CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Tribenuron-Methyl

Chemical Code # 2338, **Tolerance #** 53040
SB 950 # NA

February 11, 2008, Revised, 8/24/15, Nov. 2, 2015

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated**.**
Chronic toxicity, dog:	No data gap, no adverse effect indicated.
Oncogenicity, rat:	No data gap, no adverse effect indicated.
Oncogenicity, mouse:	No data gap, no adverse effect indicated.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, no adverse effect indicated.
Teratology, rabbit:	No data gap, no adverse effect indicated.
Gene mutation:	No data gap, no adverse effect indicated.
Chromosome effects:	No data gap, no adverse effect indicated.
DNA damage:	No data gap, no adverse effect indicated.
Neurotoxicity:	No study submitted

Toxicology one-liners are attached.

All record numbers through 282138 (vol. no. 53040-0146) were examined. This includes all records submitted through Nov. 2, 2015.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: t20151102
Revised by T. Moore, 8/24/15, Aldous, Nov. 2, 2015

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.

Table of Contents

METABOLISM AND PHARMACOKINETICS ** ... 3
GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT ... 4
Acute oral toxicity, rat ** ... 4
Acute dermal toxicity ** ... 4
Acute inhalation toxicity, rat ** ... 4
Primary eye irritation, rabbit ** ... 4
Primary dermal irritation ** ... 5
Dermal sensitization ** ... 5
SUBCHRONIC STUDIES ... 6
Rat 28-Day Oral Toxicity Study ... 6
Rat Subchronic Dietary Toxicity Study ** ... 7
Rat Subchronic Dietary Toxicity Mechanistic Study ... 7
Dog Subchronic Dietary Toxicity Study ** ... 8
Rat 28-Day Repeated Dosing Dermal Toxicity Study † ... 8
CHRONIC STUDIES ... 9
Chronic, rat ** ... 9
Chronic, dog ** ... 9
Oncogenicity, rat ** ... 10
Oncogenicity, mouse ** ... 10
GENOTOXICITY ... 11
Bacterial reverse mutation assay ** ... 11
Mutagenicity: *In vitro* mammalian cell assay ** ... 11
Chromosome damage ** ... 11
DNA damage or miscellaneous effects ** ... 12
REPRODUCTIVE TOXICITY, RAT ** † ... 12
DEVELOPMENTAL TOXICITY ... 13
Rat ** ... 13
Rabbit ** ... 13
NEUROTOXICITY ... 14

Acute neurotoxicity, rat 14
90-day neurotoxicity, rat 14
Developmental neurotoxicity, rat 14
Delayed neurotoxicity, hen 14
IMMUNOTOXICITY 14
ENDOCRINE DISRUPTOR STUDIES 14
SUPPLEMENTAL STUDIES 14
Rat 14-Day Dietary Toxicity Study 14
Metabolic disposition in lactating goat 15

METABOLISM AND PHARMACOKINETICS **

53040-0043; 230975; "Fate of Radiolabeled DPX-L5300 in Rats"; (P.T. Hardesty; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 31-87; 4/15/87, reissued, 4/28/87); Two Crl:CD BR rats/sex/group were dosed orally by gavage with 20 (Study Nos. 1 and 2) or 1800 (Study No. 3) of [Phenyl-^{14}C(U)] DPX-L5300 (no batch no. provided, radiochemical purity: 97%, specific activity: 20.5 µCi/mg). In Study No. 2, the animals were preconditioned with 100 ppm of unlabeled DPX-L5300 (no batch no. provided, purity: 94.2%) in the diet for 21 days. In Study No. 4, 2 rats/sex were dosed orally by gavage with 2000 mg/kg of [Triazine-2-^{14}C] DPX-L5300 (no batch no. provided, radiochemical purity: 97.5%, specific activity: 41.2 µCi/mg). In Study Nos. 5 and 6, 5 females/group were dosed orally with 1700 mg/kg of the phenyl-labeled or triazine-labeled test material, respectively. In the 1st four studies, urine and feces samples were recovered up to 96 hours post-dose. In the latter two studies, the samples were collected up to 7 days post-dose. In the excretion profile, at the lower dose level with no preconditioning, 65 to 69% of the recovered radiolabel was isolated in the urine and 26 to 33% in the feces. When the animals were preconditioned, the recovery in the urine rose to 83-84% and declined to 12 to 14% in the feces. In the high dose groups, the percentage of the recovered radiolabel in the urine ranged from 73 to 80% and from 14 to 20% in the feces. Although the overall percentage of radiolabel recovery from the urine and the feces did not differ between the males and the females in the higher treatment groups, the half-lives for the excretion of the radiolabel were greater for the females. The half-lives for the males were 51 and 54 hours in contrast to those of the females which ranged from 68 to 96 hours. Assessment of radiolabel recovered from various tissues 96 or 168 hours after dosing, indicated that 0.1 to 2.5% of the recovered radiolabel was found in either the blood, liver, G.I. tract or skin (note: in one instance, 28% of the recovered dose was in the G.I. tract of the females treated the 1800 mg/kg of the test material at 96 hours post-dose). Otherwise, none of the tissues assayed demonstrated a greater concentration of the radiolabel on a per gram basis. The parent compound was metabolized by hydrolysis of the amide linkage between the phenyl and triazine components which resulted in the formation of the sulfonamide moiety and the triazine amine. Further modifications were hydroxylation of the phenyl ring and demethylation of the methylated oxygen and nitrogen sites of the triazine amine. Demethylation of the methylated oxygen and nitrogen sites of the parent compound resulted in the formation of IN L5300 acid and metsulfuron methyl, respectively. Saccharin was formed by the bonding of the carbonyl carbon and the nitrogen of sulfonamide acid by dehydrolysis. The predominant

metabolites were saccharin, metsulfuron methyl, sulfonamide acid, and O-demethyl triazine amine. **Study acceptable.** (Moore, 9/13/07)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat **

53040-0012; 230943; "Median Lethal Dose (LD50) of INL-5300-20 in Rats"; (D.B. Warheit; E.I. duPont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714; Report No. 167-85; 5/31/85); Five Crl:CD (SD) BR rats/sex were dosed orally by gavage with 5000 mg/kg of INL-5300-20 (batch no. 9936-39, purity: 96.8%). No deaths resulted from the treatment. The animals demonstrated reasonable body weight gain over the two week observation period. Some of the females demonstrated a wet perineum up to 3 days post-dose. No treatment-related lesions were noted in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; **Study acceptable. (Moore, 8/1/07)

