UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 27 1995

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#642AB

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Hydramethylnon; P.C. Code #118401; Risk Assessment for Gels, Roach Bait Stations and Ant Stations; ID #:064248-00005

Tox.Chem No.: 642AB
MRID No.: None
DP Barcode No.: D210034
Submission No.: S478150

TO: George LaRocca, PM Team #13
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (7509C)
William Dykstra 12/15/94

THRU: Roger Gardner, Section Head, Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (7509C)
Roger Gardner 1-20-95 KB 1/24/94

ACTION REQUESTED: The Product Manager #13, Registration Division, requests that TB-I address the Agency's concern about single exposure/adverse effect of hydramethylnon by determining the MOE's for "worst case" single and "other possible" exposure scenarios for children who may ingest hydramethylnon from the PCO product and home use products which have been registered. The Registrant, Clorox Corporation, has submitted new additional toxicology studies for hydramethylnon and bitrex. These studies are also reviewed in this memorandum.

CONCLUSIONS: Based on MOEs resulting from the single and multiple exposure scenarios for the PCO Gel, TB-I recommends that this product, which is registered and does not contain bitrex, should be required to contain bitrex, if registration is to be continued. For the proposed home use Gel product, which is not registered, based on the MOEs for single and repeated exposure, TB-I recommends that bitrex, but not child resistant packaging, be required for registration. For Combat ant and roach bait stations, the MOEs for "worst case" exposures (total contents of bait station) are usually greater than 100 and "other possible exposures" (repeated) are less than the desired 100 in most instances. However, for a 11.4 kg child who is exposed to a removable amount (7%) only once to either the regular, large, or ant bait station or a spot of the 2% Gel, the MOEs are all substantially greater than 100.

SUMMARY: Hydramethylnon (Amdro) produces testicular effects in all species tested (rats, mice, dogs, and rabbits) and in a dominant lethal study in male rats, the NOEL was 3 and the LEL was 30 mg/kg/day. The control and treated males were mated for 17 weeks to virgin females and the antifertility effects of Amdro did not occur before week 6 of mating. Based on this and other information, Amdro is believed to interfere with sexual development at the level of spermatogonia or spermatocytes, which occurs in the latter stages of development. In rats, sexual development begins during lactation and the full sexual development occurs by Day 88. In the human 2 year old child (the subject of child-resistant packaging), this level of testicular development (spermatogonia or spermatocytes) is not present and therefore, the 2-year old child is not believed to be sensitive to the antifertility effects of Amdro. Antifertility effects in male humans would be expected to occur in children at or around puberty. For this reason, TB-I does not require child-resistant packaging. MOEs less than 100 for acute exposure to young children are possible from the misuse of this product. However, with 20 ppm bitrex, the possibility of repeated exposure is minimized. The possible toxic effects from acute overexposure are temporary diarrhea, weight loss and appetite loss, but not mortality.

RISK ASSESSMENT

1. Summary of Hydramethylnon Toxicology Studies:

A. Single-Dose Testicular NOEL: Groups of 10 young male Sprague-Dawley rats were **subcutaneously** injected with hydramethylnon in a sesame oil solution at doses of 0, 100, 500, or 1000 mg/kg BW and observed for 14 days. Rats at 500 and 1000 mg/kg had decreased weight gain and food consumption during the second week after dosing. All animals were sacrificed and the testes were weighed and examined microscopically. There were no compound-related microscopic lesions at 100, 500, or 1000 mg/kg and relative testes weight at 1000 mg/kg was slightly increased (17%). This testicular finding is not considered toxicologically significant, since decreased testes weight for hydramethylnon is considered the significant effect and this was not observed. However, due to study deficiencies: ie, subcutaneous rather than oral dosing, lack of normalization of body weights in rats prior to dosing, and possible loss of test material from leakage during the observation period, this study cannot be used for MOE purposes. Therefore, although the single-dose subcutaneous testicular NOEL = 1000 mg/kg, the study only supports other studies or data and cannot be used, by itself, for regulatory purposes.

