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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

TXR No.: 0052103

DATE: January 29, 2004

SUBJECT: **1-Naphthalene Acetic Acid: Review of Toxicity Studies**
PC Code 056002
Reregistration Case #: 0379

FROM: Abdallah Khasawinah, Ph.D., Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

THRU: Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Mark Howards, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

TASK ID: DP Code D293238

Action Requested: Review and Update of Toxicology Studies to Support Reassessment Eligibility Decision (RED)

Agency's Action:

HED has prepared/or updated the executive summaries of the Data Evaluation Records (DER's) on the subject studies in light of the new guidelines and classification systems. The updated executive summaries and DERs are attached. The study findings are listed below.

RC
03/04

1. Acute Oral Toxicity - Rat

In an acute oral toxicity study (MRID 00103128), groups of Sprague Dawley rats (5/sex) were given 1-Naphthyl Acetamide (Lot/Batch #: NOIM1007; white powder; 95% purity (HED 005377)) by single dose gavage in 0.25% methylcellulose (20 ml/kg) at the following doses of 1750, 2250, 3000, 3500, or 4000 mg/kg bw. All animals were observed for up to 14 days post-dosing. Necropsy was performed on all animals.

The oral LD_{50} (95% C.I.) for males and females combined= 2520 mg/kg (2100-3024 mg/kg) NAA is classified as **TOXICITY CATEGORY III**. This acute oral toxicity study in the rat was originally classified core-minimum (HED 005378). The study is re-classified as **Acceptable/Guideline**

2. Acute Dermal Toxicity - Rabbit

In an acute dermal toxicity study (MRID 00103129), five male and five female Albino New Zealand white rabbits received 2 g/kg of NAA ((Lot/Batch #: NOIM1007; white powder; 95% purity (HED 005377)) on the abraded skin under occlusive wrap for 24 hour exposure. Observations were made at 2, 4, 24 hour after exposure and twice daily thereafter for 14 days. Necropsy was performed on all animals. One animal died on day 11 with no visible signs of toxicity or visible lesions. At termination of study, necropsy revealed fluid filled intestines and stomach distension in one rabbit.

The dermal LD_{50} in the rabbit in this test is greater than 2 g/kg. NAA is classified as **CATEGORY III for dermal toxicity**. This acute dermal toxicity study in the rabbit is classified **Acceptable/Guideline**.

3. Acute Eye Irritation- Rabbit

In a primary eye irritation study (MRID 00103127), nine New Zealand white rabbits received 100 mg of Napthalene Acetic Acid (Lot # 0010087; 96% purity; white powder) in one eye each. The treated eyes of three of the treated rabbits were washed 20 to 50 seconds after treatment. The treated eyes of the other six animals were unwashed. Observations were made at 1, 2, 3, 4,7 10, 14, and 21 days after treatment.

The test material produced severe corneal opacity in all treated rabbits (washed and unwashed eyes), redness, chemosis, and discharge. These symptoms did not clear completely and persisted in some animals for 21 days. NAA is **corrosive** for the eyes and is classified as **Category I** for eye irritation. This study is classified as **acceptable/guideline**.

4. AcuteDermal Irritation Study - Rabbit

In a primary dermal irritation study (MRID 00103127), six New Zealand white rabbits received 500 mg of Napthalene Acetic Acid (Lot # 0010087; 96%, white powder) at two abraded and

intact skin sites per animal under wrap for 24 hour exposure. Observations were made at 24 and 72 hours after treatment. NAA did not produce irritation at 24 or 72 hours. NAA is considered non-irritating to the rabbit skin and is classified in **Category 4** for dermal irritation. This study is classified as **acceptable/guideline**.

5. Skin Sensitization - guinea pigs

In a skin sensitization study (MRID 00153217) Napthalene Acetic Acid (Lot # RTS2846AA, white powder; 98.5% purity) , was tested on male Hartley Guinea pigs using the modified Buehler method.

No irritation was produced by the test material or the vehicle control during the induction or challenge phase. Dinitrochlorobenzene produced significant skin reaction increasing in severity with each progressing dose during induction phase and well defined skin reaction at challenge phase. Under the experimental conditions employed, it was concluded that Napthalene Acetic Acid is not a skin sensitizer (contact allergen) in guinea pigs. The study was classified **Acceptable/guideline**.

