months of treatment or in the 250 (3 months of treatment) and 500 (one month of treatment) ppm groups at the termination of the study. Although the absolute and/or relative weights for the pituitary, lungs and liver among the treated groups were greater or less than the control values in certain instances, a treatment-related effect was not discernable. There were no treatment-related lesions evident in the histopathological examination. **No adverse effect.** A No-Effect Level was not assigned due to the limited assessment which was undertaken in the study (no clinical chemistry or analysis of the dietary preparations were performed); **Study supplemental** (study predated FIFRA guideline protocol). [redacted], 6/26/12)

Dog Subchronic Dietary Toxicity Study

253-0303; 265390; "Three-Month Feeding Study on Dogs with S-Methyl N-[(Methylcarbamoyl) Oxy] Thioacetimidate [Lannate Methomyl Insecticide; INX-1179]"; (H. Sherman; E.I. du Pont de Nemours & Co., Haskell Laboratories, Newark, DE; Report No. 168-67; 9/28/67); Four beagle dogs/sex/group received 0, 50, 100 or 400 ppm of Lannate Methomyl Insecticide (INX - 11791) ((Technical INX-1179: 97.5%, Hi Sil 233: 2.5%); batch no. INX-1179-68; a.i.: 90%) in the diet for 3 months ((M) 0, 1.44, 3.18, 14.7 mg/kg/day, (F) 0, 1.45, 3.01, 12.5 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect on the mean body weights or food consumption. The hematology, clinical chemistry and urinalysis parameters were not affected by the treatment. There was no apparent treatment-

related effect on organ weights. No treatment-related lesions were noted in the histopathological examination. **No adverse effect indicated. Dog 3-Month Dietary Toxicity NOEL:** (M/F) > 400 ppm ((M) 14.7 mg/kg/day, (F) 12.5 mg/kg/day) (based upon the lack of a treatment-related effect on the 400 ppm treatment group); **Study supplemental** (study does not conform with present-day guideline protocols). ([redacted], 6/22/12)

Rabbit 10-Day Repeated Dosing Dermal Toxicity Study

253-0105; 963977; "Ten-Day Subacute Exposure of Rabbit Skin to Lannate L Insecticide"; (J.W. McAlack; E.I. du Pont de Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 24-73; 1/23/73); The skin of 6 albino male rabbits/group was exposed to a 1:9 or 1:4.5 dilutions of Lannate L (batch no. not reported; a.i.: 25.52%) in water, 6 hours/day, for 10 consecutive days. The approximate exposures to methomyl were 50 and 100 mg/kg/day. No deaths occurred as a consequence of the treatment. No treatment-related clinical signs were evident. The hematology evaluation did not reveal any treatment-related effects. Although the cholinesterase activity levels for the two treatment groups were less than that of the control group after ten days of treatment, the activity level for the 100 mg/kg treatment group was actually greater than that of the 50 mg/kg group. When the level in reduction of activity between the baseline and after 10 days of treatment were compared, there was an apparent treatment-related effect, in which the 50 mg/kg group exhibited an activity level which was 93% of baseline. The activity level for the 100 mg/kg group was 83% of the baseline after 10 days of treatment. This degree of alteration is not deemed to be a significant biological effect. The histological examination did not reveal any treatment-related lesions. The organ weights were not affected by treatment. **Rabbit 10-Day Repeated Dosing Systemic Dermal Toxicity NOEL:** (M) ~100 mg/kg/day (based upon the lack of a significant treatment-related effect on the 100 mg/kg/day treatment group); **Supplemental Study** (non-guideline study) [redacted] 4/26/16)

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

253-191; 85837;"Repeated dose dermal toxicity: 21 day with DPX-X1179-394 (Methomyl) in Rabbits"; E.I. duPont de Nemours & Co., Haskell Lab. for Toxicology and Industrial Medicine, Newark, DE, Report No. 387-89, 8/29/89; 822; Methomyl (98.4% purity) in deionized water, 6hr daily dermal exposure for 21 consecutive days; 0, 5, 50, 500 mg/kg to 5 rabbits/sex/dose; two additional recovery groups lasting 14 days at 0 and 500 mg/kg; decreases ($p<0.05$) in plasma cholinesterase (ChE) activity on day 21 in males and females (36 and 55% of control, respectively) at the 500 mg/kg dose level; similar decreases ($p<0.05$) in brain ChE activity were evident in males and females (48 and 68% of control, respectively); at mid-dose level, male plasma ChE activity was 77% of control ($p<0.05$); full restoration of normal ChE activities in plasma and brain after recovery period; no adverse clinical signs consistent with ChE inhibition were observed; no compound-related effects were observed during gross and microscopic examination; NOEL > 5 mg/kg (males; decrease plasma and brain ChE), NOEL > 50 mg/kg (females; decrease plasma and brain ChE); Study **acceptable; [redacted] 2/1/90).