Acute dermal toxicity **

53040-0013; 230944; "Skin Absorption Single Dose Study in Rabbits"; (J.L. Gargus; Hazleton Laboratories America, Inc., Vienna, VA; Project No. 201-779; 12/12/84); The abraded skin of 5 New Zealand white rabbits/sex was exposed to 2000 mg/kg of INL-5300-20 (batch no. 9936-39, purity: 98.6%) for 24 hours under an occluded patch. The test material was moistened sufficiently with water to form a paste. No deaths resulted from the treatment. No treatment-related signs were noted. No necropsy was performed. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable. (Moore, 8/1/07)

Acute inhalation toxicity, rat **

53040-0015; 230946; "Inhalation Median Lethal Dose (LC50) of INL-5300-20 by EPA Protocol"; (L.A. Kinney; E.I. duPont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714; Report No. 431-85; 8/13/85); Five Crl:CD (SD) BR rats/sex/group were exposed nose-only to 1.3 or 6.7 mg/l (gravimetric) of INL-5300-20 (batch no. 9936-39, purity: 96.8%) for 4 hours. The MMAD values were 2.2 and 3.5 um, respectively. No deaths resulted from the exposures. Animals in the high exposure concentration exhibited wet or stained perineum and nasal and/or oral discharges. One female in the group demonstrated lung noise. These signs had been resolved by day 3. No treatment-related lesions were evident in the necropsy examination. LC50 (M/F) > 6.7 mg/l; Toxicity Category IV; **Study acceptable. (Moore, 8/1/07)

Primary eye irritation, rabbit **

53040-0016; 230947; "Haskell Eye Irritation Test in Rabbits'; (J.L. Gargus; Hazleton Laboratories America, Inc., Vienna, VA; Project No. 201-616; 5/18/83); The eye of one New Zealand white rabbit was treated with 10 mg/eye of INL-5300-9 (no batch no. provided; purity: 94%) by ocular instillation (note: the eye of another rabbit was treated with the test material and then rinsed 20 seconds after dosing). No corneal opacity nor iritis were evident during the 72 hour observation period. No conjunctival redness, chemosis nor discharge were noted at 24 hours post-dose. Toxicity Category not assigned; **Study unacceptable**, not upgradeable (the number of study animals was insufficient to evaluate the irritation potential of the test material). (Moore, 8/1/07)

**53040-0124 238277; Primary Eye Irritation Study; 814; Rabbit; E.I. du Pont de Nemours and Company Haskell Laboratory for Health and Environmental Sciences, Newark, Delaware; Medical Research no. 4581-560; Haskell no. 16,968; Report no. 627-87; 11/10/87; IN L5300-14; DPX-L5300; Tribenuron Methyl (96.6% purity); Notebook no's. 5103-166 and 9415-178; Off-white solid; 6 animals (F); Dose: 50 mg aliquot in the right eye; Observations: Corneal Opacity-

score 1 in 2/6 at 1 hour, with clearing in all by 24 hours; Iritis- none; Conjunctiva: (redness) score 1 in 6/6 at 1 hour, in 2/6 at 24 hours, in 1/6 at 48 hours, with clearing in all by 72 days; (Chemosis); score 1 in 4/6 at 1 hour, with clearing in all by 24 hours; Toxicity Category III; Study acceptable (Dehar, 3/18/08).

Primary dermal irritation **

53040-0020; 230951; "Primary Dermal Irritation Study with DPX-L5300-104 in Rabbits"; (C. Finlay; E.I. duPont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 376-94; 7/28/94); The skin of 6 New Zealand white rabbits was exposed to 0.5 g/site, one site/animal, of DPX-L5300-104 (lot no. C-900925-B, purity: 95.8%) for 4 hours under an occlusive wrap. The test material was moistened with deionized water. Erythema, grade 1 (1/6), was noted at 1 hour post-exposure, clearing by 24 hours. No edema was evident. Toxicity Category IV; **Study acceptable. (Moore, 8/2/07)

Dermal sensitization **

53040-0018; 230949; "Primary Irritation and Sensitization Study in Guinea Pigs"; (J.L. Gargus; Hazleton Laboratories America, Inc., Vienna, VA; Project No. 201-617; 8/31/83); The skin of 10 male Hartley guinea pigs was exposed to 7 and 70% preparations of INL-5300-9 (batch no. 8978-75; purity: 94%) in dimethyl phthalate (quantity of test material applied and duration of exposure were not reported). These animals then received 0.1 ml intradermal injections of a 1% preparation of the test material in dimethyl phthalate once per week for a total of four injections. Ten control animals also received these injections. After a two week interlude, in the challenge phase, the skin of all of the animals in both groups was exposed to 0.05 ml of the 7 and 70% preparations of the test material in dimethyl phthalate (duration of exposure was not reported). Very slight to well-defined erythema with blanching was noted at 24 hours after the intradermal injections. No signs of dermal irritation were evident for any of the animals in both groups in the challenge phase of the study. **Study unacceptable, possibly upgradeable with the submission of concurrent positive control study data to substantiate the validity of the test results. (Moore, 8/2/07)

53040-0021; 230952; "Assessment of the Skin Sensitization Potential of L5300 in the Guinea Pig (Magnusson and Kligman Maximization Test)"; (P.J.J.M. Weterings; NOTOX C.V., 5231 DD 's-Hertogenbosch, The Netherlands; Report No. NOTOX 0382/510; 10/3/86); Twenty Dunkin-Hartley female guinea pigs received a total of 6 intradermal injections of 0.1 ml each, 2 each of Freund's Complete Adjuvant: distilled water (1:1), 2% (w/v) dilution of L5300 (batch no. E43213-35, purity: not reported) in acetone, and a 4% dilution of the test material in acetone (1:1) with Freund's Complete Adjuvant: water (1:1) on day 0 of induction. On day 7, the skin of the treated animals was exposed to 0.5 ml of a 50% preparation of the test material in propylene glycol for 48 hours under an occlusive wrap as the second induction treatment. Ten control females were treated in the same manner for both induction treatments except that the test material was not included in the dosing regimen. On study day 21, the skin of each of the animals was exposed to 0.05 ml of four preparations, 50, 20, 5 and 0% preparation of the test material in propylene glycol for 24 hours in "Square" chambers. One treated animal accidently died at the initiation of the study. In the challenge, 17 of the 19 treated animals exhibited a positive response of grade 2 or 3 by 48 hours post-exposure for the 50% preparation. Nine of the 19 sites treated with the 20% preparation were positive at 48 hours post-exposure. None of the sites treated with the 5% preparation were positive. For the control, none of animals demonstrated a positive response at 24 or 48 hours post-exposure. No positive control study was included in the report. The test material is a dermal sensitizer in accordance with the Guinea Pig Maximization Test. **Study acceptable. (Moore, 8/3/07)