B. Single-Dose Reproductive NOEL: Groups of 10 Sprague-Dawley 4 week old male rats were orally gavaged with hydramethylnon at doses of 0 or 800 mg/kg. The rats were observed for five weeks until sexually mature and then mated 1:1 to untreated female Sprague-Dawley rats. Toxic signs consisted of diarrhea during the first day and decreased food consumption and weight gain during the first week, but not thereafter. There were no effects in testicular weights (histopathology was not performed, but tissues were saved) nor meaningful differences in reproductive parameters between females mated **only once** to control and 800 mg/kg rats. Since only a single dose was evaluated in this study and the treated rats mated only once, a critically sensitive period in development of the male reproductive system may not have been evaluated in this study. However, the single-dose oral NOEL approximates 800 mg/kg, if diarrhea, food consumption and body weight are not included. It should be noted that the male rat oral LD_{50} is 1131 mg/kg for hydramethylnon and that the single dose of 800 mg/kg approaches male rat mortality.

C. Five-Day Reproductive NOEL: In a dominant lethal assay in male Sprague-Dawley rats, groups of 10 rats were dosed

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orally each day for five days with 0, 3, 30, or 90 mg/kg/day of hydramethylnon in corn oil. Ten rats received 0.05 mg/kg/day of the reference compound triethylenemelamine in saline by intraperitoneal injection once daily for five days. Following treatment, the male rats in each group were mated 1:1 each week for 17 weeks to 10 virgin untreated female rats per group per week. All males survive to scheduled sacrifice. At 30 mg/kg/day, males showed decreased weight gain during treatment. At 90 mg/kg/day, the rats lost weight during treatment and had decreased weight gain the following week. The pregnancy rate for females mated to treated males were not remarkable for the first five weeks. **In week 6, 1 control, 1 low dose , 3 mid dose and 7 high dose males were infertile (females not pregnant).** By week 7, all males treated at 90 mg/kg/day were infertile. One male (041463) at 3 mg/kg/day was infertile after week 4. Two males at 30 mg/kg/day, which had been infertile for 3 consecutive matings returned to consistent fertility by week 12. There were no infertile males at 30 mg/kg/day after week 12. Two of the 90 mg/kg/day males returned to fertility in week 11 and an additional 2 males at 90 mg/kg/day regained their fertility in week 17, when the study was terminated. At necropsy, all male rats at 90 mg/kg/day, except those two which had recovered fertility in week 11 had much smaller testicular weight (below 3.0 g vs 3.64 g in controls) and epididymis. The testicular weight of the 3 and 30 mg/kg/day groups were comparable to controls (3.86 g in low dose and 3.70 in mid dose). There were no dominant lethal effects in hydramethylnon treated rats. Considering the timing of infertility, the spermatocyte or spermatogonia were probably affected by hydramethylnon. The reference compound triethylenemelamine induced a characteristic increase in early postimplantation deaths, a decrease in the number of implantation sites, and a decrease in the number of pregnancies. The 5-Day fertility NOEL is 3.0 mg/kg/day.

2. <u>Selection of Appropriate NOEL for Comparison to Exposure</u>

In selecting endpoints for calculating MOEs, the number of rat dosing days should be close to the number of human exposure days. For a single dose of hydramethylnon, the NOEL of 800 mg/kg in the oral single dose-mating study is appropriate rather than a multiple dose study for comparison to single day exposure. For multiple exposures, 5 days to 28 days, the 5 day NOEL for male fertility of 3 mg/kg/day and the 28 day testicular NOEL (not reported above) of 10 mg/kg/day are appropriate. The LEL for the 5 day fertility study is 30 mg/kg/day and the LEL for the 28 day testicular study is 20 mg/kg/day. Therefore, both the 5 day fertility NOEL of 3 mg/kg/day and the 28 day study

NOEL of 10 mg/kg/day for testicular effects are used for 5 day exposures.