253-0303; 265393; "Methomyl Technical: 21-Day Repeated Dose Dermal Toxicity Study in Rabbits"; (C. Finlay; E.I. du Pont de Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Project ID No. HL-1997-00913; 11/14/97); The skin of 6 New Zealand White rabbits/sex/group was treated with 0 (deionized water), 15, 30, 45, or 90 mg/kg/day of Methomyl technical (batch no. DPX-X1179-512; purity: 98.6%) 6 hours/day for 21 days. No deaths resulted from the treatment. No treatment-related clinical signs were evident There was no treatment-related effect upon body weights or food consumption. No treatment-related lesions were evident in the necropsy examination. Although the cholinesterase activities in the plasma, red blood cells and/or brain of the treated animals was less than that of the

controls, there was no apparent dose-related effect. **No adverse effect indicated. Rabbit 21-day repeated dosing dermal toxicity NOEL:** 90 mg/kg/day (based upon the lack of treatment-related effect on the 90 mg/kg treatment group); **Study supplemental** (clinical chemistry, hematology, ophthalmology and histopathology were not performed); [redacted], 7/2/12)

CHRONIC STUDIES

Combined, rat ** † (no oncogenicity observed)

****253-164, 253-165 037842, 037843** (with rebuttal and supplemental data in -176, 052178): Kaplan, A. M., "Long-Term Feeding Study in Rats with S-Methyl N-[(Methylcarbamoyl)Oxy] Thioacetimidate, (Methomyl; INX-1179), Final Report". (Haskell Laboratory, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware, # 235-81, 5/1/81). Methomyl technical 99+%, Lot # INX-1179-255; fed in the diet to 80/sex/group at 0, 50, 100 and 400 ppm (of these, 70/sex/group were designated for the 2 year study, and 10/sex/group were used for a 1-yr interim sacrifice). NOEL = 100 ppm (body weight decrements in both sexes: possible mild anemia). At 400 ppm there were some reductions in RBC parameters (RBC count, Hb concentration, HCT) in high dose females. There was some bone marrow hyperplasia at this dose in males, and slightly elevated extramedullary hematopoiesis in liver, spleen, or adrenals; typically marginal in scope and generally observed in only one sex. CDFA/DPR review history: study was first reviewed by [redacted] 4/18/86, who classified study as unacceptable and upgradeable (needing individual clinical observation data and historical control hematology data). Re-reviewed by [redacted] and [redacted], 10/9/87. Above requested data were provided, but study was still not acceptable for chronic data requirements for lack of eye exams. Study was considered acceptable as an oncogenicity study. With submission of additional data on eye histopathology for the 2-year dog study (CDFA # 072204), the lack of ophthalmology in the rat study was no longer considered as an issue, and the study was upgraded to **acceptable** as a combined study. [redacted] 7/21/89. Re-evaluation and consolidation of older reviews into one document by [redacted] and [redacted] Jan. 12, 1999.

EPA one-liner: Oncogenic NOEL => 400 ppm (HDT). Systemic NOEL = 100 ppm. ChE NOEL **>** 400 ppm (HDT) (Ellman method). Minimum.

Chronic, rat † (no oncogenicity observed)

-025, 024197 (With rebuttal and full report in -176, 051310): "22-Month Dietary Feeding - Rats, Lannate Methomyl Insecticide, (S-Methyl-N-[(Methyl-carbamoyl)Oxy]Thioacetimidate), Final Report". (Hazleton Laboratories, Inc., Falls Church, VA., # 201-164, 7/26/68). Lannate methomyl insecticide, 90-100% purity; 35/sex/group was fed at 0, 0, 50, 100, 200, & 400 ppm. Decreased growth at 200 and 400 ppm; dosage-related decrease in hemoglobin in females, accompanied by extramedullary hematopoiesis in the 200 and 400 ppm groups. Renal tubular dilation, hypertrophy, vacuolation at 200 and 400 ppm. Overall NOEL = 100 ppm. Unacceptable, but useful supplementary information. Reviewed by [redacted], 5/22/86. Additional information (Document No. 253-176) led to no change in status. [redacted], 7/16/87. [See acceptable combined study, above].

EPA one-liner: One year report, systemic NOEL = 100 ppm and ChE NOEL = 400 ppm (HDT).

-008, 042606; -025, 024024; -090, 963995; and 407-003, 024988-89 are summaries of 051310.

Chronic, dog ** †

****253-167 037845, 037846** "Two-year dietary administration - dogs: Lannate methomyl insecticide (S-Methyl N-[(Methylcarbamoyl)Oxy] Thioacetimidate)", (William M. Busey, Hazleton Laboratories, Inc., Falls Church, VA., Report number MRO-888-1, Project number 201-165, 25

June 1968). Three beagle dogs per sex per group received methomyl (90% purity) in the diet at 0, 50, 100, 400, and 1000 ppm for 2 years. An interim sacrifice group of one additional dog per sex per group was terminated at 1 year. Two females died at 1000 ppm. NOEL = 100 ppm (presence and/or increased degree of pigmentation of kidney proximal tubular epithelial cells, often with swelling/irregularity of the cells, and pigmentation of spleen in 400 ppm males). Common high dose findings, typically in both sexes, included the above observations, plus hematology changes (reduced HCT, Hb, RBC counts), extramedullary hematopoiesis in spleen, and increased hematopoiesis in marrow. Findings are considered to indicate "possible adverse effects". The findings which defined the LOEL were typically either uncommon findings which were "slight" in degree, or were findings commonly seen in dogs, but somewhat increased in degree over the norm. For this reason, these results do not suggest pivotal findings for toxicity evaluation. One high dose male had sustained hematology changes, plus marked changes consistent with severe anemia (greatly enlarged spleen and liver, and severe extramedullary hematopoiesis in these organs). A summary of the CDFA/DPR evaluations of this study is included in the background section of this review. This review provides tabular data supporting previous conclusions regarding methomyl toxicity. [redacted] and [redacted] 12/22/98.

