

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA
HYDRAMETHYLNON (also known as AC 217,300, CL 217,300, or "Amdro")

Chemical Code # 2203 Tolerance # 00395

SB 950 # 326

Original date: 01/03/89

Revised 8/1/89, 12/22/93, 10/31/00, 5/28/02, and 6/14/02

I. DATA GAP STATUS

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

Toxicology one-liners are attached. In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

All record numbers through 145825 were examined (Document No. 395-072). This includes all records indexed by DPR as of 6/14/02. Some record numbers for older submissions have Record Nos. > 900,000.

File name: t20020614

Revised by Aldous, 6/14/02.

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

COMBINED, RAT

****021-028 993353 to 993360** "24-month feeding study of AC 217,300 to rats". IRDC Study No. 141-014, dated 5/12/82 (original report); 1/6/83 (addendum report). Original report consisted of 024:993356 plus appendices (Vols. 25-28). Amended report (Vols. 21-23) added microscopic evaluation of intermediate groups. (Design: CD rats; 0, 25, 50, 100, and 200 ppm; 50/sex/dose; 2-year dietary administration). Original CDFA review (9/4/85) classified study as **acceptable, with possible adverse effects** (endometrial polyps, testicular atrophy). The 10/27/88 review agreed on essential points with the original review. The 8/01/89 review removed uterine endometrial stromal polyps and related tumors as "possible adverse effects" in response to the 3/21/89 rebuttal. Females had decreased body weight at 100 and 200 ppm; male weights were reduced at 200 ppm only. In 100 and 200 ppm females, and possibly also 200 ppm males, the "MTD" appears to have been exceeded, based on the magnitude of body weight decrements. Food consumption was significantly reduced in 200 ppm males and females. Yellow body fat was noted in dose-related fashion in 100 and 200 ppm males and females. Glomerulonephrosis was dose-related in females at 50 ppm and above, and in males at 25 ppm and above. Testicular atrophy was evident at 50 ppm and was marked at 100 and 200 ppm: this is the basis for a "possible adverse effect". A NOEL for females is 25 ppm based on kidney effects. There is no NOEL for males, however evidence of a glomerulonephrosis effect at 25 ppm was very marginal. J. Christopher, 9/4/85, and C. Aldous, 10/27/88, 8/01/89.

011 033575 An interim report for 024:993356, above. Semi-monthly hand-written reports, protocol, feed analysis during first year of study. (No separate review needed). C. Aldous, 11/10/88.

044 (no record number: Exhibit 1, this volume). Rebuttal document presenting reasons why study 024:993356 should not be considered to indicate a neoplastic effect on the uteri of rats. Considered in 7/20/89 review.

CHRONIC TOXICITY, DOG

****010 993362** "Twenty-six week toxicity study in dogs: AC 217,300". Hazleton Laboratories America, Inc., 6/10/80. Purebred beagles, 22-25 weeks old, 4/sex/group, were administered AC 217,300 (92% purity) in gelatin capsules at 0, 0.33, 1.0, or 3.0 mg/kg/day. The a.i. was formulated in lactose premix (2.5% AC 217,300 w/w for all treated groups, 120 mg/kg/day lactose for controls). **No adverse effect indicated**. NOEL = 1 mg/kg/day (primary sign was marked inappetence in one 3 mg/kg/day male, which was consistent with observations of 91-day oral dosing study 009:993327). **Acceptable** to fill dog chronic study data requirement. C. Aldous, 11/21/88.

042 069457, 069458 Nearly exact duplicate of 010:003362. Major difference is that this version lacks a one-page addendum following p. 272 and preceding the feed analysis appendix, which discusses investigators' evaluation of the NOEL. Retain both record numbers (one submission supports an end product and one was sent for SB950 requirements). (C. Aldous, 11/21/88)

ONCOGENICITY, MOUSE

****002-006 993350, 028449-028451, 993361** "Eighteen-month feeding study of AC 217,300 to mice". (Primary report in 002:993350). IRDC, 5/06/82 (Two additional re-evaluations of lung data followed at later dates, in Vols. 039 and 043). AC 217,300 (92%) administered in diet to CD®-1 mice at 0, 25, 50, 100, and 200 ppm. **Possible adverse effects indicated:** testicular degeneration and kidney amyloidosis and chronic nephritis, with NOEL's of 25 ppm (the latter NOEL in both sexes). Mortality was increased in dose-related fashion in both sexes at 100 and 200 ppm. Males and females at 200 ppm had marked weight gain decrements and decreased food consumption. A lesser weight gain decrement was observed in 100 ppm males, which was possibly treatment-related. Major treatment-associated lung findings were bronchopneumonia and pigment-laden macrophages in the alveoli, which were observed in 100 and 200 ppm males and in 200 ppm females: these effects may have been influenced by endemic disease. These lung and kidney effects contributed to increased mortality of 100-200 ppm animals. Study was originally found **unacceptable** in 9/5/85 CDFA review due to overly high dose levels and because the data were not presented in a manner which was convenient to evaluate. The 11/10/88 review still found the study unacceptable, on the basis that viral and/or bacterial disease may have confounded the data. Study was re-classified as **Acceptable** in the 11/18/93 review (see 395-049 114578, below) based on evidence that the Sendai infection had little or no influence on the outcome of the study. J. Christopher, 9/5/85; and C. Aldous, 11/10/88, 7/19/89, and 11/18/93.