6. 10-Day Range Finding Study - Rat

In a range finding toxicity study (NAA 733236; purity not reported) was administered by gavage to Sprague Dawley rats (3/sex/dose) at dose levels of 0, 250, 1000 or 4000 mg/kg bw/day for 10 consecutive days. All surviving rats were necropsied at the end of the study.

All animals at the 4000 mg/kg/day and one female at the 1000 mg/kg/day died after 2 - 3 days. One female from the control group died after 9 days and it was attributed to a probable inadvertent pulmonary gavage (HED 004110 wrongly put this dead female in the 250 mg/kg/day group). None of the animals in the 250 mg/kg/day group died. Clinical signs of toxicity prior to death were dyspnea, ataxia, lethargy and prostration. A dose related depression in body weight gain and food consumption was noted (no statistical analysis was performed). Necropsy of the animals which died during the study and all surviving animals at the end of the study showed an increase in discoloration of lungs, liver and kidneys, distended bladder (high dose), blood and gas in the GI tract. The maximum tolerated dose would be 250 mg/kg/day. A **LOAEL** or **NOAEL** cannot be derived from this study. This short term range-finding study is classified **Acceptable/non-Guideline**.

7. 90-Day Oral Toxicity Study - Rats

In a subchronic oral toxicity study (MRID 00043624), 1-naphthaleneacetic acid, technical (Lot # not reported; purity not reported) was administered, in the diet, to Sprague Dawley rats (20/sex/dose) at dose levels of 0, 50, 150 or 300 mg/kg bw/day for 13 weeks. Two additional group of 10 rats/sex were administered 0 or 300 mg/kg bw/day and sacrificed after 30 days and necropsied. All surviving rats were necropsied at the end of the study.

All rats survived except for one death in the control group. No abnormal behavior or toxic effects were observed in the treated rats. It was concluded that the **LOAEL** for toxic effects in this study is 300 mg/kg/day based on decreased body weight in both sexes and enlarged liver weights in females. The **NOAEL** is 150 mg/kg/day. This subchronic toxicity study in the rat was conducted prior to the current testing guidelines. However, the information generated in this study is adequate and it is classified as **Acceptable/Guideline** to satisfy the guideline requirement for a subchronic study in the rat.

8. 6-Month Oral Toxicity Study - Dogs

In a subchronic oral toxicity study (MRID 00136446), 1-naphthaleneacetic acid, technical (Lot # 16388; 98.55% purity) was fed (gelatin capsules) to beagle dogs (4/sex/dose) at dose levels of 0, 50, 150, or 300 mg/kg/day for 180 consecutive days.

Clinical signs of toxicity were evident in the high dose group. These included anorexia lasting several days, tenderness in the mouth while dosing, icteric and pale mucous membranes, steady loss in weight, lethargy, an uncoordinated gait, dark urine, and dark stools. Two of four males and all the females showed some or all of these effects at the end of the study. One dog had a great amount of edema in the hind legs progressing over 3 days until its legs were swollen to approximately the coxo femoral joint. This dog was sacrificed on day 126 of the study. Urine collected from this dog prior to sacrifice showed large amounts of bilirubin, urobilinogen and a small amount of RBC and blood. These effects are considered to treatment-related.

The mean body weight and body weight gain was significantly depressed in the high dose females ($p < 0.01$) at 2, 3, 4,5 and 6 months in comparison to the control dogs. The male dogs had also reduced body weight and body weight gain during the last two months of the study. Hematological parameters were within reference limits for the four groups. The hematology of the dog that was sacrificed showed slightly increased WBC count with a relative and absolute neutrophilia and lymphopenia which may be compound related. The clinical chemistry analysis showed that alanine amino transferase (SGPT) were elevated at 4 months (slightly) and 6 months (2x the normal value) for the high dose females. The clinical chemistry of the male dog that was sacrificed in moribund condition showed lower protein, cholesterol and glucose and greatly elevated levels of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate amino transferase (SGOT) and SGPT.