53040-0023; 230955; "Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with IN L5300-14 in Guinea Pigs"; (W.J. Brock; E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 712-87; 1/11/88); The skin of ten Duncan Hartley guinea pigs/sex was exposed to 0.4 ml/site (0.25 g) of INL-5300-14 (no batch no.; purity: 96.6%) for 6 hours, once per week, for 3 weeks. The test material was slightly moistened with dimethyl phthalate. The placement of the test material in a Hill Top Chamber was the method used to expose the skin. The skin of a control group of 5 animals/sex was treated with 0.4 ml/site of dimethyl phthalate according the same treatment protocol. After a 2-week interlude, in the challenge phase, the skin of all of the study animals was treated with 0.4 ml of the test material slightly moistened with dimethyl phthalate. One week later, a re-challenge was performed in which the test animals were treated in the same manner as previously. In addition, a naive control group of 5 animals/sex was treated the test material. During the induction treatment, four of the test animals exhibited grade 1 or grade 2 responses at 24 hours after treatment for the last exposure. The skin of the control animals was not affected by the treatment with the vehicle. In the initial challenge, the skin of 12 treated animals demonstrated a response of grade 2 (5/20) or 1 (7/20) by 48 hours post-treatment. The treatment elicited a grade 1 response from one of the 10 control animals at 48 hours after treatment. In the re-challenge, two of the 20 animals demonstrated a positive response (grades 3 (1/20) and 2 (1/20) at 24 hours, and grade 2 (2/20) at 48 hours after treatment). The skin of none of the naive control animals responded in the re-challenge. The test material is a possible dermal sensitizer according to the Buehler test protocol. The positive control study was inadequate. **Study acceptable. (Moore, 8/6/07)

SUBCHRONIC STUDIES

Rat 28-Day Oral Toxicity Study

53040-0041; 230973; "Assessment of the Subacute Oral Toxicity of L5300 in the Rat: 28-Day Study"; (M.H. Thouin; NOTOX C.V., 5231 DD 's-Hertogenbosch, The Netherlands; Report No. NOTOX 082/534; 10/30/86); In the first study, six Sprague-Dawley rats/sex/group were dosed orally by gavage with 0 (vehicle: propylene glycol), 100, 300 or 1000 mg/kg/day of L5300 (batch no. E43213-35, purity not reported) for 28 days. In 2nd study, 6 animals/sex/group were dosed in the same manner with 0 or 30 mg/kg/kg of the test material for 28 days. One female in the 1000 mg/kg group was found dead on day 17. Death was likely due to a gavage error. The mean body weights of both sexes in the 100, 300 and 1000 mg/kg groups were less than the control values by the end of the study (NS, $p<0.05$). The food consumption of the animals in these groups was less than that of the controls. The hematology evaluation did not reveal any treatment-related effects. In the clinical chemistry evaluation, the serum calcium levels were elevated for both sexes in the 1000 mg/kg group and for the females in the 300 mg/kg group ($p<0.05$). The serum total bilirubin concentration was reduced in a dose-related manner for the 100, 300 and 1000 mg/kg groups (NS, $p<0.05$). The serum alanine aminotransferase activity was elevated for both sexes in the 300 and 1000 mg/kg groups ($p<0.05$). The mean absolute liver weights of the females in the 300 and 1000 mg/kg groups and the mean relative liver weights of both sexes in the 300 and 1000 mg/kg groups were greater than the control values ($p<0.05$). The mean relative kidney weights of the females in the 300 mg/kg group and of both sexes in the 1000 mg/kg group were greater than the control values ($p<0.05$). The mean relative testes weight of the males in the 1000 mg/kg group was greater than that of the control ($p<0.05$). In the histopathology examination, hypertrophy of the centrilobular hepatocytes was noted in the livers of both sexes in the 300 and 1000 mg/kg groups ((M) 0: 0/6 vs. 300: 6/6 (slight), 1000: 6/6 (well defined), (F) 0: 0/6 vs. 300: 6/6 (slight), 1000: 5/5 (well defined)). **No adverse effect indicated. Rat 4-week Oral Toxicity NOEL:** (M/F) 30 mg/kg/day (based upon the lower mean body weights and food consumption of both sexes in the 100 mg/kg group and

the increased relative liver weight of the 100 mg/kg females); **Study supplemental** (non-guideline study) (Moore, 9/4/07)

Rat Subchronic Dietary Toxicity Study **

NOTE: Although the following 90-day subchronic study was faulted for lack of ophthalmology examination, the accepted combined rat chronic/oncogenicity study contained ophthalmology, with no associated response observed. See combined study 53040-0032; 230964, below. Aldous, Nov. 2, 2015.

53040-0024; 230956; "Ninety-Day Feeding and One-Generation Reproduction Study in Rats with Benzoic Acid, 2[[[[N-(4-Methoxy-6-Methyl-1,3,5-Triazin-2-yl)-N-Methylamino]Carbonyl] Amino] Sulfonyl]-, Methyl Ester"; (W.J. Brock; E.I. duPont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 413-83; 6/6/85); Sixteen Crl:CD(SD)BR rats/sex/group received 0, 100, 1750 or 5000 ppm of INL-5300-13 (Tribenuron Methyl Technical) (no batch no. reported; purity: 99%) in the diet for 90 days ((M) 0, 7, 118, 335 mg/kg/day, (F) 0, 8, 135, 386 mg/kg/day). Six animals/sex/group were retained for a one-generation reproduction study in which the animals were mated for 2 weeks and then maintained through the remainder of the gestation period and the 3 week lactation period. One female in the 5000 ppm group was found dead on day 28. The mean body weights of both sexes in the 1750 and 5000 ppm groups were less than the control values throughout the study ($p<0.05$). The mean food consumption for both sexes in these groups was less than that of the control group throughout the study. No treatment-related effect was evident in the hematology and clinical chemistry evaluations or the urinalysis. Although the mean relative weights of the various organs which were surveyed from both sexes in the 1750 and 5000 ppm groups were affected by the treatment, no accompanying histopathological lesions were noted in these tissues. **No adverse effect evident.** In the one-generation reproduction study, no effect upon the reproduction parameters was evident. The mean body weights of pups in the 1750 and 5000 ppm groups were lower than that of the control throughout the lactation period ($p<0.05$). The viability of the 5000 ppm pups was also lower than that of the control over the 1st four days post-partum. **Rat Subchronic Dietary NOEL:** (M/F) 100 ppm ((M) 7 mg/kg/day, (F) 8 mg/kg/day) (based upon the lower mean body weights and food consumption of both sexes in the 1750 ppm group); **Study Supplemental** (no ophthalmological examination was performed**).** (Moore, 8/8/07)

