

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TEBUTHIURON

Chemical Code # 001810, Tolerance # 00390
SB 950 # 301

September 20, 2000

I. DATA GAP STATUS

Combined (Chronic/Onco) rat:	Data gap, study is inadequate.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, mouse:	Data gap, inadequate study, no adverse effect indicated.
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated.
Teratology, rat:	Data gap, inadequate study, no adverse effect
Teratology, rabbit:	Data gap, inadequate study, possible adverse effect indicated
Gene mutation:	Data gap, inadequate study, possible adverse effect indicated.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 129815 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T000920

Compiled by: M. Silva, 9/20/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

027, 050 & 054 036451, 122584 & 122588 “The Toxicological Evaluation of Tebuthiuron (EL-103) in Rats for Two Years; Supplements: A Supplementary Inventory of Selected Tissues From Rats Given Diets Containing Tebuthiuron (EL-103, Compound 75503) For Two Years; Review of and Recommendations Regarding Mouse and Rat Oncogenicity Bioassays on Tebuthiuron,” (Todd, G.C., Gibson, W.R., Hoffman, D.G., Young, S. S., Morton, D.M.; Toxicology Report #7; Studies R-603 & R-613; Toxicological Division, Lilly Research Laboratories, Greenfield, IA; 11/76; Supplements: Negilski, D.S., Todd, G.C.; 11/1/88; ENVIRON Corporation, Washington, DC; 7/88). Tebuthiuron technical (97% pure) was fed in diet to Wistar-Derived rats ([60/sex, control + 40/sex/dose, treated] x 2) at 0, 400, 800 and 1600 ppm in concurrently performed, duplicate studies for 2 years. NOEL = 800 ppm (Bodyweight gains were decreased in both sexes (first 28 weeks on study) at 1600 ppm. Vacuolization of acinar cells was reported at 1600 ppm (10/80 males; 13/80 females). Relative kidney weights in males were slightly (but statistically significantly) increased at 1600 ppm.) This study was previously reviewed by Aldous (12/11/85) as not acceptable and not upgradeable, due to numerous, non-correctable deficiencies. Upon re-review (Silva, 9/12/00) and consideration of supplemental information, the study status remains unchanged. It was not possible to assess a possible adverse effect because of the compromised health of the rats.

055 122592 Duplicate of 054 122588.

CHRONIC TOXICITY, DOG

** 030 045103 “The Toxicologic Evaluation of Tebuthiuron (Lilly Compound 75503) Given Orally to Beagle Dogs for One Year,” (Todd, G.C., J.R. Means and J.P. McGrath; Lilly Research Laboratories, Toxicology Division, Greenfield, IA; Study D04283; 2/5/85). Compound 75503 (tebuthiuron; purity = 98.9%) was given orally (gelatin capsules) to Beagle dogs (4/sex/dose) at 0, 12.5, 25, or 50 mg/kg for 1 year. (All females at 50 mg/kg (4/4) showed anorexia. Anorexia was observed in 1 of 4 females at 25 mg/kg (57 occasions). Emesis (both sexes, 50 mg/kg), changes in stools (both sexes, \geq 25 mg/kg) and diarrhea (males at 25 mg/kg & females, 50 mg/kg) occurred. At 50 mg/kg, male body weights were intermittently significantly lower than controls. ALT (both sexes) and ALP (males) was increased at 50 mg/kg/day. Creatinine was increased in females at \geq 25 mg/kg/day. Absolute and relative liver weights were in both sexes increased at 50 mg/kg/day. Relative thyroid weights were increased in males at 50 mg/kg/day. Relative kidney weights were significantly increased in females at 50 mg/kg/day. Thrombocyte counts were significantly increased in males at 50 mg/kg/day.) NOEL = 25 mg/kg/day. ACCEPTABLE. No adverse effects. (Kishiyama & Silva, 8/16/00).