Dose-related increases in relative weights of kidneys occurred in both males and females of the high dose group. Dose-related weight increases in liver, adrenals, brain and heart occurred in high dose females. The low dose group males had increased relative kidney weights and the mid dose group females had an increase in relative heart weights. Histopathologisal examination revealed very slight evidence of pericholangistis in the low dose group (2/8), very slight to moderate degree of hepatic insult in the mid dose group (7/8)and slight to severe degree of hepatic insult in the high dose group (8/8). This hepatic insult was characterized by

pericholangistis, toxic degenration of hepatocytes and hepatocellular hypertrophy in the mid dose group and additionally centrilobular necrosis, periportal fibrosis in the high dose group and hyperplastic nodule in the male dog that was sacrificed moribund. There was also evidence of squamoid metaplasi in the tracheal epithelium of 2/8 dogs and a slight degree of myocarditis (1/8) in the high dose group. Hyperkeratosis of the skin at the thoroacolumbar junction was seen in 2/8 dogs of the mid dose and 4/8 dogs of the high dose groups.

It was concluded that there was no **NOAEL** derived from this study. The **LOAEL** was 50 mg/kg/day, the lowest dose tested, based on hepatic liver changes (pericholangistis). This subchronic toxicity study in the dog was conducted prior to the current testing guidelines. However, the information generated in this test is adequate and it is classified as **Acceptable/Guideline** to satisfy the guideline requirement for a subchronic study in the dog.

9. Prenatal Developmental Toxicity Study - Rat

In a prenatal developmental study (MRID 00042765), NAA technical (Lot # NAA 73323G; purity not reported, white powder) was administered by gastric intubation to groups (24/group) of healthy timed pregnant albino CD rats at dose levels of 0, 10, 50 or 250 mg/kg/day in 0.05% sodium carboxymethylcellulose from days 6 through 15 of gestation.

No deaths or toxic symptoms were reported at any dose level. There was a statistically significant decrease in the mean body weight gain in the 250 mg/kg/day rats with the onset of the compound administration. The dams in the 10 and 50 mg/kg/day groups did not show significant decrease in body weight gain during compound administration but showed a decrease compared to the controls from days 17-20. Litter size and fetal loss were not affected by the treatment. A slight decrease (statistically insignificant) in mean litter size (9.3, 9.3, 8.8 and 7.9 in the control, low-, mid-, and high-dose groups, respectively) was considered unrelated to treatment. There was a statistically increased ($p<0.05$) mean preimplantation loss in the mid- and high dose groups (38.1-42.6%) in comparison to the control animals (20.6%). However the means were within the range of the individual values of the control animals and were considered not treatment related. The incidence of major malformations and minor anomalies were comparable in all groups. It was concluded that NAA is not teratogenic in pregnant rats at 250 mg/kg/day, the highest dose tested. Therefor the developmental **LOAEL** is >250 mg/k/day and the **NOAEL** is 250 mg/kg/day. The maternal toxicity **LOAEL** 250 mg/kg/day based on decreased body weight gain during the compound administration and the **NOAEL** for maternal toxicity is 50 mg/kg/day. The study report did not provide the purity of the test material, otherwise the study is adequately conducted. The current reviewer agrees with the earlier review (HED 004110) and considers this study **Acceptable/Guideline** to satisfy the guideline requirement for a developmental study in the rat.

10. Prenatal Developmental Toxicity Study - Rabbit

In a prenatal developmental study (MRID 00137822), NAA (Lot # RTS2846AC; 98.55% purity)

was administered by oral gavage to groups (16/group) of artificially inseminated Dutch Belted rabbits (4 ½ to 5 months old) at dose levels of 0, 37.5, 75, or 150 mg/kg/day from days 6 through 27 of gestation. These doses were selected on the basis of a range finding study (MRID 00137821) where groups (5 rabbits/group) were dosed NAA once daily by gavage at dose levels of 0, 28, 80 or 240 mg/kg/day from days 6 through 27 of gestation.