Rat Subchronic Dietary Toxicity Mechanistic Study

53040-0042; 230974; "Ninety-Day Feeding Study with IN L5300-20: Effect on Estrous Cycle"; (J.C. Cook; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 112-89; 3/16/89); Twenty Crl:CD(SD)BR female rats/group received 0 or 5000 ppm of IN L5300-20 (no batch no. provided, purity: 94.8%) in the diet for at least 12 weeks (0, 390 mg/kg/day). No deaths occurred during the treatment. The mean body weights and food consumption of the treated animals were less than the control values throughout the study ($p<0.05$). The mean relative liver and uterus weights of the 5000 ppm females euthanized during either the estrus or the diestrus cycles were greater than those of the control ($p<0.05$). The mean relative mammary tissue weights were less than those of the control animals euthanized during either the estrus or the diestrus cycles ($p<0.05$). No treatment-related effect was noted in the number of corpora lutea or follicles in the ovaries of the treated females in either estrus or diestrus. There was an increased number of cycles with a prolonged estrus (0: 7/263 vs. 5000: 29/253, $p<0.05$). The number of rats experiencing a prolonged estrus was greater in the 5000 ppm group (0: 6/20 vs. 5000: 14/20, $p<0.05$). The number of rats experiencing 2 or more prolonged estrus cycles was greater in the treated group (0: 1/20 vs. 5000: 9/20, $p<0.05$). The serum prolactin concentration of the treated animals sacrificed during estrus was greater than that of the control animals (NS). The mean insulin

concentrations of the treated animals sacrificed during both estrus and diestrus were reduced in the serum (NS, $p<0.05$). This reduction may have been due to the lower body weight gain demonstrated by these animals. There was no treatment-related effect on the estradiol or progesterone levels in the serum. The dissociation constants (K_d) for the estrogen receptor of the treated animals were increased (lowered affinity for the agonist) in the cytosol of the uterus of the animals sacrificed during estrus and in the cytosol of the mammary gland of animals sacrificed during both estrus and diestrus. The number of progesterone receptors was increased in the cytosol of the mammary glands of the treated animals sacrificed during estrus. Increased cell proliferation was noted in the uterine tissue of the treated animals. The reduced cell proliferation noted in the mammary glands of the treated animals was likely due to the lower body weight gain demonstrated by these animals. In the *in vitro* receptor binding assay, estradiol was displaced from the estrogen receptor by several of the metabolites (sulfonamide urea>metsulfuron methyl>hydroxylated saccharin>α-hydroxy triazine amine>IN L5300 acid>N-demethyl triazine amine). No effect was noted on the binding of R5020 to the progesterone receptor. These results indicate that the test material and/or its metabolites may have a weakly agonistic effect upon the estrogen receptor. **Study supplemental** (non-guideline study). (Moore, 9/13/07)

Dog Subchronic Dietary Toxicity Study **

53040-0025; 230957; "A Three-Month Feeding Study in Dogs with H-15527"; (I.W. Daly, H.F. Bolte; Bio/dynamics Inc., East Millstone, NJ; Project No. 84-2864; 8/14/85); Four beagle dogs/sex/group received 0, 50, 500 or 2500 ppm of H-15527 (tribenuron methyl technical) (no batch no. provided, purity: 96.8%) for 3 months ((M) 0, 1.5, 14.9, 73.3 mg/kg/day, (F) 0, 1.6, 15.1, 78.0 mg/kg/day). No deaths occurred during the study. The mean body weights and food consumption were not affected by the treatment. The hematology and clinical chemistry evaluations and urinalyses did not reveal any treatment-related effects. No treatment-related effect on organ weights or lesions were noted in the necropsy/histopathological evaluations. **No adverse effect indicated. Dog Subchronic Dietary NOEL: (M/F) 2500 ppm ((M) 73.3 mg/kg/day, (F) 78.0 mg/kg/day) (based upon the lack of treatment-related effects evident for both sexes in the 2500 ppm group). **Study acceptable.** (Moore, 8/9/07)

Rat 28-Day Repeated Dosing Dermal Toxicity Study †

53040-0040; 230972; "DPX-L 5300 Technical: Toxicity Study for 28 days by Dermal Application to Rabbits"; (J. Richard; Centre International de Toxicologie (C.I.T.), Miserey, 27005 Evreux, France; Study No. 7611; 2/3/92); The skin of six New Zealand White rabbits/sex/group was exposed to 0 (sterile water, 1 mg/kg/day) or 1000 mg/kg/day of DPX-L 5300 Technical (lot no. B1026, purity: 97.7%) for 6 hours/day (4 hours/day on the weekends) for 4 weeks. The test material was moistened into a paste by mixing 1 g of the material with 1 ml of the sterile water. One male and one female in the 1000 mg/kg group died during the 4th week of the study. No reason for their deaths could be ascertained. The mean body weights of both sexes in the 1000 mg/kg group were less than those of the control group throughout the study (NS, $p<0.05$). The food consumption of the treated group was also less than that of the control group throughout the study (NS, $p<0.05$). In the hematology evaluation, the mean red blood cell count, hemoglobin concentration and hematocrit of the males in the 1000 mg/kg group were less than those of the control ($p<0.01$). In the clinical chemistry analysis, the mean inorganic phosphate levels in the serum of both sexes in the 1000 mg/kg group were less than the control values ($p<0.05$). For the females in the 1000 mg/kg group, the mean serum chloride, glucose, and creatinine were elevated in comparison the control group ($p<0.05$). In the necropsy examination, the mean relative kidney weights were greater for both sexes in the 1000 mg/kg group (NS, $p<0.05$). In the histopathology, multifocal nephrocalcinosis was noted in the kidneys of both sexes in the treated group ((M) 0: 0/6 vs. 1000: 3/6, (F) 0: 0/6 vs. 6/6). Tubular