ONCOGENICITY, MOUSE

026, 051 & 055 036450, 122584 & 122592 “The Toxicological Evaluation of Tebuthiuron (EL-103) in Mice for Two Years; Supplements: A Supplementary Report of the Numbers of Mice With Tumors From 15 to 24 Months and at Study Termination From Mice Given Diets Containing Tebuthiuron (EL-103, Compound 75503) for Two Years; Review of and Recommendations Regarding Mouse and Rat Oncogenicity Bioassays on Tebuthiuron,” (Todd, G.C., Gibson, W.R., Hoffman, D.G., Young, S. S., Morton, D.M.; Toxicology Report #8; Studies M-9153 & M-9163; Toxicological Division, Lilly Research Laboratories, Greenfield, IN; 11/76; Supplements: Negilski, D.S., Todd, G.C.; 11/1/88; ENVIRON Corporation, Washington, DC; 7/88). Tebuthiuron technical (97% pure) was fed in diet to Harlan ICR mice ([60/sex, control + 40/sex/dose, treated] x 2) at 0, 400, 800 and 1600 ppm in concurrently performed, duplicate studies for 2 years. NOEL > 1600 ppm (There were no treatment-related chronic or oncogenic effects in either study.) This study was previously reviewed by Aldous (12/10/85) as not acceptable and not upgradeable, due to numerous, non-correctable deficiencies. Upon re-review (Silva, 9/8/00) and consideration of supplemental information, the study status remains unchanged.

054 122588 Duplicate of 390-055/122592.

REPRODUCTION, RAT

060 129815 “A Two-Generation Reproduction Study with Tebuthiuron (compound 75503) in the Wistar Rat,” (Adams, E.R., Owen, N.V., Hoyt, J.A.; Studies R03780 & R08780; 11/81; Lilly Research Laboratories, Toxicology Division, Greenfield, IN). Tebuthiuron (98% pure by HPLC) was fed in diet to Wistar rats (25/sex/dose) at 0, 0.01, 0.02 and 0.04% through 2 (F0 & F1) generations (2 litters/generation). Parental NOEL > 0.04 %; 28 mg/kg/day (No treatment-related effects were observed at any dose.) Reproductive NOEL > 0.04% (28 mg/kg/day). No reproductive effects were observed at any dose. Pup NOEL > 0.04% (28 mg/kg/day). No toxicologically significant treatment-related effects were observed at any dose. Not acceptable. Not upgradeable. No adverse effect identified. (Kishiyama & Silva, 8/24/00).

060 129815 is the same study as 029 36466 (see worksheet 1-liner, above), with some additional data.

029 36466. Addendum to 010 013431 (contains individual data): Reproductive NOEL = 400 ppm (28 mg/kg/day); conservative parental NOEL = 200 ppm (reported reduced body weight and efficiency of food utilization may be artifactual). MTD not achieved. UNACCEPTABLE. Not upgradeable. (C. Aldous, 12/31/85).

029 036461 & 036462 “Multi-Generation (3) Reproduction Study with EL-103 (Tebuthiuron Technical) in the Rat,” (Todd, G.C., E.R. Adams, N.V. Owen, F.O. Gossett, D.M. Morton; Lilly Research Laboratories, Report No. R-913, R-94 & R-624; 4/75 & 2/78). Tebuthiuron technical (purity not stated) was fed in diet to Harlan rats (20/sex/dose/generation) at 0, 400 and 800 ppm for 3 generations. No NOELs. **Possible adverse effect indicated: Decreased parental and pup weight gain at = 400 ppm.** UNACCEPTABLE. Not upgradeable (not complete). (C. Aldous, 12/20/85).

010 013431. A follow up study to 029 36461 & 36462: Adams, E.R., N.V. Owen, and J.A. Hoyt. Two-Generation Reproduction Study with Tebuthiuron (Compound 75503) in the Wistar Rat. Lilly Research Laboratories, report No. R03780 & R08780. November 1981. Tebuthiuron Technical was admixed with the feed at concentrations of 0.0, 0.01, 0.02, and 0.04 percent or 7, 14, 28 mg/kg for 25 Wistar rats/ sex/group/generation (F0 and F1) throughout their growth and reproductive stages (2 litters/generation). Body weight was lower for F1 females at the end of 124 days and mean efficiency of food utilization reduced for high dose males and females. Reproductive NOEL = 28 mg/kg/day. UNACCEPTABLE (individual data are lacking). (C. Aldous, 8/20/85).

059 129813 This volume, completed 5/79, contained an addendum to 029 036461 & 036462. Additional statistical analyses and a discussion of body weight data in the multi-generation reproduction study (Report No. R-913, R-94 & R-624), with EL-103 in the rat. These data were supplemental (no worksheet). M. Silva, 8/25/00.