Data review history of Record No. 037845, above:

The 1985 "reviews" by [redacted] and [redacted] on this study were simply references to brief summary data in Document/Record Nos. 253-025:024203 and 407-003:033910. These submissions were by Shell and Union Carbide, respectively. The "final report" was later submitted as Document/ Record Nos. 253-167:037845, submitted by du Pont in October, 1985. E. I. du Pont de Nemours and Company has been the primary or exclusive source of data since then, and has retained the Tolerance No. of 253. The 1986 CDFA review by de Vlaming and Gee highlighted study results and identified study deficiencies, including a lack of ophthalmology data. A rebuttal response to Document No. 253-176 (no record number) shows all data requirements except for ophthalmology to be satisfied [redacted] and [redacted], 11/6/87). A meeting of E. I. du Pont de Nemours and Company representatives and CDFA (including CDFA reviewers [redacted] and [redacted]) was held on 6/14/88, in which it was agreed that du Pont should submit histopathology data based on multiple sections of eyes to address the primary remaining deficiency of the dog chronic study. Following submission of the dog eye histopathology data (Document/Record No. 253-186:072204), the study was upgraded to acceptable status ([redacted] 7/18/89). There were no treatment-related ocular effects. The Dec. 1998 examination of the original report provides data tables which can be used for risk assessment evaluation. [redacted], 12/22/98.

EPA one-liner: Systemic NOEL = 100 ppm. Enlargement of prostate gland. Increase kidney pigmentation and swelling of the proximal convoluted tubules. Minimum.

-008, -025, -090, 024203, 042607, 035859; and 407-003, 033910 are summaries of 037845-46.

-186 072204 Supplement to 037845. Results of additional sections of the eyes made as a result of the meeting held April 21, 1988, between the registrant and CDFA.

Oncogenicity, mouse **

**253-166 037844, "104-week Chronic Toxicity and Carcinogenicity Study in Mice", (David G. Serota, Hazleton Laboratories America, Inc., Report # HLO-253-81, Project # 201-510, 12 February 1981). 80 CD®-1 mice per sex per group received methomyl in the diet at 0, 50, 100 (reduced to 75 ppm at week 39), and 800 ppm (reduced to 400 ppm at week 28, and further reduced to 200 ppm at week 39) for 104 weeks. Chronic NOEL = 75 ppm (modest RBC

parameter reductions: Hb levels, HCT: increased mortality). **No adverse effects**. **Acceptable** with diet analyses and clarifications on pathology data provided in Document No. 253-176 (no record No.) (and , 4/22/86; acceptability upgrade by , 7/16/87; worksheet updated by and 12/16/98).

EPA one-liner: Oncogenic NOEL => 200 ppm (HDT). Systemic NOEL = 50 ppm. Decreased hematocrit and hemoglobin. Increased adrenal weight at 200 ppm. Histologic NOEL = 200 ppm. Minimum.

GENOTOXICITY

Bacterial reverse mutation assay

-169, 037848 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, May 1977). Lannate 99% purity, lot no. 6602-82; Salmonella typhimurium strains TA1535, TA1537, TA1538, and TA100 tested at 0, 1, 10, 50, 100, 500, or 1000 µg/plate, with/without S9 (not described). **No increased reversion rate.** Unacceptable (lacks adequate positive controls, no justification of 1000 µg/plate as highest concentration no indication of cytotoxicity), no individual plate counts, no TA98, source of S9 not stated). , 4/4/86.

EPA one-liner: None in Branch library.

-025, 142 964002 Reference material, insufficient information for review.

-025, 024205 Reference material, no methomyl data.

Mutagenicity: *In vitro* mammalian cell assay **

** -169, 037852 "CHO/HGPRT Assay for Gene Mutation". (Haskell Laboratory, 1/13/84) Methomyl ~ 99%; CHO cells were exposed to 0, 10, 20, 40, 50, or 55 mM (-S9 Aroclor-induced rat liver fraction) with EMS as positive control, or 0, 100, 150, 200, 250, or 350 mM (+S9 Aroclor-induced rat liver fraction) with DMBA as positive control and selected for resistance to 6-TG; **No increased mutation frequency.** Survival decreased at higher concentration. Complete, acceptable. , 4/4/86.

EPA one-liner: Negative. Acceptable.

Mutagenicity: *In vivo* cytogenetics **

-169, 037851 "In Vivo Bone Marrow Chromosome Study in Rats, H# 15,000, Final Report." (Hazleton (VA), 12/18/84). Methomyl ~ 99% purity; in water @ 0, 2, 6, & 20 mg/kg, 5/sex/group, by single gavage; Sacrificed @ 6, 24, & 48 hr. **No increase in chromosomal aberrations. Complete, acceptable. , 4/1/86.

EPA one-liner: Negative. Acceptable.

** 253-0303; 265392; “Mouse Bone Marrow Micronucleus Assay of DPX-X1179-394"; (K.S. Bentley; Report No. 413-95; 10/19/95); Fifteen Crl:CD-1(ICR) BR mice/sex/group were dosed orally by gavage with 0 (vehicle: sterile water), 3.0 or 6.0 mg/kg of Methomyl Technical (batch no. DPX-X1179-394; purity: 98.35%) and 5 animals/sex/time point were euthanized at 24, 48 and 72 hours post-dose. Another 18 animals/sex were dosed with 12.0 mg/kg of the test material and 6 animals/sex/time point were euthanized at the same time intervals. A positive control group of 5 animals/sex was treated orally by gavage with 40 mg/kg of cyclophosphamide and euthanized at 24 hours post-dose. Bone marrow samples from the femur were examined and the mean number of polychromatic erythrocytes (PCE) with a micronucleus per 2000 PCEs/animal, the mean number of micronucleated normochromatic erythrocytes (NCE) per 2000 PCEs and the mean number of PCEs per 1000 erythrocytes were determined. Hyperactivity and/or lethargy were the only clinical signs which were noted. There was no

treatment-related increase in the number of micronucleated PCE's. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** [redacted], 6/27/12)

Other genotoxicity studies (not currently required)

-169, 037853 "Assessment of Methomyl (INX-1179-255) in the In Vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes." (Haskell Laboratory, 8/2/85). Methomyl, 99% purity; primary rat hepatocytes were exposed to 0, 1, 10, 100, 1000, 5000, & 75,000 µM for 18 hr. **No increase in net grain counts, 4 slides/each concentration, 2 trials. Complete, Acceptable. [redacted], 4/4/86.