degeneration/necrosis was also observed in the kidneys of both sexes in the treated group ((M) 0: 0/6 vs. 1000: 1/6, (F) 0: 0/6 vs. 1000: 6/6). Microscopic examination of the treated skin revealed an increased incidence of acanthosis, hyperkeratosis, degeneration/necrosis of the epidermis and dermis, edema, and aggregation of inflammatory cells. **Possible adverse effect:** tubular degeneration/necrosis in the kidney; **Rabbit 4-Week Repeated Dosing Dermal Toxicity NOEL:** (M/F) <1000 mg/kg/day (based upon the incidence of lesions in the kidneys and the lower mean body weights and food consumption of both sexes in the 1000 mg/kg group); **Dermal Irritation NOEL:** (M/F) <1000 mg/kg/day (based upon the dermal lesions noted for both sexes in the 1000 mg/kg group); **Study supplemental** (only one treatment group was included in the study; a NOEL could not be established based upon the limited data base). (Moore, 8/31/07)

CHRONIC STUDIES

Chronic, rat **

** 53040-0032; 230964; “Combined Chronic Toxicity/Oncogenicity Study with INL-5300 Long-Term Feeding Study in Rats”; (A.J. Tobia; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 61-87; 3/10/87); Sixty Crl:CD(SD)BR rats/sex/group received 0, 25, 250 or 1250 ppm of INL-5300 (INL-5300-20) (no batch no. provided, purity: 96.8%) in the diet for 2 years ((M) 0, 0.95, 10.0, 55 mg/kg/day; (F) 0, 1.2, 13, 76 mg/kg/day). An additional 10 animals/sex/day received the same concentrations of the test material in the diet for 12 months. No treatment-related effect on the survival of the test animals was evident. The mean body weights of both sexes in the 250 and 1250 ppm groups were less than the control values throughout the study ($p<0.05$). The mean food consumption of the 250 and 1250 ppm groups was less than that of control group as well. The hematology, clinical chemistry, urinalysis and ophthalmology did not reveal any treatment-related effects. Although the mean absolute and/or relative weights of several organs were significantly different from the control values, no treatment-related histopathological lesions were observed in these organs. In the histopathological examination, an increased incidence of particular lesions was noted in the 1250 ppm group. The lesions appeared to be in response to the general ill effects experienced by the high dose animals as indicated by their lower mean body weights over the course of the study. The females in the 1250 ppm group did demonstrate an increased incidence of multiple adenocarcinomas in the mammary glands (0: 1/60 vs. 1250: 11/61, $p<0.05$). However, the treatment level was in excess of the maximum tolerated dose (mean body weight more than 10% less than that of the control). **No adverse effect evident. Rat Chronic Dietary Toxicity NOEL:** (M/F) 25 ppm ((M) 0.95 mg/kg/day, (F) 1.2 mg/kg/day) (based upon the lower mean body weights of both sexes in the 250 ppm group); **no oncogenicity evident. Study is acceptable.** (Moore, 8/23/07)

Chronic, dog **

** 53040-0030; 230962; “One-Year Feeding Study in Dogs with IN L5300"; (W.J. Brock; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 565-86; 10/10/86); Five beagle dogs/sex/group received 0, 25, 250 or 1500 ppm of INL-5300 (INL-5300-22) (no batch no. provided; purity: 94.2%) in the diet for one year ((M) 0, 0.79, 8.16, 51.5 mg/kg/day, (F) 0, 0.90, 8.18, 52.0 mg/kg/day). No deaths resulted from the treatment. The mean body weight gain of both sexes in the 1500 ppm group over the course of the study was less than that of the controls (NS). No treatment-related effect upon food consumption was evident. No treatment-related effects were noted in the hematological, urinalysis or ophthalmological examinations. In the clinical chemistry evaluation, the mean serum bilirubin values of both sexes in the 1500 ppm group were elevated in comparison to the

control values at various time points during the study (p<0.05). The serum creatinine values of both sexes in the 1500 ppm group were greater than those of the control as well (NS, p<0.05). The mean absolute and/or relative organ weights were not affected by the treatment. No treatment-related lesions were noted in the histopathological examination. **No adverse effect indicated. Dog Chronic Dietary NOEL:** (M/F) 250 ppm ((M) 8.16 mg/kg/day, (F) 8.18 mg/kg/day) (based on treatment-related effects upon serum creatinine levels and lower body weight gain demonstrated by both sexes in the 1500 ppm group). **Study acceptable.** (Moore, 8/17/07)

Oncogenicity, rat **

See Chronic, rat above.