ORAL NOEL's AND LEL's for Testes

	NOEL	LEL
	mg/kg/day	
Single Dose	800	-
5 Day gavage	3	30
28 day feeding* in weanlings	10	20
90 day rat	2.5	5.0
90 day dog	3.0	6.0
3-gen. repro.	2.5	5.0
2-year rat	2.5	5.0
18 mo.mouse	3.75	7.5

* = NOEL = 100 ppm x 0.10 mg/kg/day/ppm (confirmed by study report)

3. Hydramethylnon Baits Available

A. **Gel Bait:** 60 gm/syringe x .0215 a.i. x 1000 mg/gm = 1290 mg hydramethylnon

WORST CASE EXPOSURE

If a 20 lb (11.4 kg) child consumed the entire contents of the syringe, exposure would be 113 mg/kg BW

MOE's

MOE for Single Dose NOEL = 800 mg/kg/113 mg/kg = 7.1

MOE for 5%, 10% and 20% of total GEL = 142, 71, and 36, respectively

For repeated exposure directly from the GEL syringe, the MOE's would be less than 1.0. Exposure exceeds the NOEL and approaches the LEL for infertility and testicular injury.

EXPOSURE FOR APPLICATION RATE

0.5 gm x 1000 mg/kg x 0.0215 a.i. x 13 spots/treatment = 140 mg hydramethylnon; therefore, one spot = 10.7 mg; five spots = 53.5 mg; and all the spots = 140 mg

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If a 11.4 kg child consumed the one, five or all the spots of the entire application of hydramethylnon over time, exposure would be for one spot: 10.7 mg/11.4 kg = 0.93 mg/kg; for five spots: 53.5 mg/11.4 kg = 4.69 mg/kg; for all the spots: 140 mg/11.4 kg = 12.2 mg/kg BW

MOE

One Spot: MOE for Single Dose Study = 800 mg/kg ÷ 0.93 mg/kg/day = 860

Five Spots Over a Five Day Period: MOE for 5-Day Male fertility = 3.0 mg/kg/day ÷ 0.93 mg/kg = 3.2

Five Spots in One Day: MOE for Single Dose Study = 800 mg/kg ÷ 4.69 mg/kg = 170

All the Spots in One Day: MOE for Single Dose Study = 800 mg/kg ÷ 12.2 mg/kg = 66

B. **Regular Roach Bait Station:** 0.635 ounces/box x 28.5 gm/ounce x 1000 mg/gm x 0.02 a.i. ÷ 12 = 33 mg hydramethylnon

WORST CASE EXPOSURE

If a 11.4 kg child consumed the entire contents of a bait station, exposure would be 33 mg/11.4 kg = 2.9 mg/kg

MOE

MOE for Single NOEL = 800 mg/kg/2.9 mg/kg = 276

OTHER POSSIBLE EXPOSURE

(A) If a 11.4 kg child removed 7% of the contents of a bait station in one day, exposure would be 2.31 mg/11.4 kg/1 day = 0.20 mg/kg/day

MOE

MOE for Single Dose Male NOEL = 800 mg/kg ÷ 0.20 mg/kg/day = 4000

(B) If a 11.4 kg child removed 7% of the contents of a bait station each day for five days (a total of 35%), exposure would be 2.31 mg/11.4kg = 0.20 mg/kg/day

MOE

(1) MOE for 5-Day Male fertility = 3.0 mg/kg/day ÷ 0.20 mg/kg/day = 15

(2) MOE for 28 Day Testicular Study = 10 mg/kg/day ÷ 0.20 = 50

C. **Large Roach Bait Station:** 2.11 ounces x 28.5 gm/ounce x 0.02 a.i. x 1000 mg/gm ÷ 8 = 165 mg hydramethylnon

WORST CASE EXPOSURE

If a 11.4 kg child consumed the entire contents of a bait station, exposure would be 165 mg/11.4 kg = 14.4 mg/kg

MOE

MOE for Single Dose NOEL = 800 mg/kg/14.4 mg/kg = 56

OTHER POSSIBLE EXPOSURE

(A) If a 11.4 kg child removed 7% of the contents of a bait station in one day, exposure would be 11.55 mg/11.4 kg/1 day = 1.01 mg/kg/day