039 067113 "A histopathological evaluation of mouse lungs: Chronic feeding study of AC 217,300" (Submitted to American Cyanamid Co. by Robert A. Squire Associates, Inc., May 1987). Re-evaluation of lung slides of male and female mice in study 002:993350. Conclusion: data do not support the supposition that there is a treatment effect on lung tumors. Lung pathology was confounded by disease, possibly Sendai virus plus secondary infection. Considered in C. Aldous review of 002:993350, 11/10/88.

046 087825 Virtual duplicate of 039:067113 (additional header pages in this re-submission). No review needed. Aldous, 1/25/90.

043 067725 "Chronic dietary toxicity and oncogenicity study with AC 217,300 in mice. Amended pathology report." (W. M. Busey, Experimental Pathology Laboratories, Inc., Sept. 15, 1988). Male and female lung slides re-examined; initially blind, then re-examined again in all cases in which Busey's diagnosis was different from Squire's. Some conclusions were changed on re-examination; hence this review was not entirely "blind" nor entirely independent. Conclusion: confirms evaluation of Squire (039:067113, above). Considered in C. Aldous review of 002:993350, 11/10/88.

395-049 114578 (addendum to Record No. 993350). "Second peer review of Amdro", U.S. EPA peer review dated 17 Apr. 1991. Primary reason for non-acceptability of the study was possible confounding effect of Sendai virus infection in the study. This peer review noted very few cases of "atypical bronchial hyperplasia", which pathologists Squire and Busey agreed represented Sendai virus-associated changes. Only 1 or 2 mice dosed below the MTD had such signs of Sendai virus hyperplasia, hence the disease does not appear to have confounded study results. The "Second Peer Review" classified Hydramethylnon as "Group C" (Possible human

carcinogen), based on lung adenomas or adenomas plus carcinomas in females. Examination of the "Second Peer Review" in light of the other data available supports upgrading the study to **Acceptable** status. Aldous, 11/18/93.

046 087826 Virtual duplicate of 039:067725 (additional header pages in this re-submission). No review needed. Aldous, 1/25/90.

039 067112 3-page "Weight of evidence" statement by J. E. Harris regarding rat and mouse oncogenicity. (Considered in 11/10/88 review of mouse study).

011 033574 6-month interim report for 002:993350, above.

044 (no record Number, Tab "Exhibit 1"). Rebuttal ref study 002:993350, above. (Considered in 7/19/89 review of mouse study).

044 072614 Partial duplicate of 039:067113.

REPRODUCTION, RAT

029 993344 "A three-generation reproduction study with AC 217,300 in rats". Bio/dynamics Inc., May 14, 1982. AC 217,300 (92%) administered in diet to CD® rats, 12 males and 24 females/treatment group. Controls plus 4 treatment groups (25, 50, 100, and 200 ppm) were initiated. The higher two groups were discontinued after F0 generation parents had been evaluated in a recovery experiment. **Possible adverse effects indicated:** parental toxicity and reproductive effects: findings at 100 ppm and above were body weight decrements in males and females during the growth phase; markedly reduced pregnancy rate; increased gestation length; increased total litter losses; small mean litter size; diminished pup weight gain during lactation; seminiferous tubular degeneration with diminished or absent sperm in tubular lumen or in epididymal ducts. **Unacceptable: an additional study is needed** to establish a valid NOEL for testicular lesions in F1 adults. [J. Christopher had placed apparent NOEL values for parental toxicity and reproductive effects lower than 50 ppm, based on data from one or more individual generations or mating periods, whereas the 1/3/89 review determined that available information is insufficient to establish a NOEL. The latter review indicated that the NOEL is at or below 50 ppm]. J. Christopher (9/3/85), C. Aldous (1/3/89, 7/20/89: see Aug. 1989 CDFA Rebuttal Response for the latter re-examination).

030 993345 Individual data for 029:993344, considered in reviews above.

011 993349 Status report for 029:993344 (no new data), C. Aldous 11/10/88.