Oncogenicity, mouse **

** 53040-0031; 230963; "Oncogenicity Study with INL-5300, Eighteen Month Feeding Study in Mice"; (A.J. Tobia; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 60-87; 3/6/87); Eighty CD-1 (ICR) mice/sex/group received 0, 20, 200 or 1500 ppm of INL-5300 (INL-5300-22) (no batch no. provided; purity: 94.2%) in the diet for 18 months ((M) 0, 2.5, 25, 197 mg/kg/day; (F) 0, 3.1, 31, 247 mg/kg/day). The survival of both sexes in the 1500 ppm group was less than that of the control ((M) 0: 49% vs. 1500: 35%, (F) 0: 46% vs. 1500: 40%). The mean body weights of both sexes in the 1500 ppm group were less than those of the controls throughout most of the study (p<0.05). There was no treatment-related effect upon food consumption. The hematology examination did not reveal any treatment-related effects. The mean relative liver weights of both sexes in the 1500 ppm group were greater than the control values (p<0.05). In the histopathology examination, the incidence of amyloid deposits in the glandular stomach of both sexes in the 1500 ppm group was greater than that of the controls ((M) 0: 31/78 vs. 1500: 48/78, p<0.01, (F) 0: 39/79 vs. 1500: 51/79, p<0.05). An increased incidence of amyloid deposition was also noted in the lymph nodes and testes of the 1500 ppm males, the testes of the 200 ppm males and the salivary glands of the 1500 ppm females (lymph nodes: 0: 28/77 vs. 1500: 44/76, p<0.01, testes: 0: 20/79 vs. 200: 34/80, p<0.05, 1500: 42/78, p<0.01; salivary glands: 0: 11/80 vs. 1500: 25/80, p<0.01). Atrophy was noted in the kidneys of the 1500 ppm males, secondary to amyloid deposition (0: 11/80 vs. 1500: 21/80, p<0.01). An increased incidence of bilateral seminiferous degeneration was noted in the testes of the 1500 ppm males (0: 38/79 vs. 1500: 54/78, p<0.01). This lesion correlated with the increased incidence of oligospermia in the epididymides of the 200 and 1500 ppm males (0: 22/80 vs. 200: 36/80, p<0.05, 1500: 43/78, p<0.01). An increased incidence of inflammation in the thyroid was noted for both sexes in the 1500 ppm group ((M) 0: 0/80 vs. 1500: 8/79, p<0.01, (F) 0: 9/79 vs. 1500: 27/79, p<0.01). An increased incidence of hematopoietic and granulocytic hyperplasia were noted in the bone marrow of the males and females of the 1500 ppm group, respectively (M) 0: 2/79 vs. 1500: 9/80, p<0.05, (F) 0: 7/80 vs. 1500: 16/79, p<0.05). Osteodystrophia fibrosa was noted more frequently in the nasal turbinates of the 1500 ppm males than in the control group (0: 4/80 vs. 1500: 14/80, p<0.01). In the kidneys of the 1500 ppm males there was also an increased incidence of both cysts and papillary necrosis (cysts, 0: 19/80 vs. 1500: 37/80, p<0.01, papillary necrosis, 0: 4/80 vs. 1500: 12/80, p<0.05). In the kidneys of the 1500 ppm females, an increased incidence of perivascular lymphocytic infiltrate was noted (0: 34/80 vs. 1500: 50/80, p<0.01). The list of lesions noted in the histopathological examination were attributable to the increased incidence of amyloidosis. **No adverse effect indicated. Mouse Chronic Dietary NOEL: (M)** 20 ppm (2.55 mg/kg/day) based upon the increased incidence of amyloid deposition in the testes and oligospermia in the epididymides of the 200 ppm males; **(F)** 200 ppm (31 mg/kg/day) (based upon the increased incidence of amyloidosis and associated complications in the females of the 1500 ppm group); **oncogenicity was not evident. Study acceptable.** (Moore, 8/21/07)

GENOTOXICITY

Bacterial reverse mutation assay **

** 53040-0034; 230966; "Mutagenicity Evaluation in *Salmonella typhimurium*"; (S.L. Massado, revision: L.B. Rickard; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 245-83; 6/23/83, reissued, 3/13/86); *S. typhimurium* strains TA97, TA98, TA100 and TA1535 were incubated for 48 hours at 37° C with INL-5300-9 (no batch no. provided, purity: 94%) at concentrations ranging from 5 to 500 µg/plate under conditions of non-activation and from 10 to 2000 µg /plate under conditions of activation in two trials. Each treatment level was plated in duplicate. An S9 fraction derived from the liver of young male Sprague-Dawley rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/23/07)

Mutagenicity: *In vitro* mammalian cell assay **

** 53040-0036; 230968; "Mutagenicity Evaluation of INL-5300-20 in the CHO/HPRT Assay"; (L.B. Rickards; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 58-85; 5/30/85); Chinese Hamster Ovary (CHO-K_1-BH_4) cells were exposed to INL-5300-20 (no batch no. provided, purity: 96.8%) at concentrations ranging from 0.5 to 5.0 mM for 16 to 20 hours at 37° C w/o activation and for 5 hours with activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related statistically significant increase in the mutant frequency of the treated cells. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/23/07)

Chromosome damage **

** 53040-0037; 230969; "Mouse Bone Marrow Micronucleus Assay of INL-5300-20"; (D.V. Ullman; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; 7/22/85); Eighteen Crl:CD-1®(ICR) BR mice/sex were dosed orally by gavage with 5000 mg/kg of INL-5300-20 (no batch no. provided, purity: 96.8%) and 6 animals/sex/time point were euthanized at 24, 48 and 72 hours post-dose. Another 15 animals/sex were dosed with corn oil (16 ml/kg) and 5 animals/sex/time point were euthanized at the same time intervals. A positive control group of 5 animals/sex were 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 1000 PCEs/animal was determined. The frequency of micronucleated normochromatic erythrocytes (NCE) was determined as well. The ratio of PCE to NCE was reported. One male and two females in the treated group died. Treatment-related clinical signs included tremors and hyperactivity. No treatment-related increase in the number of micronucleated PCE's was noted. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 8/24/07)

** 53040-0038; 230970; "*In Vivo* Assay of INL-5300-20 for Chromosome Aberrations in Rat Bone Marrow Cells"; (D.V. Ullman; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 286-85; 6/14/85); Fifteen Crl:CD-1®(ICR) BR rats/sex/ were dosed orally by gavage with 0 (vehicle: corn oil), 50, 500 or 5000 mg/kg of INL-5300-20 (no batch no. provided; purity: 96.8%) and 5 animals/sex/group/time point were euthanized at 6, 24 and 48 hours post-dose. A positive control group of 5 animals/sex were treated orally by gavage with 20 mg/kg of cyclophosphamide and euthanized at 24 hours

post-dose. Bone marrow cells from the femur were examined for chromosomal aberrations . No deaths resulted from the treatment. No treatment-related increase in the incidence of chromosomal aberrations was noted. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 8/27/07)

DNA damage or miscellaneous effects **

** 53040-0039; 230971; "Assessment of INL-5300-20 in the *In Vitro* Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes"; (G.T. Arce; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 565-84; 7/18/85); Primary rat hepatocyte cultures were exposed to INL-5300-20 (no batch no. provided; purity: 96.8%) at concentrations ranging from 0.1 to 2500 µM for 18 hours at 37° C. Vehicle control (DMSO) and positive control (DMBA, 100 µM) cultures were included in the assay. There were 4 cultures/treatment level with the results of two trials being reported. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated.** The positive control was functional. **Study acceptable**. (Moore, 8/29/07)