TERATOLOGY, RAT

028, 053 036459, 007061, 122587 “Rat Teratology Study With EL-103: Study R-632; A Supplementary Report of a Rat Teratology Study With Tebuthiuron (EL-103, Compound 75503); Summary: Teratology,” (Todd, C.C., Markham, J.K., Adams, E.R., Owen, N.V., Gibson, W.R., Kiplinger, G.F. (Main Study-9/72); Todd, G.C., Higdon, G.L. (1/13/88-Supplement); The Lilly Toxicology Laboratories, Eli Lilly & Co., Greenfield, IN). Tebuthiuron technical (Purity not stated) was fed in diet to mated Harlan rats (25/dose) at 0, 0.06, 0.12 and 0.18% (0, 600, 1200 & 1800 ppm; 0, 15, 30, 45 mg/kg/day) for days 6 – 15 of gestation. Maternal NOEL > 1800 ppm; 45 mg/kg (No effects at any dose.) Developmental NOEL > 1800 ppm; 45 mg/kg (No effects at any dose.) This study was previously reviewed (Aldous, 8/20/85) as unacceptable and not upgradeable. Upon submission of additional data (individual dam bodyweights and food consumption; fetal parameters/individual litter; reproduction parameters/individual dam), the study status remains the same. M. Silva, 9/14/00.

004 974952 This is an exact duplicate of 028 036459, reviewed by DPR.

013 007061. This volume contains summary data of the definitive rat developmental study (DPR volume/record 390-028/036459), reviewed by DPR. M. Silva 8/28/00.

TERATOLOGY, RABBIT

028, 052 036460, 122585, 122586 “A Teratology Study With EL-103 in the Rabbit”; #1: “A Supplementary Report in Support of a Teratology Study With Tebuthiuron (EL-103, Compound 75503) in the Rabbit”; #2: “A Supplementary Report for a Rabbit Teratology Study (B-7014) With Tebuthiuron (EL-103, Compound 75503) – A Response to the U.S. EPA’s Request for Certain Additional Information to Upgrade the Rabbit Teratology Study From Core Supplementary to Core Minimum,” (Todd, C.C., Markham, J.K., Adams, E.R., Owen, N.V., Gossett, F.O., Morton, D.M; Report #3; (Main Study-4/75); Negilski, D.S., Higdon, G.L. (6/8/88-Supplement #1); The Lilly Toxicology Laboratories, Eli Lilly & Co., Greenfield, IN; Negilski, D.S., Rutherford, B.S., Higdon, G.L.; U.S. EPA; 3/8/88). Tebuthiuron technical

(96.5% pure) was administered by gavage to artificially inseminated Dutch Belted rabbits (15/dose) at 0, 10 and 25 mg/kg for days 6 – 18 of gestation. Maternal NOEL = 10 mg/kg/day (There was decreased body weight at 25 mg/kg/day.) Developmental NOEL = 10 mg/kg/day (**Possible adverse effects:** There was a significant decrease in fetal body weights at 25 mg/kg.) Previously reviewed as not acceptable and not upgradeable (Aldous, 12/13/85), upon re-evaluation the study status remains unchanged due to too many deviations from FIFRA Guidelines. M. Silva, 9/18/00.

052 122586. Supplement to a teratology study (B-7014) with tebuthiuron (EL-103, compound 75503) in the rabbit. A response to the U.S. EPA's request for certain additional information to upgrade the rabbit teratology study from core supplementary to core minimum.

GENE MUTATION

028 036457 “The Effect of Tebuthiuron (Lilly Compound 75503) on Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells.” Lilly Research Laboratories, Report No. 84040MLA655. August 1984. Tebuthiuron, purity 98.8%, at concentrations of 10 to 1000 ug/ml with metabolic activation (S-9 Mix) and at 100 to 800 ug/ml without metabolic activation (S-9 Mix) were evaluated for the potential on the induction of forward mutation of L51784Y TK +/- cells after 4 hours with 48 hours expression time. Repeat trials. **Adverse effect: small increase (>2x) without activation at the high concentration.** UNACCEPTABLE. Upgradeable (no individual plate counts). (Remsen, 12/12/85).

028 036454 “The Effect of Tebuthiuron (Lilly Compound 75503) on Induction of Bacterial Mutation Using a Modification of the Ames Test,” (Report #: 840410GPA655; Lilly Research Labs, 7/84). Tebuthiuron, purity 98.8%, at 0.1 to 1000 ug/ml, gradient plate method, with and without S-9 Mix and using Salmonella typhimurium tester strains (TA1535, TA1537, TA1538, TA98 and TA100). UNACCEPTABLE (no cytotoxicity or precipitation—test of 1 mg maximum is inadequate; no repeat test to verify negative findings; incomplete protocol description—Appendix B not included). (Remsen, 12/12/85).