EPA one-liner: None in Branch library.

-169, 037850 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, May 1977). Methomyl 99% purity, Saccharomyces cerevisiae were tested in mitotic recombinant assay; Two trials @ 2.0 and 3.0 % (w/v); Table of data only no protocol. Incomplete, unacceptable, with adverse effect (increased mitotic recombinants) indicated. [redacted] 4/4/86.

EPA one-liner: None in Branch library.

-003, 024991: Insufficient information for review.

Comment: There are conflicting results in the two studies in this test area. They, however, measure different endpoints and are not directly comparable. In accordance with most thinking, the acceptable study in mammalian cells, which was negative for UDS, would be given more weight than the study in yeast, especially in view of the deficiencies in the report. Because of the negative findings in other acceptable studies in the area of genotoxicity, the biological significance of the result in yeast is questionable. [redacted], 11/6/87.

REPRODUCTIVE TOXICITY, RAT **

253-177 051313 Lu, C. C., "Nudrin® two-generation reproduction study in rats", WIL Research Laboratories, Inc., 12/13/82. Laboratory Study # WRC RIR-275. CD® rats were tested in a 2-generation study with one littering period per generation at dietary levels of 0, 75, 600, or 1200 ppm NUDRIN® (SD-14999 Technical = methomyl). Groups sizes were 13 males and 26 females for F0 parents, and 20 males and 40 females for F1 parents. A conservative NOEL for reproductive and non-reproductive effects is 3.5 mg/kg/day (typical intake of 75 ppm rats which were not rapidly growing, prior to mating). Substantially higher intake on an animal weight basis for 75 ppm rats, such as occurred during maternal lactation and rapid growth of young pups, led to marginally reduced pre-weaning pup body weights and reduction in weights of young post-weanling rats. These findings corresponded to intakes on the order of at least 14 mg/kg/day for maternal rats and 18 mg/kg/day for rapidly growing offspring. Levels of 600 to 1200 ppm reduced food consumption and body weights in both parental rats and pre-weanling pups. The highest dose reduced pup survival during the first few days of life. There was a marginally reduced live litter size for the 600 ppm parental F1 group, which may have been treatment-related. There were marginal reductions in RBC parameters, in females only, at 600 to 1200 ppm (reduced HCT, Hb, and RBC count). There was a general increase in spleen weights in weanling 1200 ppm pups, without associated histopathology. The latter findings are consistent with those of several other studies. The highest dose elicited clinical signs of "increased activity, piloerection, depressed righting reflex and myoclonic body tics". These signs were primarily limited to the first three weeks of treatment. Study remains **acceptable with **no adverse effects**. Re-examination by [redacted], Jan. 12, 1999.

CDFA/DPR review history: An abbreviated version of the present report (Document No. 253-113, Record Nos. 035815 and 035816) was evaluated by de Vlaming and Martz on 1/13/86. They determined that the available data appeared to reflect a viable study, but they did not have the information to do an analysis of the findings. These reviewers requested individual data to upgrade the study. The complete report was later submitted (Document No. 253-177, Record No. 051313). This was examined by Martz and Carlisle (11/6/87). They upgraded the study to acceptable status, but provided only a summary paragraph of the findings. The 1998 worksheet provides tabular presentations and re-analyses of the study results.

EPA One-liner: None in Branch library.

253-255 140400 Hurtt, M. E. (author of supplement). "Nudrin, Two-generation Reproduction Study in the Rat" (Supplement No. 1). Information was sent in response to U.S. EPA request for additional data. CDFA had accepted the study as presented in 1987. Most complete report is Document No. 253-177, Record No. 051313. Final Report Date: 12/13/82. Laboratory Study #: 61531. Mean daily mg/kg/day intakes during premating periods for 75, 600, and 1200 ppm groups were 5, 37, and 74 for F0 males; 5, 39, and 76 for F0 females; 7, 56, and 117 for F1 males; and 7, 59, and 128 mg/kg/day for F1 females. Test article stability was proven over the period of the study, and stability was shown at RT for at least 3 weeks. This supplement included summary data for gross observations, and summary and individual data for clinical observations. These data did not change the NOEL's nor did they indicate adverse effects. Study remains acceptable. [redacted], Jan. 11, 1999.
-176, 051311 (With partial versions in -008, 964001): "Three-Generation Reproduction Study, Lannate Methomyl Insecticide, Final Report" (Hazleton Laboratories, Inc., # 201-166, 7/18/68). Lannate methomyl insecticide, no purity stated, administered in the diet at 0, 50, or 100 ppm to 10 males and 20 females per group with 2 litters/generation for 3 generations (an additional post-weaning growing phase was conducted with F_{3C} females). **No adverse reproductive effects**. Unacceptable, not upgradeable (only 10 males/group, no individual data, no MTD). ([redacted], [redacted] 5/28/85; [redacted], [redacted] 4/4/86; [redacted], [redacted] 8/12/87; [redacted] 11/5/87).

EPA one-liner: Reproductive NOEL > 100 ppm (HDT). Fetotoxic NOEL = 100 ppm. Minimum.