MOE

MOE for Single Dose Male NOEL = 800 mg/kg ÷ 1.01 mg/kg/day = 792

(B) If a 11.4 kg child removed 7% of the contents of a bait station each day for five days (a total of 35%), exposure would be 11.55 mg/11.4kg = 1.01 mg/kg/day

MOE

(1) MOE for 5-Day Male fertility = 3.0 mg/kg/day ÷ 1.01 mg/kg/day = 2.97

(2) MOE for 28 Day Testicular Study = 10 mg/kg/day ÷ 1.01 mg/kg/day = 9.9

D. **Ant Control Station:** 0.177 ounces x 28.5 gm/ounce x 0.009 a.i. x 1000 mg/gm ÷ 3 = 15.1 mg hydramethylnon

WORST CASE EXPOSURE

If a 11.4 kg child consumed the entire contents of a bait station, exposure would be 15.1 mg/11.4 kg = 1.32 mg/kg

MOE

MOE for Single Dose NOEL = 800 mg/kg/14.4 mg/kg = 606

OTHER POSSIBLE EXPOSURE

(A) If a 11.4 kg child removed 7% of the contents of a bait station in one day, exposure would be 1.06 mg/11.4 kg/ 1 day = 0.093 mg/kg/day

MOE

MOE for Single Dose Male NOEL = 800 mg/kg ÷ 0.093 mg/kg/day = 8602

(B) If a 11.4 kg child removed 7% of the contents of a bait station each day for five days (a total of 35%), exposure would be 1.06 mg/11.4kg = 0.093 mg/kg/day

MOE

(1) MOE for 5-Day Male fertility = 3.0 mg/kg/day ÷ 0.093 mg/kg/day = 32

(2) MOE for 28 Day Testicular Study = 10 mg/kg/day ÷ 0.093 mg/kg/day = 108

Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 12/14/94
Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Tox Branch I Roger Gardner 1-20-95

DATA EVALUATION REPORT

STUDY TYPE: Not A Guideline Study

TOX. CHEM NO: 642AB

MRID NO.: None

TEST MATERIAL: Bitrex

SYNONYMS: Amdro

STUDY NUMBER: None

SPONSOR: Clorox Corp.

TESTING FACILITY: Peryam & Kroll Research Corp.

TITLE OF REPORT: Gel with 20 ppm Bitrex Evaluated for Tolerability and Food Action

AUTHOR(S): Dennis Irving

REPORT ISSUED: 11/10/94

CONCLUSION: Fifty human males, 18 to 45 years old, were recruited to participate in this study. The study was conducted by Peryam & Kroll Staff (714-572-6888) and no Quality Assurance was noted in the report. Panelists were evaluated for their ability to taste bitterness with separate samples of water and 0.07% caffeine. Each panelist first evaluated the Control Gel (Combat Gel without bitrex and amdro), then the Test Gel (Combat Gel with 20 ppm bitrex but without amdro).

Panelists felt that the Combat Gel with 20 ppm bitrex was less tolerable (score = 6.8; 1 to 8 scale, lower score more tolerable) than control Combat Gel (without bitrex) (score = 2.1). Of the 50 people tested, 86% felt the 20 ppm bitrex gel was intolerable, where only 8% felt the control gel was intolerable. Panelists also rejected the 20 ppm bitrex gel on the "food action scale". The rating for the control gel was 3.6. The 20 ppm bitrex gel received a score of 8.2 (1 to 9 scale, where lower score = more likely to eat). Of the 50 people tested, 68% felt that they would eat the 20 ppm bitrex sample if they were forced to, where none of the people felt this way about the control sample.

The results between the controls and the 20 ppm bitrex group were statistically significantly different ($p < 0.001$) for both tolerability and food action criteria.

Core Classification: **CORE SUPPLEMENTARY**

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Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 12/14/94
Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head Roger Gardner 1-20-95
Review Section I, Tox Branch I

DATA EVALUATION REPORT

STUDY TYPE: 81-1; Acute Oral Dose of Hydramethylnon

TOX. CHEM NO: 642AA

MRID NO.: 250997

TEST MATERIAL: Hydramethylnon technical

SYNONYMS: Amdro

STUDY NUMBER: AX83-5 (project No. 0422)

SPONSOR: Cyanamid and Clorox Co.