****395-068 139742** Schroeder, R. E., "A two-generation reproduction study with AC 217,300 in rats," Pharmaco LSR, Inc., 7/19/95. Report No. 92-4046. Crl:CD® BR rats, 30/sex/group, were dosed with 0, 25, 50, or 75 ppm hydramethylnon (98.2%) in diet continuously for 2 generations, with one mating period per generation. This supplemental study design covered all elements of a primary reproduction study. NOEL = 25 ppm (2.0 mg/kg/day, a "possible adverse effect": based on diffuse bilateral degeneration of seminiferous tubules in 1/30 F0 males at 50 ppm). Germinal epithelial degeneration of scattered tubules was common at 75 ppm, but diffuse degeneration of

seminiferous tubules (unilateral or bilateral) was observed only in 3/30 F0 75 ppm males, and in 1/30 F1 75 ppm males. This study did not find any seminiferous tubule degeneration at 25 ppm nor in controls. This study did not identify general somatic toxicity at any dose level. The primary reproduction study (Record No. 993344) had identified diffuse bilateral degeneration of seminiferous tubules in 9/12 males at 200 ppm and 1/12 males at 100 ppm, supporting the single finding in the present study as a treatment effect. Functional reproductive changes at 75 ppm were: (1) a reduction in F1 high dose males with evidence of mating, (2) associated reduction in F1 females pregnant, and (3) tendency toward low implantation rates in 75 ppm matings. Also, live litter sizes were reduced in both generations, although statistical significance was limited to the first generation. Valid supplemental study, which complements the primary (non-accepted) reproduction study to fill the reproduction study data requirement. Aldous, 10/31/00.

011 993331 "CL 217,300: An 8-week feeding and recovery study in maturing rats". American Cyanamid Co., Agricultural Research Division, 6/23/80. 5 groups of 12 males, ca. 100 g body weight at onset. Treatment groups: unrestricted controls, 200 and 400 ppm AC 317,300, and restricted diet groups with feed limited to that taken by 200, and 400 ppm groups, respectively. Six of each group were killed after 4-week treatment period, balance killed after a 4-week recovery period. Marked, dose-related decreases in food consumption accounted for substantially reduced body weight gains in treatment groups. Paired-feeding controls had comparable weight gain decrements. Lesions observed at the end of the treatment period included spermatid giant cells in testes and cellular debris within epididymal tubules in 200 and 400 ppm groups, and focal hepatic cell cytoplasmic degeneration in 400 ppm males. After the recovery period, there was no residual hepatic effect, but gonadal toxicity progressed to dose-related testicular tubular atrophy and altered or damaged germ cells. At this time one 400 ppm male was noted with aspermiogenesis, and in 4 of the 400 ppm males, no spermatozoa could be found within the epididymis. There was no corresponding pathology in restricted feeding groups. C. Aldous, 11/15/88.

011 993332 "CL 217,300: An 8-week feeding and recovery study in mature rats". American Cyanamid Co., Agricultural Research Division, report issued approx. 6/23/80. Five groups of 12 males, weighing 351-368 g at onset. Treatment groups: unrestricted controls, 200 and 400 ppm AC 317,300, and restricted diet groups with feed limited to that taken by 200 and 400 ppm groups respectively. Six of each group were killed after a 4-week treatment period, balance killed after a 4-week recovery period. Dose-related decreases in food consumption accounted for reduced body weight gains in treatment groups. Paired-feeding controls had weight gain decrements comparable to treated groups. Lesions observed at the end of the treatment period included spermatid giant cells in testes, prostate atrophy, and (germ cell) cellular debris within epididymal tubules in the 400 ppm group, and focal hepatic cell cytoplasmic degeneration and hepatic cell atrophy in 400 ppm males. After the recovery period there was no residual liver effect, however gonadal toxicity progressed to testicular tubular atrophy in 400 ppm rats, and debris of damaged germ cells in epididymides of 200 and 400 ppm rats. There was no corresponding pathology in restricted feeding groups. C. Aldous, 12/30/88.

395-019 993346 "Reproductive performance of male albino rats after receiving a single oral dose with AC 217,300 (Amdro)". American Cyanamid, 6/1/83. Ten males per treatment received 0 or 800 mg/kg in a single oral dose at about 4 weeks of age. Males were then placed on basal diet for 4 weeks, and mated with untreated females. Male and female reproductive performance was examined, and there were no treatment effects. Male reproductive organs were

weighed and examined grossly, again without treatment effects. No microscopic examinations of tissues were made. Study is **unacceptable, not upgradeable, with no adverse effects indicated**. Study was faulted for single dose mode of treatment, use of inappropriately young test animals, small group sizes, and especially for failure to do histopathology exams in males, despite the fact that testicular lesions might have been expected, based on chronic and subchronic studies. J. Christopher, 9/4/85.

395-072 145825 Duplicate of 395-019 993346, above.