-008, 964001, and -168, 37847 are partial duplicates of #51311.

-008, 024201, -025, 042601, and 407-003, 024990 are summaries of # 051311.

DEVELOPMENTAL TOXICITY

Rat **

**253-176 051312 (Full report: -008, 96500 and -170, 037854 are partial versions) "Oral Teratogenic Study in Rats with Lannate (INX-1179)", (E. I du Pont de Nemours & Co., Haskell Laboratory, # 498-78, 9/5/78). Lannate (methomyl), 99% purity; was fed in the diet to 25 females per group at 0, 50, 100, or 400 ppm on days 6 through 15 of gestation. NOEL: maternal = 100 ppm (body weight and food consumption); developmental ≥ 400 ppm (no effects). Original review by J. Gee, 4-18-86: unacceptable with insufficient information for evaluation. Re-reviewed by F. Martz, 9-11-87: additional information (complete report including diet analysis) did not result in change of status because there was no MTD. On April 21, 1988, a meeting was held with the registrant, and the dose selection was discussed with respect to the oral gavage LD50. As a result, the dose selection was considered as justified and the study

was upgraded to acceptable status ([redacted], 6/15/88). A worksheet was produced by [redacted] on 12/29/98, with no change in study status.

EPA one-liner: NOEL (maternal toxicity) = 100 ppm. Minimum.

-008, 964000, and -170, 37854 are partial reports of #51312.

-025, 24200, and 407-003, 33909 are summaries of #51312.

Rabbit **

253-170 037855, "Embryo-Fetal Toxicity and Teratogenicity Study of Methomyl in the Rabbit", Elizabeth L. Feussner (Study Director), Argus Research Laboratories, Inc., Horsham, PA., Report # HLO-331-83, 9/18/83). Twenty artificially-inseminated New Zealand White (DLI:NZW) female rabbits per group received methomyl by gavage at 0, 2, 6, and 16 mg/kg/day on gestation days 7 through 19. Maternal NOEL = 6 mg/kg/day (7 high-dose females died: common signs in this group included tremors, hyperactivity, body jerks, excessive salivation, convulsions, and ataxia). Developmental NOEL = 16 mg/kg/day (no adverse effects**). Initially classified as unacceptable (dosing solution analyses required). Dosing solution analysis, reported in Document No. 253-176, prompted an upgrade to **acceptable** status (see rebuttal response of 11/9/87). CDFA reviews were by de Vlaming and Remsen [redacted]), 4/18/86; and [redacted] (in 11/9/87 rebuttal). An updated worksheet (with additional tables) was produced by [redacted] and [redacted] on 12/09/98. This re-evaluation did not result in any change of study status.

EPA one-liner: NOEL (teratogenicity and fetotoxicity) > 16 mg/kg/day. Maternal NOEL = 2 mg/kg/day. Minimum.

-008, 963999: "Teratology Study - Rabbits, Lannate Methomyl Insecticide, Final Report" (Hazleton, 7/28/67). Lannate methomyl insecticide 90-100% purity, lot no. H-4429 and H-5116; fed in the diet in two non-concurrent trials at 0, 50, and 100 or 0, 45, and 90 mg/kg/day to 12 pregnant females/group from days 8 through 16 of gestation. No teratogenic effect reported. Unacceptable and not upgradeable (two non-concurrent studies combined, unclear protocol, only two dosage levels with no justification, all results are missing). [redacted], 5/28/85.

EPA one-liner: None in Branch library.

-008,- 025, 042605, 035858, 024199, and 407-003, 024986 are summaries of 963999.

NEUROTOXICITY

Acute neurotoxicity, rat ** † (marked, reversible AChE effects)

** **253-272 160438** "Methomyl Technical (DPX-X1179-512): Acute Oral Neurotoxicity Study in Rats"; (K. A. Mikles; E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Project ID: HL-1998-01080; 2/2/98); Fifty two rats/sex/group were dosed orally by gavage with 0, 0.25, 0.50, 0.75 or 2.0 mg/kg of Methomyl technical (purity: 98.6%). Twelve rats/sex/group were included in the neurobehavioral study in which they were examined in the functional observational battery (FOB) and motor activity assessments prior to dosing, 30 minutes after dosing (day 1) and on study days 8 and 15. Six animals/sex/group of this cohort were randomly chosen for histological examination of the nervous system and muscle. Erythrocyte and plasma blood cholinesterase activities were measured in 10 animals/sex/group of the clinical pathology subgroup on the day prior to dosing, at 30 minutes post-dose (Day 1) and one day after treatment (Day 2). At the latter two time points, brain cholinesterase activities were determined as well. No test material-related mortality resulted from the treatment. Among the animals in the clinical pathology group, males (5/40) and females (5/40) in the 2 mg/kg group exhibited tremors 30 minutes after dosing. The incidence