One animal in the range finding study dosed at 240 mg/kg/day aborted on GD 28 following signs of toxicity consisting of hair loss, decreased feces and significant weight loss. In the main study, one low dose animal died on GD 25 and three high dose gravid animals died during the study on GD 20, 22 and 27. Only two of the high dose animals showed signs of toxicity (hair loss on the forelimbs, clear or white nasal discharge with dried material around the nose, decreased defecation and dry red material, presumably died blood, beneath the cage) prior to death. Necropsy observations of the dead animals showed foamy fluid or congested lining in the trachea, congested lungs, fluid in the thoracic and/or abdominal cavities, reddening and/or erosions on the stomach mucosa, mucoid material or fluid in the intestines and pale liver or pitted kidneys. Weights of the pregnant animals varied over the gestation period with some indication of treatment related loss in the high dose. No compound-related abnormalities were observed in the pregnant animals at necropsy. No compound-related effect was observed on implantation or fetal viability. However, in the range finding study, an increase in the mean preimplantaion loss (23.2% at the low dose to 42.1% at the high dose compared to 11.4% in the concurrent control) occurred at all doses in the treated animals and appeared to be treatment related. However, this increased preimplantation loss was considered problematic by the EPA reviewer since historical control data on 343 animals showed a preimplantaion loss of 30.8%. Examination of the fetuses derived from the main study did not reveal any teratogenic effects.

It was concluded that the maternal toxicity **NOAEL** is 75 mg/kg/day based on lethality at the **LOAEL** of 150 mg/kg/day. The teratogenic and fetotoxic **NOAEL** was 150 mg/kg/day based on lack of developmental and fetoxic effects at the highest dose of 150 mg/kg/day tested. This developmental toxicity study in the rabbit is considered **acceptable/guideline.**

11. Bacterial Gene Mutation - *Salmonella typhimurium*

In a microbial/mammalian microsome plate incorporation mutagenicity study (MRID 00042764), *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to 1-naphthaleneacetic acid, (Lot # GN-2095; purity not reported but described as a white powder) 0.5, 2, 8, 40, 200, 1000 or 5000 µg/plate with and without S9 rat liver microsomal activation system. The test material was delivered to the test system in DMSO. In preliminary toxicity screen, strain TA100 showed partial inhibition at 5000 and 1000 µg/plate with very slight inhibition at 200 µg/plate. Strain TA1535 showed partial inhibition at 200 µg/plate and very slight inhibition at 1000 µg/plate. Appropriate positive controls were used in the test system.

NAA was negative in all strains in this test. The study was considered core-minimum in an earlier review (HED 004110). However, the purity of test material was not reported but adequately described as a white powder. Therefore, this study in *Salmonella typhimurium* strains

is considered **Acceptable/Guideline.**

12. *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice

In a mouse micronucleus assay (MRID 00042763), NAA (Lot # GN 2095; purity not reported but described as a white powder) was administered i.p. once daily for two days to groups of four male and four female mice at 60 or 125 mg/kg. The doses selected were based on a preliminary dose range finding study where NAA was administered daily for two days to groups of 10 mice at concentrations of 250 or 125 mg/kg. No overt symptoms or mortality was observed at the 125 mg/kg dose. The test material was delivered to the animals as suspensions prepared in distilled water and administered at 20 ml/kg. Concurrently, triethylenemelamine at 0.5 mg/kg was used as a positive control and water at 20 ml/kg was used as a negative control.

NAA was negative in this micronucleus test. There was no statistical increase in the number of micronuclei per 1000 polychromatic RBC in the treated versus the control animals. The study report did not provide the purity of the test material, otherwise the test is adequately conducted. Therefore the current reviewer agrees with the earlier review (HED 004110) and considers this study to be **Acceptable/Guideline.**

13. Mitotic Gene Conversion - *Saccharomyces cerevisiae*

In a mitotic gene conversion assay (MRID 00042758 &00042759, 00042760) NAA (lot # N-2095, purity not reported: white powder) was tested for mutagenic properties in yeast cells using the D7 strain of *Saccharomyces cerevisiae*. In one test heteroallelic ade 2-40/ade 2-119 diploid strain was used (MRID 00042758). In the second test homoallelic ilv I-292 diploid strain was used (MRID 00042759) and in the third test (MRID 00042760) the heteroallelic diploid trp 5-12/trp 5-27 strain was used. NAA was solubilized in phosphate buffer at pH 7 using DMSO to enhance solubility. In all the tests, NAA was tested in preliminary screen at 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} M. The assay was repeated at the same concentrations.