TERATOLOGY, RAT

007 993338 "Teratogenesis study in rats with AC 217,300". Bio/dynamics, 9/14/79. 26 CD® rats/group gavaged 0, 3, 10, or 30 mg/kg/day AC 217,300 (92% a.i.) days 6-15 of gestation. **No adverse effects. Maternal toxicity NOEL = 3 mg/kg/day (dose-related decrease in maternal body weight, marked at 30 mg/kg/day). Other maternal toxicity signs: decreased thymus size and signs of general weakness or toxicity (30 mg/kg/day) and yellow body fat (10 and 30 mg/kg/day). Developmental toxicity limited to 30 mg/kg/day (slight decrease fetal weight, slight ossification delays such as incomplete supraoccipital ossification, and increased incidence of rudimentary ribs. **Acceptable**, J. Christopher, 8/25/85. (One-liner by C. Aldous, 11/16/88).

TERATOLOGY, RABBIT

001 993342 "Teratology study with AC 217,300 in rabbits". IRDC, 4/7/82. 16 New Zealand White rabbits per group gavaged on gestation days 6-18 with 0, 5, 10, and 20 mg/kg/day AC 217,300 in 0.5 ml/kg corn oil vehicle. **No adverse effects: Maternal NOEL = 5 mg/kg/day (reduced dam body weight, reduced stool amounts or soft stools: all dose-related in 10-20 mg/kg/day dams. Matting and/or discharge in anogenital region in 10 and 20 mg/kg/day dams. Also, 10 and 20 mg/kg/day dams had 1 and 8 cases of yellow body fat at necropsy, respectively). Developmental toxicity NOEL = 10 mg/kg/day (decreased fetal weights at 20 mg/kg/day). **Acceptable**. Reviewed by J. Christopher, 8/30/85. Supplementary review by C. Aldous, no change in status, 12/30/88.

001 993341 Pilot for 001:993342. Examined, no written review. Aldous, 11/17/88.

GENE MUTATION

** 039 067116 "Forward Mutation in Schizosaccharomyces pombe P1 - Test Substance: AC 217,300." (Life Science Research, Roma Toxicology Centre, Italy, 1/14/86, LSR-ETC report no. 129005-M-07585) AC 217,300, 91.5%, lot AC 3196-99B, tested with Schizosaccharomyces pombe P1 haploid strain for mutation in the adenine biosynthesis pathway; without rat liver activation at 0 (DMSO and untreated), 0.781, 1.56, 3.13, 6.25 or 12.5 : g/ml; with activation, at 0, 3.13, 6.25, 12.5, 25 or 50 : g/ml; 16 hours in liquid culture with compound, 5 days after plating for colony formation; number of white (mutant) and sectorial colonies counted, 10 plates per concentration, 2 trials; positive controls functioned as expected; high

concentration with activation not cytotoxic but precipitation formed at 100 : g/ml; some decreased survival without activation; **no adverse effect; Acceptable.** Gee, 12/6/88.

** 011 993368 "Mutagenicity Testing of CL 217,300; 1,4-pentadien-3-one, 1,5-bis(a,a,a-trifluoro-p-tolyl)-(1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)-hydrazone in the Ames Bacterial Test." (American Cyanamid, 5/14/79) CL 217,300, 91.64%, batch AC 3196-99-B; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and E. coli strain WP-2 uvrA⁻; with and without Aroclor 1254-induced rat liver activation; plate incorporation method and disc method; disc at 1000 : g/disc and at 0 (DMSO), 10, 100 or 1000 : g/plate, duplicate plates, 2 trials; precipitation at 1000 : g; toxic to bacterial lawn at 100 and 1000 : g for TA100 and TA1537 without activation; no consistent increase in reversion rate; **no adverse effect; Acceptable.** Christopher, 8/28/85 and Gee, 12/7/88.

CHROMOSOME EFFECTS

** 039 067114 "Clastogenic Evaluation of AC 217,300 Insecticide, Lot AC3196-99B in an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: Final Report." (Litton Bionetics, MD, 10/85, LBI Project No. 20990) AC 217,300, hydramethylnon, lot AC3196-99B, purity of 91.6% from record #'s 993368 and 993370 in 011 for same lot; tested with Chinese hamster ovary cells (CHO) with and without Aroclor-induced male rat liver activation at 0 (DMSO), 0.5, 0.75, 1.0, 1.25 or 1.5 : g/ml without activation with cells harvested at 10 and 20 hours (equivalent to 7.5 and 17.5 hours actual exposure); with activation, tested at 0 (DMSO), 1.0, 2.5, 5.0 or 10.0 : g/ml, 2 hours actual exposure followed by additional incubation in complete medium and harvests at 10 and 20 hours; concentrations selected based on preliminary toxicity and cell cycle study; scored 200 cells, 100 from each duplicate treated culture; two trials for 10 hours with the first showing a high incidence of dicentric in control and treated culture; not confirmed in repeat trial or in 20-hour trial; no increase in aberration due to treatment; positive controls of mitomycin C and cyclophosphamide functioned as expected; **Acceptable, no adverse effect.** Gee, 12/6/88.