REPRODUCTIVE TOXICITY, RAT ** †

** 53040-0028, -0029; 230960, 230961; "Two-Generation Reproduction Study in Rats with IN L5300" (L.S. Mullin; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 193-86; 4/14/86, supplemental report: 11/3/88); Twenty three Crl:CD (SD) BR rats/sex/group (P Generation) received 0, 25, 250 or 1000 ppm of INL-5300 (INL-5300-22) (no batch no. provided, purity: 94.2%) in the diet for 10 weeks prior to mating, mating for the F1A generation, 3 weeks of gestation and 3 weeks of lactation, followed by the mating for the F1B generation, 3 weeks of gestation and 3 weeks of lactation. At the time of weaning, 23 F1A animals/sex/group were selected as parents and treated for an additional 11 weeks, mating for the F2A generation, 3 weeks both for gestation and lactation, followed by the mating for the F2B generation, and 3 weeks both for gestation and lactation. None of the deaths which occurred during the study were attributable to the treatment. The mean body weight gains of both sexes in the 1000 ppm group of both parental generations were less than those of the controls ($p<0.05$) during the premating period. The mean body weight gains of the males in the 250 ppm group, P generation, and the 250 ppm females, F1A generation, were less than the control values during the premating period as well ($p<0.05$). The mean food consumption of both sexes in the 1000 ppm group, both generations, was less than that of the controls ($p<0.05$). The mean relative testes weights of the 1000 ppm males in both generations were greater than the control values ($p<0.05$). However, no corresponding histopathological lesion was evident. The mating parameters of either generation were not affected by the treatment. The mean pup weights of the 1000 ppm treatment group for all four matings were less than those of the control from day 4 *post-partum* through to the end of the lactation period (NS or $p<0.05$). The mean pup weights of the 250 ppm F1B and F2B generations were less than those of the control by day 7 *post-partum* (NS, $p<0.05$). The mean relative spleen weights for the female weanlings in the 250 and 1000 ppm groups of the F2B generation were less than that of the controls ($p<0.05$). However, no corresponding histopathological lesion was evident. **No adverse effect indicated. Parental NOEL: (M/F)** 25 ppm ((M) 1.4 to 3.6 mg/kg/day, (F) 1.7 to 3.9 mg/kg/day) (based upon reduced body weight gain of the adults in the 250 ppm group); **Reproductive NOEL:** 1000 ppm ((M) 58.3 to 148.1 mg/kg/day, (F) 73.7 to 154.6 mg/kg/day) (based upon the lack of a treatment-related effect in the 1000 mg/kg group in all four matings); **Developmental NOEL:** 25 ppm ((M) 1.4 to 3.6 mg/kg/day, (F) 1.7 to 3.9 mg/kg/day) (based upon the lower mean body weights of the 250 ppm pups during the lactation period of the F1B and F2B matings). **Study acceptable.** (Moore, 8/16/07)

53040-0044; 230976; "Two Generation (4 Litters) Reproduction Study in Albino Rats"; (M.L. Aggarwal, U.Y. Sangamwar; Shriram Institute for Industrial Research, Delhi - 110 007, India; Project No. TOX/3; 3/22/95); Ten male and 20 female Wistar rats in the P1 and P2 generations were dosed orally by gavage with 0 (vehicle: corn oil), 10, 50 or 250 mg/kg/day of Express Technical (lot no. not provided, purity: 95%) during a premating period, 1st mating, gestation and lactation periods and 2nd mating, gestation, and lactation periods. One male in the 250 mg/kg group, P1 generation died during the premating period. The terminal body weights for both sexes in the 250 mg/kg group, P2 generation, were less than those of the control animals. The number of pregnant dams in the 250 mg/kg group in the F1b, F2a and F2b matings was lower than the control number. The viability and lactation/weaning indices of the pups in the 50 and 250 mg/kg groups in the F1b, F2a and F2b matings were less than those of the control animals. The mean pup weights of the offspring in the 250 mg/kg group (all four matings) and the 50 mg/kg group (F1b, F2a and F2b matings) were less than those of the control group at some time during the 3-week lactation period. **Possible adverse effect**: depressed development of the offspring. **Parental NOEL:** (M/F) 50 mg/kg/day (based upon the lower mean terminal body weights of the P2 generation); **Reproduction NOEL:** 50 mg/kg/day (based upon the reduced number of pregnancies for the dams in both generations); **Developmental NOEL:** 10 mg/kg/day (based upon the lower viability and lactation/weaning indices and lower mean pup weights for both generations); **Summary Study** (data for individual animals was not well documented in the report). (Moore, 9/14/07)

DEVELOPMENTAL TOXICITY

Rat **

** 53040-0026; 230958; "Developmental Toxicity Study of L-5300 in the Rat'; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; Project ID. 104-010; 8/16/85); Twenty five mated Crl:COBS CD (SD) BR female rats/group were dosed orally by gavage with 0, 20, 125 or 500 mg/kg/day of L-5300 (INL-5300-22) (no batch no. provided; purity: 94.2%) from day 6 through day 15 of gestation. One female in the 20 mg/kg died on day 11 of gestation as a consequence of a intubation error. The mean body weight gain and food consumption of the dams in the 125 and 500 mg/kg groups were less than the control values ($p<0.01$). The mean fetal weights of the 125 and 500 mg/kg groups were less than that of the controls ($p<0.01$). In incidence of litters with fetuses having bifid centra of the thoracic vertebrae was increased for the 125 and 500 mg/kg groups (0: 0/22 vs. 125: 5/23 ($p<0.05$), 500: 7/22 ($p<0.01$)). In addition, there was an increased incidence in delayed development of the skeleton for the fetuses in the 125 and 500 mg/kg groups. **No adverse effect indicated. Maternal NOEL:** 20 mg/kg/day (based upon the lower mean body weights and food consumption of the dams in the 125 mg/kg group); **Developmental NOEL:** 20 mg/kg/day (based upon the delayed development and lower mean weights of the fetuses in the 125 mg/kg group); **Study acceptable.** (Moore, 8/10/07)

Rabbit **

** 53040-0027; 230959; "L-5300. Developmental Toxicity Study in Rabbits Dosed by Gavage on Days 7-19 of Gestation"; (J.E. Zellers; E.I. duPont de Nemours and Co. Inc., Haskell Laboratory for Toxicology & Industrial Medicine, Newark, DE; Report No. 150-86; 4/8/86); Twenty two artificially inseminated New Zealand White female rabbits/group were dosed orally by gavage with 0, 5, 20, or 80 mg/kg/day of L-5300 (INL-5300-22) (no batch no. provided, purity: 94.2%) from day 7 through day 19 of gestation. The vehicle was aqueous 0.5% methyl cellulose. One female in the 20 mg/kg group and two females in the 80 mg/kg group died during the study. The mean body weight gain and food consumption of the 80 mg/kg does during the treatment period were less than the control values ($p<0.05$). The incidence of abortions for the 80 mg/kg does was greater than that of the controls (0: 1/18 vs. 80: 7/19,

(p<0.05)). Among the fetal development parameters, the number of litters in which at least one fetus suffered a malformation was increased for the 80 mg/kg treatment group (0: 0/16 vs. 80: 4/11). **No adverse effect indicated. Maternal NOEL:** 20 mg/kg/day (based upon the abortion incidence and lower mean body weights and food consumption of the does in the 80 mg/kg treatment group); **Developmental NOEL:** 20 mg/kg/day (based upon the increased incidence of litters with malformed fetuses in the 80 mg/kg treatment group). **Study acceptable.** (Moore, 8/13/07)

NEUROTOXICITY

Acute neurotoxicity, rat

No study has been submitted.