NAA was not mutagenic in this test system. There was no increase of aberrant cells at any dose over the phosphate buffer control and the DMSO control. The positive control agent NQQ produced significant increase of aberrant cells over the controls. The study was considered **Acceptable** by the original EPA reviewer. However, these assays had several deficiencies (purity of the test material not reported, it was not run with microsomal activation, and it was not run at toxic doses). Therefore these assays are **Unacceptable/Guideline.**

14. Bacterial DNA Repair - *E. coli pol A*

In a bacterial DNA repair assay (MRID 00042761) NAA (lot # GN-2095, purity not reported but described as a white powder) was tested for mutagenic properties in *Escherichia coli polA* in the presence and absence of Aroclor 1254 induced rat liver metabolic activation system. Strains W3110 and p3478 were grown to exponential phase and the test material was applied to test wells at concentrations of 1, 2 or 4 mg/ml in distilled water except for the high dose in 10%

DMSO. Diethylnitrosoamine and ethylmethanesulfonate were used as positive controls for the activated and non-activated systems, respectively. The solvents (DMSO or water) were included as negative controls. NAA did not produce a zone of inhibition in either strain indicating lack of genetic effects in *E. Coli.* It was concluded that NAA is not mutagenic in this assay. The study was considered core-minimum in an earlier review (HED 004110). However, the purity of test material was not reported but adequately described as a white powder. Therefore, this study in *E. coli* is considered **Acceptable/Guideline**.

15. Rodent domonant Lethal Assay - Rat

In a dominant lethal assay (MRID 00042764) Sprague Dawley COBS CD (SD) rats (10/group) were administered NAA (lot # 16388; purity not reported, white powder) orally at doses of 125, 250 or 500 mg/kg/day for 5 days. Concurrently, triethylenemelamine (as a positive control), was administered orally to a group of 10 male rats at 0.8 mg/kg/day for 5 days. Another group of 10 male rats received 0.25% methylcellulose at 20 ml/kg/day for 5 days as a negative control. Twenty four hours after the last dose each male was co-housed with two virgin females for 7 days. The matings were repeated weekly with 2 virgin females for a total of 8 weeks. The females were sacrificed 14 days from mid-week lutea and live and dead implants were counted and recorded.

NAA did not produce dominant lethal effects in the male rats at the doses administered as measured by pre-implantation and post-implantation losses. Post implantation fetal deaths were significantly increased after the first four matings in those groups mated to male rats receiving the positive control substance. It was concluded that NAA is not a dominant lethal chemical in this test. The study report did not provide the purity of the test material, otherwise the test is adequately conducted. Therefore the current reviewer agrees with the earlier review (HED 004110) and considers this study to be **Acceptable/Guideline**.

B

Supplement to HED Document No. 005377 - DER for MRID No. 00103128 - Acute Oral Toxicity Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W Dykstra Date 9/8/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - [Rat] OPPTS 870.1100 [§81-1]; OECD 401.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Napthalene Acetic Acid (95% purity (HED 005337))

SYNONYMS: NAA

CITATION: Mallory, V.; Matthews, R.; Naismith, R.; et al. (1982) Acute OralToxicity Study in Rats (14-Day): Napthalene Acetic Acid: Study No. PH 402-UC-001-82. Pharmakon Research International, Inc. April 29, 1982. MRID 00103128. Unpublished.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In an acute oral toxicity study (MRID 00103128), groups of Sprague Dawley rats (5/sex) were given 1-Naphthyl Acetamide (Lot/Batch #: NOIM1007; white powder; 95% purity (HED 005377)) by single dose gavage in 0.25% methylcellulose (20 ml/kg) at the following doses of 1750, 2250, 3000, 3500, or 4000 mg/kg bw. All animals were observed for up to 14 days post-dosing. Necropsy was performed on all animals.

The oral LD_{50} (95% C.I.) for males and females combined= 2520 mg/kg (2100-3024 mg/kg)

Signs of toxicity were convulsions, piloerection, abnormal gait, twitches, abnormal stance, decreased activity and body tone, arched back, prostration, salivation, ptosis, tremors, hypersensitivity to touch, red exudate in nasal area, ataxia, body drop, straub tail and brown discoloration of genital anal area. Necropsy revealed red adrenals, stomach and intestines filled

and distended, hemorrhages and white foci present on the lungs.

NAA is classified as **TOXICITY CATEGORY III**. This acute oral toxicity study in the rat was originally classified core-minimum (HED 005378). The study is classified **Acceptable/Guideline** and satisfies the OPPTS 870.1100 [§81-1]; OECD 401 requirement for Acute Oral Toxicity

COMPLIANCE: Predated the GLP guidelines.