044 073353 "A dominant lethal test in male rats treated with CL 217,300 by gavage for 5 days." (American Cyanamid, 6/24/80) CL 217,300, batch AC 3196-99-B, 91.6% purity; given by oral gavage in corn oil at 0, 3, 30 or 90 mg/kg/day, 10 males/group; dosed daily for 5 days, mated with one female per week for 8 consecutive weeks with males in control and high dose groups mated in week 10; all males in control and treatment groups mated in weeks 11 - 17. Male fertility was markedly decreased beginning in week 6 at 90 mg/kg/day and continued through week 17 for 6 males. Fertility was somewhat decreased at 30 mg/kg/day with apparent recovery by week 12. Report states mating behavior was not affected; testes weights were low in high dose group. Report was initially reviewed as indicating a "possible adverse effect" on testes and spermatocytes/spermatogonia and as unacceptable (report missing every other page - see 011:993370, no justification of dose - notation of a possible adverse effect from table III). See Christopher, 8/28/85 and Gee, 12/7/88. Complete report was submitted in 395-044. Report is still **unacceptable** (inadequate numbers of animals for a dominant lethal assay). Changed to no adverse affect with no evidence of a dominant lethal affect. Gee, 8/1/89.

011 993370 (Incomplete report of 044:073353, above).

DNA DAMAGE

** 039 067115 "Mitotic Gene Conversion in *Saccharomyces cerevisiae* D4 - Test Substance: AC 217,300." (Life Science Research, Roma Toxicology Centre, Italy, 1/14/86, LSR-RTC No 129006-M-07685) AC 217,300, lot AC 3196-99B, 91.6%; concentrations not corrected for purity of a.i.; tested with *Saccharomyces cerevisiae* strain D4, diploid with two defective, non-complementing alleles of adenoma-2 and trp-5 loci; tested with and without phenobarbitone- induced male rat liver; 0 (DMSO and untreated), 1.56, 3.13, 6.25, 12.5 or 25 : g/ml, 16 hours incubation followed by plating for viability, tryptophan and adenine prototrophy, 3 plates each, two trials; colonies counted and survival and mutation frequency calculated; 25 : g/ml in 0.1 M phosphate buffer, pH 7.4, was considered close to the limit of solubility when diluted from DMSO stock solution; marginal cytotoxicity (10% and 12% decrease) in survival at high concentration without activation only; **no adverse effect, Acceptable.** Gee, 12/6/88.

NEUROTOXICITY

(Not required at this time)

METABOLISM STUDIES

395-050 116894 Fung, C.H., "CD 217,300: Rat metabolism study", American Cyanamid Co., Princeton, NJ, 5/21/92. Sprague-Dawley rats were dosed with Hydramethylnon (designated as CL 217,300) by gavage in corn oil at low (3 mg/kg) or high (100 mg/kg) single doses. Also, multiple-dosing was done with 14 consecutive daily treatments of 3 mg/kg, followed by 3 mg/kg of labeled Hydramethylnon. In all cases, both phenyl and pyrimidinyl ring-labeled treatments were evaluated. There were no substantial differences associated with sex, dose level, or duration of treatment. Elimination was relatively rapid. Most of the label was excreted within 36 hr. Label was excreted principally in feces (about 90%). Parent compound was the major labeled fecal component (70-85% of administered doses, see p. 59). Urinary elimination was about 1-4% of total administered compound (p. 54). The two main identified urinary metabolites were a substituted cinnamic acid and a substituted p-toluic acid. Residues remaining in tissues after 7 days ranged from 3 to 10% of administered dose. The major labeled component of tissues was parent compound, with appreciable amounts of "moderately polar" material as the second-most abundant fraction. Data suggest inefficient absorption and a modest rate of metabolism of absorbed hydramethylnon. Aldous, 12/22/93.

395-062 126488 This is the same study as 395-050 116894, above. This version credits Zdybak, J. M. L. and R. A. Robinson as authors and Xeno Biotic Laboratories, Inc. as test facility. Record 116894 listed C. H. Fung as the author and American Cyanamid Co. as test facility (using similar title page formats, with the same study date listed). The present volume gives a laboratory report number of XBL 90043. Robinson was Study Director, Zdybak was one of the Research Scientists, and Fung signed as Sponsor to the study (pp. 3 and 7 of this volume). The present citation listing Zdybak and Robinson as authors should be used in the future for this report. Aldous, 10/24/00.