90-day neurotoxicity, rat

No study has been submitted.

Developmental neurotoxicity, rat

No study has been submitted nor is required at this time.

Delayed neurotoxicity, hen

No study has been submitted nor is required at this time.

IMMUNOTOXICITY

No study has been submitted.

ENDOCRINE DISRUPTOR STUDIES

No study has been submitted nor is required at this time.

SUPPLEMENTAL STUDIES

Rat 14-Day Dietary Toxicity Study

0144; 281086; “IN-A4098: Repeated-Dose Oral Toxicity 14-Day Feeding Study in Rats” (Hoban, D., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-38579, 09/15/2014). IN-A4098 (Lot 005, purity = 98.7%) was admixed to the diet at dose levels of 0 (diet only), 1000, 3000, or 6000 ppm (for males, 0, 68, 149, and not determined mg/kg/day, respectively, and for females, 0, 71, 158, and not determined mg/kg/day, respectively) and fed to 5 Crl:CD(SD) rats per sex per dose for 14 days except for animals at 6000 ppm that were sacrificed on test day 8 due to severe reductions in body weight and food consumption. There were no mortalities at the other dose levels during the 14-day dosing interval. No treatment-related clinical signs were observed except for high posture in 2 males at 6000 ppm prior to sacrifice on day 8. A treatment-related decrease in mean body weight was observed at all dose levels in both sexes. A treatment-related decrease in mean food consumption was observed at all dose levels in both sexes. Hematological investigations revealed elevated mean red blood cell, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration levels in males at 1000 and 3000 ppm. Serum clinical chemistry investigations revealed elevated mean alanine aminotransferase and cholesterol levels in males at 1000 and 3000 ppm and in females at 3000 ppm. Urinalysis revealed no treatment-related effects. Decreases in mean relative thymus and spleen weights in both sexes at 1000 and 3000 ppm, an increase in mean relative testes weight at 1000 and 3000 ppm, and decreases in mean relative prostate and seminal vesicles with coagulating glands and fluids weights at 3000 ppm were observed. Macroscopic examination revealed large testes

and small epididymides at 6000 ppm and small seminal vesicles at 3000 ppm. Microscopic examination revealed lymphoid degeneration/atrophy in the thymus at 3000 and 6000 ppm in males and at 6000 ppm in females, decreased erythrocytic extramedullary hematopoiesis and decreased sinusoidal blood in the spleen in males at 3000 and 6000 ppm, hematopoietic atrophy of the bone marrow in both sexes at 3000 and 6000 ppm, testicular edema at 3000 and 6000 ppm, and decreased fluid in the seminal vesicles and coagulating glands at 3000 and 6000 ppm. **No adverse effects.** NOEL (M) < 68 mg/kg/day (1000 ppm) and NOEL (F) < 71 mg/kg/day (1000 ppm) based on decreases in mean body weight and mean food consumption. **Supplemental study** (the test article, IN-A4098, is an environmental and mammalian triazine metabolite associated with tribenuron methyl and other sulfonylurea active ingredients). (Corlett and Leung, 07/08/2015)

Metabolic disposition in lactating goat

53040-0146 282138 Quistad, G. B., A. Bautista, and C. Hatton, "Metabolism of [^{14}C]tribenuron methyl in lactating goats." In-life phase was conducted at Genesis Midwest Laboratories, Neillsville, WI. Analytical phase was conducted at PRTL West, Hercules, CA. Dec. 10, 2014. Report designation: DuPont-36473. Lactating goats were dosed with tribenuron methyl, labeled either at the phenyl ^{14}C-U locus or at the triazine-2-^{14}C locus, with an average daily (oral capsule) dose of 0.7 mg/kg/day for 7 days. Urine, feces, and milk were collected. Goats were sacrificed about 7 hours after the final dose. Kidneys, liver, muscle, omental fat, subcutaneous fat, and renal fat were assessed for all identifiable metabolites by radio-HPLC, with confirmation of structure by HPLC/MS or HPLC/MS/MS as needed. About 55%-73% of administered dose was found in urine, compared to 24%-34% in feces. The primary structure of tribenuron methyl was largely preserved in excreta: the amide bond remaining intact for 55% to 59% of administered dose in urine plus feces. There were in excreta about equal parts of parent tribenuron methyl and IN-QKK48 (parent with hydroxylation of the triazine methyl group). The dominant urinary metabolite involving amide bond hydrolysis following phenyl-labeling was IN-00581 [1,2-benzisothiazol-3(2H)-one, 1,1-dioxide] (saccharin acid, comprising 18.2% of administered dose in urine). Following triazine ring labeling, IN-UZJ04 (4-amino-6-methoxy, 1,3,5-triazine-2-carboxylic acid) was the most abundant small metabolite (5.2% of administered dose in urine). Relative amounts of major metabolites in feces were similar to urinary results for both label positions. Milk of goats dosed with triazine-2-^{14}C yielded 0.86% of recovered dose, compared to 0.06% in milk of phenyl ^{14}C-U goats. Composite milk sampling of triazine-2-^{14}C goats indicated 76% of total recovered milk residues were composed of a single component, IN-A4098 (4-methoxy-6-methyl-1,3,5-triazin-2-amine). This compound has been sparingly tested for endocrine effects summarized in the Interactive Chemical Safety for Sustainability (iCSS) Dashboard, and was negative for endocrine disruption in all assays except for 1 of 18 nuclear receptor assays. A rigorous reproductive toxicity study for this compound was negative (see Summary of Toxicology Data). Thus, although this study was submitted as FIFRA 6(a)(2) data indicating a "possible adverse effect" due to detection of metabolites such as IN-A4098, there is no further evidence at this time to indicate special concern. There was no remarkable tissue accumulation in this study, regardless of label position. Aldous, Nov. 2, 2015.

NOTE: Study 53040-0042; 230974 under the heading: "Rat Subchronic Dietary Toxicity Mechanistic Study," also explored endocrine disruption effects.