028 036455 “The Effect of Tebuthiuron (Lilly Compound 75503) on Induction of Reverse Mutations in Salmonella typhimurium using the Ames Test,” (Study #: 840326AMS655; Lilly Research Labs; 4/84). Tebuthiuron, purity 98.8%, at 100 to 5000 ug/ml was evaluated for mutagenic potential using Salmonella typhimurium tester strains (TA1535, TA1537, TA1538, TA98 and TA100) with and without activation by rat liver enzymes. No increase in revertants reported. UNACCEPTABLE (no repeat test, no individual plate counts, justification for 100 mg/kg Aroclor). (Remsen, 12/12/85).

010 13433. Effect of Lilly Compound 75503 (Tebuthiuron) upon Bacterial Systems Known to detect Mutagenic Events - Salmonella typhimurium and Escherichia coli. Lilly Research Laboratories. February 1978. Tebuthiuron purity unstated, 10-fold range of test article concentration up to 1000 ug/ml, was evaluated for mutagenicity potential using Salmonella typhimurium strains G46, C3076, TA1537, TA1535, TA1538, TA98, TA100 and Escherichia coli strains WP2 and WP2 uvrA-. UNACCEPTABLE (major variances, insufficient information). (C. Aldous, 8/19/85).

CHROMOSOME EFFECTS

**** 057 122595** “The Effect of Tebuthiuron (EL-103, Compound 075503) on the In Vitro Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells,” (Negilski, D.S., Garriott, M.L., Kindig, D.E.F.; Lilly Research Labs, Lab Project ID#’s: 890111CTX655, 890125CTX655, 890201CAB655 & 890228CAB655; 4/12/89; 1989). Tebuthiuron (purity = 99.1%) was used on Chinese hamster ovary cells for 4 hours at 0, 1650, 1800 and 1950 ug/ml (no S9) and at 0, 1350, 1450 and 1550 ug/ml (+S9) and was evaluated for its potential to induce chromosomal aberrations in vitro (2 trials). Chromosomal aberrations (% of cells) was increased at the high dose (+/- S9). ACCEPTABLE. Possible adverse effect. (Kishiyama & Silva, 9/6/00).

057 122594 “The Effect of Tebuthiuron (EL-103, Compound 075503) on the *In Vivo* Induction of Sister Chromatid Exchange in the Bone Marrow of Chinese Hamsters,” (Negilski, D.S., Garriott, M.L., Brunny, J.D.; Toxicology Division, Lilly Research Laboratories, Laboratory Project ID #: 880511SCE655; Greenfield, IN; 7/13/88). Tebuthiuron (purity = 99.1%) was administered by gavage (single dose) to female Chinese Hamsters (3/dose) at concentrations of 0 (10% aqueous acacia), 3000, 4000 and 5000 mg/kg (3/dose). At 21 hours post-dosing, hamsters were terminated and bone marrow cells were removed for assessment of SCE (25 second division metaphases/animal scored). Tebuthiuron treatments did not induce SCE. Cyclophosphamide (positive control) gave a positive response for the induction of SCE, as expected. Tebuthiuron, at 3,000 and 5,000 mg/kg showed indications of cytotoxicity by increases in percent of cells in M1 phase. Not acceptable and not upgradeable (too few animals/treatment group; no justification for excluding males). (Kishiyama & Silva, 9/5/00).

057 122596 This volume contains a review by the US EPA of study #: 880511SCE655 (“*In Vivo* Sister Chromatid Exchange Assay in Chinese Hamster Bone Marrow,” reviewed by DPR volume/record #: 390-057/122594).

028 36458 “The Effect of Tebuthiuron (Lilly Compound 75503) on In Vivo induction of Sister Chromatid in Bone marrow of Chinese Hamsters.” Lilly Research Laboratories, Report No. 840710SCE655. July 1984. Tebuthiuron Technical, purity 98.8% at concentrations of 0, 200, 300, 400, and 500 mg/kg was administered via gavage to 3 Chinese hamster females/group (sacrifice after 19 hours). No adverse effect reported. UNACCEPTABLE (only females and too few animals/group. (Remsen, 12/12/85).