395-037 060118 Hussain, M. "The absorption, excretion pattern, tissue residues and metabolism of Carbon-14 labeled CL 217,300 [Tetrahydro-5,5-dimethyl-2-(1H)-pyrimidinone[3-[4-(trifluoromethyl)phenyl]-1-[2-[4-(trifluoromethyl)phenyl]ethenyl]-2-propenylidene] hydrazone in the rat." No worksheet has been made by Medical Toxicology Branch, however the study has been examined by Worker Health and Safety Branch because of its relevance to human exposure. This rat study found that 71.5% of oral dose was eliminated in feces unchanged. The lesser amounts of label found in urine yielded no parent compound, but rather a number of polar metabolites. In tissues sampled (including liver), parent compound was generally the most abundant labeled moiety. The most abundant metabolite was CL 98,724: 1,5-bis(α,α,α -trifluoro-*p*-tolyl)-1,4-pentadien-3-one. Aldous, 10/24/00.

395-016 993298 This is an old summary of metabolism information, containing a 3-paragraph summary referring to 395-062 126488, above. Aldous, 10/24/00.

395-018 993374 This is not a metabolism study, but rather a brief report of a study to see whether orally ingested antidotes would affect uptake of hydramethylnon. There was no advantage to treatment with "universal antidote" of charcoal:magnesium oxide:tannic acid (2:1:1), nor was magnesium oxide:tannic acid (1:1) of any value. No Medical Toxicology Branch worksheet. Aldous, 10/24/00.

395-018 065618 This is a one-page report, possibly relating to Record No. 126488, above. No reviewable data are included. Aldous, 10/24/00.

395-064 131636 Frantz, S. W. and Beskitt, J. L., "Hydramethylnon: Pharmacokinetics and material balance study following cutaneous administration to male Sprague-Dawley® rats," Bushy Run Research Center (10/93). Laboratory Project ID: 92N1073. Young male rats were dosed on shaved dorsal skin with hydramethylnon as "Maxforce Professional Insect Control Roach Killer Bait Gel" (nominally 2.15% a.i.), using a non-occlusive dressing. Four rats/group were exposed for 10 hr prior to washing application site in all cases. Dose levels of ^{14}C -labeled hydramethylnon ranged from 110 to 167 mg/kg. Sacrifice times for the 4 groups were 10 hr, 24 hr, 7 days, and 14 days, with measurement of urinary and fecal excretion for respective study durations. Urinary excretion never exceeded 0.11% of dose. Maximal fecal excretion was found in the longer duration groups: 0.30 to 0.34% of dose. Dose site washed skin retained 0.90 and 0.93% of dose in the 10 and 24-hr groups, respectively, and 0.22 and 0.04% of dose in respective 1-wk and 2-wk groups. From 89-94% of dose was recovered in the residual gel on the skin surface, body rinses, and dressing in each case. Thus hydramethylnon in this matrix was not efficiently absorbed. Aldous, 5/28/02 (no DPR worksheet).

395-063 131263 Sharp, D. E., "Dermal absorption of AC 217,300 Gel in male rats," Hazleton Wisconsin, Inc., 10/26/93. Lab ID No. HWI 6123-180. Two groups of 4 Sprague-Dawley rats each were dosed on shaved dorsal skin with hydramethylnon as "AC 217,300 Gel," 2.16% active ingredient. Each rat received about 2 mg a.i. in 100 mg of the gel. ^{14}C label was on the phenyl rings. Rats were about 8 wk old and weighed 269-282 g at dosing. Skin was exposed for 10 hr under a non-occlusive dressing, then application sites were washed. One group of rats was sacrificed at this time, and another was maintained for 336 hr. Urine and feces were collected in both cases, and the following were collected at termination: fat, kidneys, liver, lungs, testes, and residual carcass. Only 0.01 to 0.02% of dose was found in urine. No residues were found in 10-

hr group feces, however 0.41% of dose was found in 336 hr group feces. Tissue levels were no more than 0.01% of dose for either group of rats. Residual carcass levels were 0.46% and 0.16% of dose in 10-hr and 336-hr rats, respectively. About 95% of administered dose was found in the skin wash collection. Thus hydramethylnon in this matrix was not efficiently absorbed. Aldous, 5/28/02 (no DPR worksheet).