Supplement to HED Document No. 005377 - DER for MRID No. 00103129 - Acute Dermal Toxicity Study - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/8/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - [Rabbit] OPPTS 870.1200 [§81-2]; OECD 402.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): 1-Naphthyl Acetic Acid (95% purity (HED 005377))

SYNONYMS: NAA

CITATION: Mallory, V.; Matthews, R.; Naismith, R.; et al. (1982) Acute Dermal Toxicity Test in Rabbits: NAA: Study No. PH 422-UC-001-82. Pharmakon Research International, Inc. May 11, 1982. MRID 00103129. Unpublished.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In an acute dermal toxicity study (MRID 00103129), five male and five female Albino New Zealand white rabbits received 2 g/kg of NAA ((Lot/Batch #: NOIM1007; white powder; 95% purity (HED 005377)) on the abraded skin under occlusive wrap for 24 hour exposure. Observations were made at 2, 4, 24 hour after exposure and twice daily thereafter for 14 days. Necropsy was performed on all animals. One animal died on day 11 with no visible signs of toxicity or visible lesions. At termination of study, necropsy revealed fluid filled intestines and stomach distension in one rabbit.

The dermal LD_{50} in the rabbit in this test is greater than 2 g/kg.

NAA is classified as **CATEGORY III for dermal toxicity**. This acute dermal toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the OPPTS 870.1200 [§81-2]; OECD 402 requirement for Acute Dermal Toxicity.

COMPLIANCE: Predated the GLP guidelines.

D

Supplement to HED Document No. 005377 - DER for MRID No. 00103127 - Primary Eye Irritation - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/8/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400 [§81-4]; OECD 405.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): 1-Naphthyl Acetic Acid (96%, white powder)

SYNONYMS: NAA, Napthalene Acetic Acid

CITATION: Myers, R.; Mika, E.; Fowler, E.; et al. (1982) Napthalene Acetic Acid (NAA): Skin and Eye Irritancy Study: Project Report 45-51. May 11, 1982. Pharmakon Research International, Inc. MRID 00103127. Unpublished.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a primary eye irritation study (MRID 00103127), nine New Zealand white rabbits received 100 mg of Napthalene Acetic Acid (Lot # 0010087; 96% purity; white powder) in one eye each. The treated eyes of three of the treated rabbits were washed 20 to 50 seconds after treatment. The treated eyes of the other six animals were unwashed. Observations were made at 1, 2, 3, 4,7 10, 14, and 21 days after treatment.

The test material produced severe corneal opacity in all treated rabbits (washed and unwashed eyes), redness, chemosis, and discharge. These symptoms did not clear completely and persisted in some animals for 21 days. NAA is **corrosive** for the eyes and is classified as **Category I** for eye irritation. This study is classified as **acceptable/guideline** and it satisfies the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Predated the GLP guidelines.

E

Supplement to HED Document No. 006166 - DER for MRID No.: 00153217 Napthalene Acetic Acid - Skin Sensitization Toxicity Study - Guinea Pig. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W Dykstra Date 9/8/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Skin Sensitization Study - Guinea Pig, OPPTS 870.2600 [§81-6], OECD 406.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Napthalene Acetic Acid (98.5%)

SYNONYMS: NAA

CITATION: Myers, R.; Christopher, S. (1984) Naphthalene Acetic Acid (NAA): Dermal Sensitization Study in the Guinea Pig: Project Report 47- 80. Unpublished study prepared by Union Carbide Corporation Bushy Run Research Center. 26 p. July 11, 1984. MRID 00153217. Unpublished

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a skin sensitization study (MRID 00153217) Napthalene Acetic Acid (Lot # RTS2846AA, white powder; 98.5% purity) , was tested on male Hartley Guinea pigs using the modified Buehler method. Three groups of 5 male and females were treated with one of the following substances: test material at 10% w/v suspension of NAA in 0.25% aqueous methyl cellulose, 0.25% aqueous methyl cellulose (vehicle control), or 0.5% w/v suspension of dinitrochlorobenzene in 0.25% aqueous methyl cellulose)positive control). Each group received three 0.3 ml doses of the appropriate material, once a week for 3 weeks during induction phase. Two weeks after third induction phase a challenge dose of the above substances was applied. Observations were made frequently during induction phase and at 24 and 48 hours after challenge phase.