TESTING FACILITY: American Cyanamid Agricultural Research Division

TITLE OF REPORT: Reproductive Performance of Male Albino Rats After Receiving a Single Oral Dose with AC 217,300

AUTHOR(S): J.E. Fischer

REPORT ISSUED: 6/1/83

CONCLUSION: Sexually immature, approximately 4 week old, Sprague-Dawley rats, weighing 81-89 g (males) and 80-87 g (females), were fed Purina Rodent Chow #5001 and tap water ad libitum. Groups of 10 males were orally dosed once with 0 (corn oil) or 800 mg/kg of hydramethylnon in corn oil at a dosing volume of 10 mL/kg. All animals were observed twice daily for toxicity and mortality. Clinical examinations were performed weekly. Body weight and food consumption were measured weekly before mating and following mating female body weight was taken on Days 0, 4, 8, 12, and 18 of gestation. During week 5 following dosing, when the rats were sexually mature, males were mated to untreated females from their respective groups. Following evidence of mating, females were continued on basal diet until Day 18 of gestation. At that time, the females were sacrificed, grossly examined and reproductive parameters and fetal status were determined. After mating, the males were sacrificed, grossly examined and testicular weight determined. After sacrifice of the females, the number of viable and dead pups, early and late resorptions and gross pup abnormalities were recorded for each female. Statistical analyses of body weight,

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food consumption, organ weights, relative organ weights and reproductive data were done by ANOVA using Dunnett's procedure.

There were no mortalities and clinical signs in treated male rats consisted of diarrhea and decreased food consumption on the first day following dosing. Food consumption continued to be decreased through day 7 and recovery occurred by day 14. There were no clinical signs in control male and untreated female rats. Food consumption and weight gain were statistically significantly decreased in treated male rats during days 1-7 after dosing by 19% and 29%, respectively. Food consumption and body weight gain were comparable between control and treated male rats during the remainder of the study. Weight gain and food consumption for female rats were comparable between those female rats mated to control or treated male rats during the 4 week growth phase and during gestation. Days to impregnation averaged 1.8 days for control males and 1.6 days for treated male rats. There were no dead pups in any control or untreated female (mated to 800 mg/kg males) uterus and the number of viable pup/dam was 11.3 for both the control and untreated female (mated to 800 mg/kg males) rats. Total resorptions were 0.56/dam in the controls and 0.40/dam in the untreated females mated to 800 mg/kg male rats. Absolute and relative testicular weights were comparable between control and treated male rats at sacrifice.

Since only a single dose was evaluated in this study and the treated rats mated only once, a critically sensitive period in development of the male reproductive system may not have been evaluated in this study. However, the single-dose oral NOEL approximates 800 mg/kg, if diarrhea, food consumption and body weight are not included. It should be noted that the male rat oral LD_{50} is 1131 mg/kg for hydramethylnon and that the single dose of 800 mg/kg approaches male rat mortality.

Core Classification: **CORE-SUPPLEMENTARY**

QUALITY ASSURANCE: This study was done before GLP requirements and there was no Quality Assurance Statement. There was a signature page with signatures of the members of the laboratory who performed the study.

TEST MATERIAL: Hydramethylnon; 91.6% purity; yellow powder

METHODS: Sexually immature, approximately 4 week old, Sprague-Dawley rats, weighing 81-89 g (males) and 80-87 g (females), were fed Purina Rodent Chow #5001 and tap water ad libitum. Groups of 10 males were orally dosed once with 0 (corn oil) or 800 mg/kg of hydramethylnon in corn oil at a dosing volume of 10 mL/kg. All animals were observed twice daily for toxicity and mortality. Clinical examinations were performed weekly. Body weight and food consumption were measured weekly before mating and following mating female body weight was taken on Days 0, 4, 8, 12, and 18 of gestation. During week 5 following dosing, when the rats were sexually mature, males were mated to untreated females from their respective groups. Following evidence of mating, females were continued on basal diet until Day 18 of gestation. At that time, the females were sacrificed, grossly examined and reproductive parameters and fetal status were determined. After mating, the males were sacrificed, grossly examined and testicular weight determined. After sacrifice of the females, the number of viable and dead pups, early and late resorptions and gross pup abnormalities were recorded for each female. Statistical analyses of body weight, food consumption, organ weights, relative organ weights and reproductive data were done by ANOVA using Dunnett's procedure.