SUBCHRONIC AND ACUTE/SUBACUTE STUDIES

395-008 993326 Tegeris, A. S., "AC 217,300: 91-day study in the rat," Pharmacopathics Research Laboratories, Incorporated, Laurel, MD, 5/31/79. Sponsor's Report # P-981-78-143-1. Twenty Sprague-Dawley rats/sex/group were dosed in diet with 0, 25, 50, 100, or 200 ppm Hydramethylnon (AC 217,300), 92% purity, for 91 days. This 25 ppm group had been initially dosed at 400 ppm, which proved to be excessively toxic, then dose for this group was reduced to 25 ppm after 2 weeks on study. Estimated achieved dosages for the 50, 100, and 200 ppm groups were 4.5, 8.6, and 17.0 mg/kg/day in males, and 5.0, 9.6, and 19.1 mg/kg/day in females. Incidences of bilateral testicular atrophy were 0, 4, 0, 5, and 20 in respective dosage groups. There was a dose-related decrease in testicular weights in all treated male groups. Given the irregular dosing regimen for the "25 ppm" group, NOEL is best expressed as "< 50 ppm" (LOEL = 4.5 mg/kg/day based on testicular weights: treatment-related testicular atrophy at 8.6 to 17.0 mg/kg/day). Transient food consumption decrement (F) was found at 100 ppm. Ovarian weights were statistically significantly elevated at 100-200 ppm, with no associated histopathology. High dose males had 10 cases of mild prostatic atrophy, compared to none in other groups. There was no other remarkable histopathology. Food consumption was significantly reduced in both sexes at 200 ppm. Body weight decrements after 13 weeks were 12% and 14%, respectively at 200 ppm, with no effects at lower dose levels. Food consumption and body weights were markedly affected at 400 ppm, showing this dose to be excessive. This older study does not meet current guidelines for a subchronic study (deficiencies are noted in DPR review), but provides useful data. Testicular atrophy and low testicular weights are **possible adverse effects**, since findings were not related to apparent general toxicity at 50-100 ppm. Aldous, 6/13/02.

395-007 993325 Fischer, J. E. (Study Director), "Experiment L-1742: 28-day rat feeding study with CL 217,300," American Cyanamid Co., Princeton, NJ, Sept. 5, 1979. Toxicology Report No. AX79-2. Three CD rats/sex/group were dosed in diet with Hydramethylnon (formerly CL 217,300) (91.6% purity) at 0, 50, 100, 200, 400, or 800 ppm for up to 28 days. The 800 ppm group was sacrificed moribund after 2 weeks of treatment. Study design was limited to a few parameters (clinical signs, body weight, food consumption, necropsy, and histopathology). The study pre-dates modern guidelines, and does not address standard data requirements. Small sample sizes make this study of limited value for rigorous evaluation of NOEL's. Apparent NOEL = 50 ppm (5.6 mg/kg/day), based on slight but statistically significant reduction in food consumption in males at 100 ppm, associated with a slight but non-significant reduction in body weight. A similar modest decrement in food consumption (not statistically significant) occurred in females at week 2 only. Testicular lesions (especially focal tubular degeneration and formation of giant cells) occurred at 200 ppm (18.7 mg/kg/day) and above, making the NOEL for organ toxicity = 100 ppm = 10.3 mg/kg/day. These lesions are "possible adverse effects." Supplemental study, suitable mainly as a range-finding study. Aldous, 6/13/02.

395-007 066135 Fischer, J. E. (Study Director), "Experiment L-1743: 28-day rat feeding study with CL 217,300," American Cyanamid Co., Princeton, NJ, 9/24/79. Toxicology Report No. AX 79-4. Six CD rats/sex/group were dosed in diet with hydramethylnon (formerly CL 217,300) (91.6% purity) at 0, 25, 50, 75, and 100 ppm for up to 28 days. In addition to the limited parameters evaluated in the range-finding study conducted at the same facility immediately preceding this study (see Record No. 993325, Cyanamid Toxicology Report No. AX 79-2), the present study included hematology and clinical chemistry (limited to BUN, ALT, and AST). The study pre-dates modern guidelines, and does not address standard data requirements, but provides useful data for parameters evaluated. Apparent NOEL = 75 ppm (9.2 and 9.5 mg/kg/day in M and F, respectively, based on diminished body weight gains in females, and diminished food consumption in both sexes). There were no treatment effects in hematology, clinical chemistry, or gross or microscopic pathology. No adverse effects indicated. The only organs weighed were kidneys and liver: these were unaffected by treatment. Aldous, 6/14/02.

**395-001 993335 Thompson, G. W., "Subchronic 21-day dermal toxicity study of AC 217,300 in rabbits," Hazleton Raltech, Inc., 4/15/82. Raltech Study No. 80033. Ten NZW rabbits per sex per group were dermally exposed on shaved dorsal skin (oleic acid vehicle) for 3 weeks, 6 hr/day, 5 days/week. One-half of animals per group had skin abraded weekly. Test article was hydramethylnon (purity 91.6%), applied 0, 10, 50, or 250 mg/kg per treatment day. Collars prevented disturbance of the taped gauze dressing. Primary parameters evaluated were daily evaluations of treated skin (Draize criteria), and gross examinations and histopathology of treated areas and of a full set of protocol tissues. Hematology and clinical chemistry were performed pre-study and at sacrifice. NOEL = 50 mg/kg/day, based on reduced food consumption and body weights (M and F), and increased relative liver weights (M and F). Plausibly incidental although statistically significant findings seen in only 1 sex at 250 mg/kg/day were decreased platelet counts (F) and elevated cholesterol (M). There were no increases in lesions of treated skin noted in daily clinical observations nor at histopathologic examinations. Except for splenic congestion (5 high dose females vs. 0 control females), no histopathology of non-dermal tissues suggested treatment increases, and this finding is likely to be incidental. Study is acceptable, with no adverse effects. Aldous, 5/24/02.