of other possible treatment-related signs were not significant from that of the control group. By 24 hours after dosing, no clinical signs were evident. The mean body weight gain for females in the 2 mg/kg group was significantly less ($p<0.05$) than that of the control between days 2 and 8. In the FOB, treatment-related tremors were noted in 4/12 males in the 2 mg/kg group 30 minutes after dosing. Lacrimation was observed for 1/12 males in this group at this time point. No signs of toxicity were noted 24 hours after dosing. No treatment-related effect was evident for the forelimb and hindlimb grip strength or foot splay measurements. No significant alteration in motor activity was noted. Significant cholinesterase inhibition ($p<0.05$) was evident in the plasma for both the males and females in the 0.75 and 2 mg/kg groups ((M) 77 and 58% of control, (F) 60 and 64% of control, respectively) at 30 minutes post-dose. Erythrocyte cholinesterase was significantly inhibited ($p<0.05$) 30 minutes post-dose for the males in the 2.0 mg/kg group (54% of control) and the females in the 0.5, 0.75 and 2.0 mg/kg (75, 62, and 43% of control, respectively). Brain cholinesterase activity was significantly inhibited ($p<0.05$) 30 minutes after dosing for the males and females in the 0.5, 0.75, and 2.0 mg/kg groups ((M) 81, 75, and 53% of control, (F) 80, 70, and 49% of control, respectively). All of the cholinesterase activity parameters for the treated animals were comparable to those of the control animals by 24 hours after dosing. No gross lesions nor treatment-related neuropathology were evident. **Adverse effect indicated:** tremors occurred in conjunction with significant brain cholinesterase inhibition. **NOEL:** (M/F) 0.25 mg/kg (based upon inhibition of brain cholinesterase activity in the 0.5 mg/kg group). **Study acceptable**. ([redacted], 4/28/98)

253-271; 159979; “Reversibility Study with Carbamate Insecticides in Rats”; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Study No. HL-1997-00641; 11/10/97); Forty rats/sex/group were orally gavaged with 0 or 1 mg/kg of oxamyl technical (purity: 98.3%) or 0 or 3 mg/kg of methomyl technical (purity: 98.6%). Plasma, RBC, and brain cholinesterase (ChE) activities were measured for 10 animals/sex/group at 30 minutes and 2, 3 and 4 hours post-dose. Tremors were noted at 30 minutes post-dose in animals treated with both of the test materials. This sign was not evident at 2 hours after dosing. For the oxamyl treated animals, at 30 minutes after dosing, plasma, RBC and brain ChE activities were significantly inhibited (plasma: (M) 43%, (F) 50% of control; RBC: (M) 42%, (F) 39% of control; brain: (M) 55%, (F) 52%). By two hours, ChE activity had returned to control levels. Likewise, for the methomyl treated animals, at 30 minutes post-dose, plasma, RBC and brain ChE activities were significantly inhibited (plasma: (M) 73% of control; RBC: (M) 44%, (F) 59% of control; brain: (M) 54%, (F) 61% of control). By 2 hours, the ChE activities had returned to control levels. Study data indicate that significant ChE inhibition is largely reversible by 2 hours after dosing for both of the test materials. **Possible adverse effect indicated:** tremors and significant brain cholinesterase inhibition evident. **NOEL:** (oxamyl) < 1 mg/kg, (methomyl) < 3 mg/kg; **Study supplemental.** ([redacted], 3/26/98)

253-0287; 220034; “Methomyl (DPX-X1179) Technical: Comparison of Cholinesterase Activity in Adult and Preweanling Rats”; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-15433; 9/12/05); Three studies were performed. In the first study, approximately 35 Crl:CD®(SD)IGS BR 11-day old pups/sex were dosed orally by gavage with 0.3 mg/kg of Methomyl (DPX-X1179) Technical (sample no. 22577; purity: 98.08%). Five animals/sex/time point were euthanized at 30, 60, 90, 120, 180, 240, and 360 minutes post-dose and red blood cell (RBC) and brain cholinesterase (ChE) activities were assayed. A control group of 15 animals/sex were dosed orally by gavage with distilled water and 5 animals/sex/time point were euthanized at 60, 120 and 240 minutes post-dose. RBC and brain ChE activities were assayed for these animals. In the second study, 10 11-day old pups/sex/group were dosed orally by gavage with 0, 0.1, 0.2, 0.3 or 0.4 mg/kg of the test material and euthanized at 30 minutes post-

dose. The RBC and brain ChE activities were assayed for these animals. In the third study, twenty 42-day old rats/sex/group were dosed with 0, 0.3, 0.5 or 0.75 mg/kg of the test material and 10 animals/sex/group were euthanized at 30 and 240 minutes post-dose. RBC and brain ChE activities were assayed for these animals. In the first study, maximal inhibition of both enzymes was noted at 30 minutes post-dose. Therefore, ChE activity in both the RBC and brain were assayed at 30 minutes post-dose in both the 2nd and 3rd studies. A dose-response of ChE inhibition was noted in both the RBC and brain of the pups and young adults. A maximal inhibition of RBC ChE of 49% was observed at a dose of 0.4 mg/kg in the pups. The % inhibition noted in the brain of the pups at this dose was 41 to 42%. In the RBC of the adult rats, ChE was inhibited 41 and 25% for the male and females, respectively, at 30 minutes post-dose at the highest dose level of 0.75 mg/kg. At that dose level, brain ChE was inhibited 19 and 29% in the males and females, respectively, at 30 minutes post-dose. These data indicate that the percentage of cholinesterase inhibition in the RBC and brains of the11-day old rats was greater at comparable dose levels in comparison to the young adult animals. **Possible adverse effect:** significant brain cholinesterase inhibition demonstrated in both pups and adult rats. **Study supplemental** (non-guideline study). [redacted], 9/18/07)