RESULTS: There were no mortalities and clinical signs in treated male rats consisted of diarrhea and decreased food consumption on the first day following dosing. Food consumption continued to be decreased through day 7 and recovery occurred by day 14. There were no clinical signs in control male and untreated female rats. Food consumption and weight gain were statistically significantly decreased in treated male rats during days 1-7 after dosing by 19% and 29%, respectively. Food consumption and body weight gain were comparable between control and treated male rats during the remainder of the study. Weight gain and food consumption for female rats were comparable between those female rats mated to control or treated male rats during the 4 week growth phase and during gestation. Days to impregnation averaged 1.8 days for control males and 1.6 days for treated male rats. There were no dead pups in any control or untreated female (mated to 800 mg/kg males) uterus and the number of viable pup/dam was 11.3 for both the control and untreated female (mated to 800 mg/kg males) rats. Total resorptions were 0.56/dam in the controls and 0.40/dam in the untreated females mated to 800 mg/kg male rats. Absolute and

relative testicular weights were comparable between control and treated male rats at sacrifice.

CONCLUSION: Groups of 10 Sprague-Dawley 4 week old male rats were orally gavaged with hydramethylnon at doses of 0 or 800 mg/kg. The rats were observed for five weeks until sexually mature and then mated 1:1 to untreated female Sprague-Dawley rats. Toxic signs consisted of diarrhea during the first day and decreased food consumption and weight gain during the first week, but not thereafter. There were no effects in testicular weights (histopathology was not performed, but tissues were saved) nor meaningful differences in reproductive parameters between females mated **only once** to control and 800 mg/kg rats. Since only a single dose was evaluated in this study and the treated rats mated only once, a critically sensitive period in development of the male reproductive system may not have been evaluated in this study. However, the single-dose oral NOEL approximates 800 mg/kg, if diarrhea, food consumption and body weight are not included. It should be noted that the male rat oral LD_{50} is 1131 mg/kg for hydramethylnon and that the single dose of 800 mg/kg approaches male rat mortality.

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Review Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Tox Branch I Roger Gardner 1-20-95

DATA EVALUATION REPORT

STUDY TYPE: 81-1; Acute Subcutaneous Injection

TOX. CHEM NO: 642AB

MRID NO.: None

TEST MATERIAL: Hydramethylnon technical; vehicle: cottonseed oil

SYNONYMS: Amdro

STUDY NUMBER: HWI 20100567

SPONSOR: The Clorox Company

TESTING FACILITY: Hazleton Wisconsin

TITLE OF REPORT: Acute Subcutaneous Toxicity Study of Hydramethylnon in Rats

AUTHOR(S): S.M. Glaza

REPORT ISSUED: May 13, 1992

CONCLUSION: Young adult male Sprague-Dawley rats, 230-290 g BW, divided into groups of 10/group, were subcutaneously injected with hydramethylnon dissolved in cottonseed oil at a volume of 10.0 ml/kg at doses of 0, 100, 500, and 1000 mg/kg. Animals were fed Purina Rodent Chow #5001 or #5002 and tap water ad libitum during a 14 day observation period. Body weight was measured at days 0, 7, and 14. Food consumption was measured from days 0 to 7 and 8 to 14. After the observation period, all animals were sacrificed and given a gross necropsy. Individual testes weight was recorded. All testes were fixed in Bouin's fixative and examined microscopically. ANOVA was used to determine significance and Dunnett's t-test was used for pairwise comparisons.