**009 993327 "AC 217,300: 91-day study in the dog". American Cyanamid Co. Pharmacopathics Research Laboratories, Inc, 5/31/79. Purebred beagles were dosed by gelatin capsule with 0, 3, 6, or 12 mg/kg/day AC 217,300. Occasional slight decrements in food consumption were observed at 3 mg/kg/day. Marked anorexia was observed in both sexes at 6 and 12 mg/kg/day, which led to marked body weight losses and necessitated premature sacrifices. All 12 mg/kg/day dogs died by day 54, and only 1/sex survived to termination at 6 mg/kg/day. Severe inanition preceded these deaths, despite substituting canned dog food, and also milk where indicated, for the normal dry rations. Food consumption was slightly reduced in 3 mg/kg/day dogs compared to controls (statistically significant in 2 of the 13 weeks in each sex). This appears to reflect a mild treatment effect. Body weight gains were not remarkably different between controls and 3 mg/kg/day dogs. Absolute liver weights were slightly but significantly elevated in 3 mg/kg/day males compared to concurrent controls, and to historical controls of comparable age. There was no comparable change in females, and there was no corresponding histopathology. Tremors, occasional convulsions, emaciation, inactivity, and wastage of muscle and subcutaneous fat were commonly observed in males and females at 6 or

12 mg/kg/day. All 6 and 12 mg/kg/day males had mild to moderate bilateral testicular atrophy. This was justifiably considered by investigators to be a result of starvation rather than a primary toxic effect. There were no testicular lesions at 3 mg/kg/day. Study is **acceptable** (as a subchronic study), and **no adverse effect is indicated**. Based on the steep dose-response curve and very mild responses at the low dose level, the NOEL appears to be only slightly below 3 mg/kg/day. C. Aldous, 11/18/88, with 1-liner expanded by Aldous on 6/7/02.

395-072 145824 Glaza, S. M., "Acute subcutaneous toxicity study of hydramethylnon in rats," Hazleton Wisconsin, Inc., 5/13/92. Lab Project ID: HWI 20100567. Ten young male Crl:CD® BR rats/group of average body weight 267 g were dosed once with hydramethylnon (a yellow solid: purity and lot number not stated) in cottonseed oil vehicle (10 ml/kg) at hydramethylnon dose levels of 0, 100, 500, or 1000 mg/kg. Rats were observed for 2 weeks prior to sacrifice, general necropsy, weighing of testes and epididymides, and histopathology of the latter organs plus seminal vesicles. Body weight gain during days 7-14 was reduced slightly at 500 to 1000 mg/kg. Food consumption was reduced during days 8-14 at 500 mg/kg and during days 1-14 at 1000 mg/kg. Clinical signs were limited to the injection site (yellow staining, subcutaneous mass at site, yellow discharge from mass). Body weights were significantly reduced in 1000 mg/kg rats on day 0 (group assignments were not stratified on body weight), and differences were slightly larger at day 14, possibly due to a minor body weight effect of treatment. Average absolute testes weights in respective groups were 1.65, 1.66, 1.58, and 1.71 g. Although absolute weights were comparable, relative weights of testes in 1000 mg/kg group were statistically significantly elevated. There was no gross or histopathologic response in organs examined. Supplemental data, with no adverse effects indicated. Aldous, 6/14/02 (no DPR worksheet).

395-072 145825 Fischer, J. E., "AC 217,300: reproductive performance of male albino rats after receiving a single oral dose with AC 217,300." American Cyanamid Co., 6/1/83, Toxicology Report AX83-5. Ten CD rats/group of initial body weight of 85 g were dosed by gavage with 0 or 800 mg/kg of hydramethylnon (91.6% purity) in corn oil vehicle. Treated males had diarrhea and decreased food consumption during the first 24 hr, followed by rapid recovery. During the 5th week after dosing, these males were mated to untreated females. Males were then sacrificed, and combined testes weights were recorded (there was no dose effect). Males were not further evaluated. There were no differences in parameters evaluated in females: time to impregnation, numbers of viable pups or dead pups, or resorption incidence. This is a supplemental study, which does not address any standard data requirements, and which has little value for hazard evaluation. Aldous, 6/14/02 (no DPR worksheet).