010 13434. Dominant Lethal Study with EL-103 (Tebuthiuron) in the Rat. Lilly Research Laboratories, Report No. R-655. December 1975. Tebuthiuron purity unstated, at 75 mg/kg (1/5 LD₇₇) was intraperitoneally injected once in 10 males mated with 80 female Wistar-derived rats (over 8 weeks of age). No dominant lethal effects. Study is UNACCEPTABLE. Not upgradeable. (C. Aldous, 8/19/85).

DNA DAMAGE

056 122593 “The Effect of Tebuthiuron (EL-103, Compound 075503) on the Induction of DNA Synthesis in Primary Rat Hepatocytes,” (Negilski, D.S., Garriott, M.L., Yount, D.J.; Lilly Research Laboratories, Project ID #: 880510DS0655 and 880517UDS0655; 5/13/88). Tebuthiuron (purity = 99.1%) was used on primary cultures of rat hepatocytes (20 cells evaluated/dose) at 0 (4 replicates), 300, 400, 500, 600,

700, 800, 900 and 1000 ug/ml (2 trials, 1 replicate/trial/dose for treated & positive controls) to evaluate potential induction of UDS. Tebuthiuron was cytotoxic at \geq 800-900 ug/ml and did not induce UDS at the lower doses (300 – 800 ug/ml) in two trials. DMSO controls were unaffected, while positive controls (MNNG & 2AAF) showed induction of UDS. No adverse effect indicated. The study is currently unacceptable (Too few cells counted/treatment; no individual data) but is possibly upgradeable with submission of individual data and initial cellular viability data. (Kishiyama & Silva, 8/31/00).

** 028 36456 “The Effect of Tebuthiuron (EL-103, Compound 075503) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes.” Lilly Research Laboratories, Report No. 840503UD5655. June 1984. Tebuthiuron, purity 98.8%, 0 to 1000 ug/ml exposure for 20 hours to rat hepatocytes was evaluated for induction of DNA repair synthesis. Cytotoxicity at 1000 ug/ml and no increase in mean grains/nucleus in 2 trials with 1 rat each. ACCEPTABLE. (Remsen, 12/12/85).

NEUROTOXICITY

Not required at this time.

ADDITIONAL INFORMATION

048 (No record number). This volume contains the USEPA Toxicology Chapter of the Registration Standard for Tebuthiuron.

049 122583 “Metabolism of a New Herbicide, Tebuthiuron (1-[5-(1, 1-dimethylethyl)-1,3,4, thiadiazone-2-YL]-1,3-dimethylurea), in Mouse, Rat, Rabbit, Dog, Duck, and Fish,” (Morton, D.M., Hoffman, D.G.; Toxicology Division, Lilly Research Laboratories, Greenfield, IA; Reported in: Journal of Toxicology and Environmental Health, 1:757-768, 1976). Tebuthiuron technical (99.6% pure) at 10 mg/kg (containing 5% w/w [¹⁴C]-EL103) was administered to ICR mice, Harlan rats, Dutch-belted rabbits and mallards by gavage (vehicle = water or 5% (w/v) acacia) and to beagle dogs by gelatin capsule. Bluegills received 25 ppm EL103 (plus 0.01% w/w [¹⁴C]-EL103) in the aquarium water. Tebuthiuron was readily absorbed by mice, rats, rabbits, dogs and ducks. It was extensively metabolized (with differences in proportions of metabolites produced) and metabolites were excreted in urine of mice, rats, rabbits and dogs and in urine/feces mix in ducks. By 96 hours, approximately 3% of metabolites were in feces of rats, dogs, rabbits and ducks, with 30% detected in feces of mice. The major metabolite was an N-demethylation of the substituted urea side chain in each species examined, including fish (only detected metabolite in fish). The N-demethylation reaction at the 3-position of the urea proceeded through a stable N-hydroxymethyl intermediate (significant quantities isolated from urine of rats & dogs, not mice, rabbits or ducks). Tebuthiuron did not accumulate (nor did metabolites) in tissues of any species tested. These data are supplemental. Not a FIFRA Guideline study. M. Silva, 8/28/00.

050 122584 This volume contains “Review of and Recommendations Regarding Mouse and Rat Oncogenicity Bioassays on Tebuthiuron,” which was prepared by ENVIRON Corporation, Washington,

DC (July, 1988). No worksheet.

051 (No record number) This volume contains comments by USEPA on the mouse oncogenicity study performed with tebuthiuron.