383-0296; 264057; "Reversibility Study with Carbamate Insecticides in Rats"; (L.A.. Malley; E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Project ID. HL-1997-00641; 11/10/97); Two cohorts of Crl:CD BR rats of both sexes were treated with either 0 (vehicle: deionized water) or 3 mg/kg of methomyl technical (batch no. DPX-X1179-512, purity: 98.6%) or 0 (vehicle: deionized water) or 1 mg/kg of oxamyl technical (batch no. DPX-D1410-196, purity: 98.3%) by oral gavage. Ten animals/sex/time point were euthanized at 30 minutes and 2, 3, and 4 hours post-dose and cholinesterase (ChE) activity in the brain, red blood cells and plasma was assayed (note: no effort was made to differentiate between acetylcholinesterase and butylcholinesterase activities). The dose levels were selected from dose range finding studies in which the time to peak effect and the appropriate treatment level which resulted in approximately 50% inhibition of ChE activity was achieved. In the methomyl cohort, ChE activity in the red blood cells and brain of both sexes was reduced by 40 to 55% of the control values at 30 minutes post-dose. ChE activity in the plasma was not as severely affected by the treatment. The effect on the RBC and brain ChE activities had largely been reversed by 3 and 2 hours post-dose for the males and females, respectively. For the oxamyl cohort, ChE activity at all 3 sites ranged from 39 to 55% of the control values for both sexes at 30 minutes post-dose. Recovery to control levels was observed at 2 to 3 hours post-dose for both sexes. **Possible adverse effect:** significant inhibition of brain ChE. **Supplemental Study** (non-guideline protocol employed). ([redacted], 4/2/12)

253-268; 155722; "Acute Dietary Toxicity Study for Cholinesterase Inhibition with DPX-X1179-394 in Male Rats"; (T.A. Filliben; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; HLR No. 861-96; 12/12/96); DPX-X1179-394 Technical (purity: 98.35%) was administered orally in the diet over a two hour feeding period at doses of 0, 30, 60, 120, and 360 ppm (0, 0.953, 1.88, 3.74 and 9.98 mg/kg) to 10 male rats/group. In a modified functional observational battery, no treatment-related effects were noted for the in-cage observations. In the free roaming observations, the animals in 360 ppm group exhibited low arousal. In the manipulation sequence, no differences were noted in regards to auditory stimulus. However, animals in the 360 ppm group exhibited no response to the approach-and-touch stimulus. In addition, animals in the 60 ppm and above treatment groups had no response to the tail-pinch stimulus. Mean cholinesterase activities in the plasma (P-ChE), blood (RBC-ChE), and brain (B-ChE) were significantly reduced in the 120 and 360 ppm groups (P-ChE, 83 and 63% of control, respectively, RBC-ChE, 68 and 50% of control, respectively, B-ChE, 71 and 53% of control, respectively) as determined 3 hours after the

initiation of dosing. **Indicated adverse effect:** lack of response to tail-pinch stimulus. **NOEL:** 30 ppm (0.953 mg/kg, based on lack of response to tail-pinch stimulus among animals in the 60 ppm treatment group). **Study supplemental.** [redacted], 8/25/97)

90-day neurotoxicity, rat **

253-273 164573 Mikles, K. A., "Methomyl Technical (DPX-X1179-512): Subchronic oral neurotoxicity study in rats", Haskell Laboratory Project ID# DuPont HL-1998-01639, 9/25/98. Forty-two Crl:CD®BR rats/sex/group were dosed with 0, 20, 50, 150, or 1500 ppm methomyl (98.6% purity) in diet for up to 91 days. Three sets of 10/sex/dose were used in cholinesterase studies. These were sacrificed at weeks 4, 8, and 13, respectively for assays of RBC, plasma, and brain cholinesterase. The other 12/sex/dose underwent neurobehavioral testing (FOB and motor activity) at pre-test and at weeks 4, 8, and 13. Of these, six/sex/dose were perfused *in situ*. Neuropathology was performed on control and high dose central and peripheral nervous system preparations. NOEL = 150 ppm. Body weights and food consumption were markedly reduced at 1500 ppm in both sexes throughout the study. The most prominent of the clinical observations were tremors in most 1500 ppm males and females during the first 4 weeks, and occasionally thereafter. Common FOB observations included increased resistance to handling and removal from the cage, ptosis, and absent pupillary response in both sexes. In addition, females tended to have increased urination during open field observations, and decreased urination during motor activity assessment. None of these findings were progressive over time. Histopathology was negative. Brain cholinesterase was marginally inhibited at 1500 ppm (significant for each sex at one of three assay times). Plasma and RBC cholinesterase activities were unaffected. Since findings were consistent with expected acute responses to a cholinesterase inhibitor, no "adverse effects" are indicated. **Acceptable. [redacted], 1/4/99.

253-275 169902 Exact duplicate of 253-273, 164573.

Developmental neurotoxicity, rat

No studies of this type were submitted.

Delayed neurotoxicity, hen (not required at this time)

253-171 037856 (with rebuttal in 253-176): "Oral LD_{50} and Delayed Paralysis Tests (Hens)." (Haskell Laboratory, 9/25/67). Methomyl technical, no purity given; was administered in acetone/water mixture at 28 mg/kg to 10 hens (cross of Barred Rock and Rhode Island Red varieties) without atropine; TOCP positive control. Evidently 4/10 died. Four additional hens were dosed with atropine pre-treatment at methomyl doses of 60, 90, 120, or 200 mg/kg (all survived). Salivation, lacrimation, and some convulsions, but no paralysis, were observed in the survivors. No microscopic lesions in sciatic nerve (which was evidently the only histopathologic feature assessed). No paralysis or sciatic nerve lesions arose in hens given 60, 90, 120, or 200 mg/kg with atropine. Original review by J. Gee, 4/12/86, Unacceptable, not upgradeable (no repeat dosing, inadequate protocol and data presentation). Rebuttal containing no additional data did not upgrade study; no change in status. [redacted], 7/22/87. One-liner updated by [redacted] and [redacted], 12/8/98.

EPA one-liner: Negative. Minimum.