There were statistically significant differences between control and high dose rats in mean body weight at the beginning of the study. However, body weight gain was statistically significantly decreased for the 500 and 1000 mg/kg dose groups for days 7-14, but not for days 0-7. Food consumption was also significantly decreased for the 500 and 1000 mg/kg groups during days 8-14. At necropsy, subcutaneous masses filled with yellow oily material were located in the subcutis of the injection site

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in 29/30 rats given hydramethylnon. This yellow material is the residual test material which was not absorbed. No cysts or yellow material were seen in the control animals. There was a 17% significant increase in relative testes weight in the high dose in comparison to controls. There were no compound-related macroscopic or microscopic findings in the testes, seminal vesicles, or epididymides.

Core Classification: **CORE - SUPPLEMENTARY**

REVIEW: Acute Subcutaneous Toxicity Study of Hydramethylnon in Rats (Hazleton #HWI 20100567; 5/13/92)

QUALITY ASSURANCE STATEMENT: The report had a GLP statement signed by the Study Director and a Quality Assurance Statement, listing inspection dates, signed by Rebecca S. Nelson of the Quality Assurance Unit on 5/13/92.

TEST MATERIALS: Hydramethylnon technical ; Lot #92-001, yellow solid; Vehicle: cottonseed oil - a viscous, light yellow liquid; solutions were administered by subcutaneous injection at dosing volume of 10.0 mL/kg

METHODS: Young adult male Sprague-Dawley rats, 230-290 g BW, divided into groups of 10/group, were subcutaneously injected with hydramethylnon dissolved in cottonseed oil at a volume of 10.0 ml/kg at doses of 0, 100, 500, and 1000 mg/kg. Animals were fed Purina Rodent Chow #5001 or #5002 and tap water ad libitum during a 14 day observation period. Body weight was measured at days 0, 7, and 14. Food consumption was measured from days 0 to 7 and 8 to 14. After the observation period, all animals were sacrificed and given a gross necropsy. Individual testes weight was recorded. All testes were fixed in Bouin's fixative and examined microscopically. ANOVA was used to determine significance and Dunnett's t-test was used for pairwise comparisons.

RESULTS: There were statistically significant differences between control and high dose rats in mean body weight at the beginning of the study. However, body weight gain was statistically significantly decreased for the 500 and 1000 mg/kg dose groups for days 7-14, but not for days 0-7. Food consumption was also significantly decreased for the 500 and 1000 mg/kg groups during days 8-14. At necropsy, subcutaneous masses filled with yellow oily material were located in the subcutis of the injection site in 29/30 rats given hydramethylnon. This yellow material is the residual test material which was not absorbed. No cysts or yellow material were seen in the control animals. There was a 17% significant increase in relative testes weight in the high dose in comparison to controls. There were no compound-related macroscopic or microscopic findings in the testes, seminal vesicles, or epididymides as shown below.

	DOSE (mg/kg)			
	0	100	500	1000
No. examined	10	10	10	10
seminal ves.				
N.R.	10	10	10	10
Testes				
N.R.	10	9	10	10
degeneration, seminiferous tubule	0	1	0	0
Epididymides				
N.R.	4	5	3	4
infiltrate, lymphocytic	6	5	7	6

N.R. = not remarkable

CONCLUSION: Groups of 10 young male Sprague-Dawley rats were **subcutaneously** injected with hydramethylnon in a sesame oil solution at doses of 0, 100, 500, or 1000 mg/kg BW and observed for 14 days. Rats at 500 and 1000 mg/kg had decreased weight gain and food consumption during the second week after dosing. All animals were sacrificed and the testes were weighed and examined microscopically. There were no compound-related microscopic lesions at 100, 500, or 1000 mg/kg and relative testes weight at 1000 mg/kg was slightly increased (17%). This testicular finding is not considered toxicologically significant, since decreased testes weight for hydramethylnon is considered the significant effect and this was not observed. However, due

to study deficiencies: ie, subcutaneous rather than oral dosing, lack of normalization of body weights in rats prior to dosing, and possible loss of test material from leakage during the observation period, this study cannot be used for MOE purposes. Therefore, although the single-dose subcutaneous testicular NOEL = 1000 mg/kg, the study only supports other studies or data and cannot be used, by itself, for regulatory purposes.