-008,-025, 042608, 024202, and 407-003, 024987 are summaries of 037856.

Comment: Delayed neurotoxicity testing is not a current data requirement for this class of compounds. [redacted], 10/20/87.

IMMUNOTOXICITY

No studies of this type were submitted.

ENDOCRINE DISRUPTOR STUDIES

No studies of this type were submitted.

SUPPLEMENTAL STUDIES (including human volunteer subjects)

253-274 165908 "A randomized double blind ascending oral dose study with methomyl to establish a no adverse effect level" (McFarlane, P., Sanderson, J. and Freestone, S. Inveresk Clinical Research, Research Park, Riccarton, Edinburgh, Scotland, Project #HLO-1998-00969, 11/30/98). Lannate® SP (Methomyl, Lot T101397-00, purity 89%) was administered by capsule to 19 human male volunteers at doses of 0 (placebo capsule), 0.1, 0.2, or 0.3 mg/kg; the subjects were observed for two days, with one follow-up visit 7 (±2) days after dosing. A subject given 0.3 mg/kg reported headache 1 hr and 45 minutes after dosing, lasting for approximately 1 hr and somnolence and lethargy beginning 3 days after dosing, lasting about 1 day. A significant increase in salivation occurred in the 0.2 and 0.3 mg/kg dose groups between 1 and 3 hours after dosing. Two of 5 subjects that received 0.3 mg/kg methomyl demonstrated a greater than 40% inhibition of RBC ChE. At 0.2 mg/kg, one subject had greater than 40% RBC ChE inhibition and none of these individuals reported abnormal clinical signs. Based on the data presented in the study, a human NOEL for oral exposure to Lannate® SP could be established at 0.1 mg/kg. Supplemental study. (Kellner, 11/7/99) (Full DPR review is found in the volume.)

253-0286 219344 "Lannate sweating study in monkeys to determine if emesis or an increased compound effect is induced by exposure to heat and humidity during testing" Hazelton Laboratories Inc. Falls Church, VA, 08/14/1970. This study pre-dated GLP standards, and protocol was adjusted during the study, based on step outcomes. A total of 15 juvenile (restrained) Rhesus monkeys was used to assess whether increased heat and humidity shortened time to response and duration or intensity of response to topical doses of Lannate (90% purity), when applied to intact clipped skin as 40-50 mg/ml aqueous solutions. After a pilot study, all subsequent exposures were for 2 hours at 40 mg/kg. Some animals received the same dose twice, two days apart, the first time at about 26°C and 20-26% humidity, the second time at 34-36°C and 58-70% humidity. A preliminary study confirmed that the latter conditions greatly increased sweating. After single-dose treatment with normal heat and humidity, miosis was observed in all animals, and some animals showed rapid and audible breathing, head tremors, and fasciculations, with occasional additional clinical signs. Most signs dissipated within 2 hours post-dose, but miosis persisted for at least the 3-hr post-dose observation period. A single-dose treatment at 34-36°C led to earlier onset of symptoms, and extended symptoms post-dose (including 5/6 monkeys with fasciculations 3 hrs post-dose). The latter animals appeared normal the following day. Attempts to evaluate monkeys treated for 2 or more 2-hr sessions in the hot conditions in one day led to deaths of some monkeys. Use of narrative instead of tables and unclear explanations of treatment conditions limit the usefulness of this report. No DPR worksheet. [redacted], 3/12/14.

253-0016; 963992; "Acute Dermal Methomyl-Cholinesterase Response Study in Male Rats"; (J.C. Sumner; E.I. du Pont de Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 303-81; 6/4/81); The skin of 10 Crl:CD male rats/group was exposed to 0 (vehicle: acetone), 25 or 100 mg/kg of Methomyl technical (batch no. not reported; purity: 99 to 100%) for 24 or 72 hours. Red blood cell acetylcholinesterase (AChE) and plasma

cholinesterase (PChE) activity levels were assayed at those time points. The AChE activity was not affected by the treatment. At 24 hours of exposure, PChE activity was reduced in a dose-related manner. At the 25 and 100 mg/kg treatment level, the percent of control activity was reduced to 54 and 34% of the control, respectively. After 72 hours of exposure, the percent of control activity was 52 and 87% for the 25 and 100 mg/kg treatments, respectively. At least after 24-hours of exposure, a treatment-related effect was evident for PChE activity. **Rat Acute Dermal Toxicity NOEL:** (M) <25 mg/kg (based upon the reduced PChE activity noted for the 25 mg/kg treatment group); **Supplemental Study** (non-guideline study). ([redacted], 4/22/16)

LOG OF RECORDS NOT WARRANTING REVIEWS

Duplicate records:
Record No. 116109 in Document No. 253-201 is a duplicate of Record No. 113703.
Record No. 116110 in Document No. 253-201 is a duplicate of Record No. 113701.
Record No. 126009 in Document No. 253-217 is a duplicate of Record No. 113701.
Record No. 126010 in Document No. 253-217 is a duplicate of Record No. 113703.

Records not reviewed due to procedural errors:
Record No. 126011 in Document No. 253-217 was not reviewed by DPR because of errors in study conduct (see Document No. 253-219).

Older records pre-dating modern quality control, and/or data too limited to evaluate:
Record No. 44313 in Document No. 253-0078.
Record No. 44315 in Document No. 253-0078.
Record No. 963986 in Document No. 253-0078.
Record No. 963998 in Document No. 253-090.
Record No. 964011 in Document No. 253-090.
Record No. 42620 in Document No. 253-090.

Records assigned to Worker Health and Safety due to Exposure Assessment Content:
Record No. 964004 in Document No. 253-0024.