No irritation was produced by the test material or the vehicle control during the induction or challenge phase. Dinitrochlorobenzene produced significant skin reaction increasing in severity with each progressing dose during induction phase and well defined skin reaction at challenge phase. Under the experimental conditions employed, it was concluded that Napthalene Acetic Acid is not a skin sensitizer (contact allergen) in guinea pigs.

The study was classified **Acceptable/guideline** and it meets the Guideline requirements OPPTS 870.2600 [§81-6]/OECD 406 for a dermal sensitization study in the Guinea pig.

COMPLIANCE: Quality Assurance and Confidentiality statements were not provided.

F

Supplement to HED Document No. 004110 - DER for MRID: 00043623 Naphthalene Acetic Acid - 10-Day Range Finding Toxicity Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: 10-Day Range Finding Toxicity Study (Gavage)- Rats; Non-Guideline

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid technical (purity not reported).

SYNONYMS: NAA

CITATION: McElroy, K.E.; Ward, C.O. (1976). Ten-Day Range Finding Study with NAA by Daily Gavage to Rats: HRC # R-4216-4. Huntingdon Research Center. Unpublished Study. 8 pages. August 16, 1976. MRID 00043623.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a range finding toxicity study (MRID 00043623), 1-naphthaleneacetic acid, technical (Lot # NAA 733236; purity not reported) was administered by gavage to Sprague Dawley rats (3/sex/dose) at dose levels of 0, 250, 1000 or 4000 mg/kg bw/day for 10 consecutive days. All surviving rats were necropsied at the end of the study.

All animals at the 4000 mg/kg/day and one female at the 1000 mg/kg/day died after 2 - 3 days. One female from the control group died after 9 days and it was attributed to a probable inadvertent pulmonary gavage (HED 004110 wrongly put this dead female in the 250 mg/kg/day group). None of the animals in the 250 mg/kg/day group died. Clinical signs of toxicity prior to death were dyspnea, ataxia, lethargy and prostration. A dose related depression in body weight gain and food consumption was noted (no statistical analysis was performed). Necropsy of the animals which died during the study and all surviving animals at

the end of the study showed an increase in discoloration of lungs, liver and kidneys, distended bladder (high dose), blood and gas in the GI tract. The maximum tolerated dose would be 250 mg/kg/day. A **LOAEL** or **NOAEL** cannot be derived from this study.

This short term range-finding study is classified **Acceptable/non-Guideline**.

COMPLIANCE: This study predates the GLP guidelines.

G

Supplement to HED Document No. 004110 - DER for MRID: 00043624 Naphthalene Acetic Acid - Subchronic Toxicity Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W Dykstra Date 9/9/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Feeding Toxicity - Rats; OPPTS 870.3100 [§82-1b] (rodents); OECD 408.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid technical (purity not reported).

SYNONYMS: NAA

CITATION: Larson, E.J.; Germano, A. (1979) Ninety-Day Toxicity Study in Rats with Technical Naphthalene acetic acid: Study No. CDC-AM-006-78. Final rept. prepared by CDC Research, Inc. Unpublished Study. March 10, 1979. MRID 00043624.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a subchronic oral toxicity study (MRID 00043624), 1-naphthaleneacetic acid, technical (Lot # not reported; purity not reported) was administered, in the diet, to Sprague Dawley rats (20/sex/dose) at dose levels of 0, 50, 150 or 300 mg/kg bw/day for 13 weeks. Two additional group of 10 rats/sex were administered 0 or 300 mg/kg bw/day and sacrificed after 30 days and necropsied. All surviving rats were necropsied at the end of the study.

All rats survived except for one death in the control group. No abnormal behavior or toxic effects were observe din the treated rats. Fluctuations in food consumption occurred in control ane treated groups. Body weights in males and females of the high dose group were depressed particularly in the females where they gained only one third of the body weight achieved by

the controls. All hematologic values were within the reference limits. Hematocrit, hemoglobin, and/or RBC values in the mid and high dose males and females were slightly reduced, but considered not compound related. Alkaline phosphatase in the high dose group was elevated, probably associated with the rate of body growth. Urinalysis values wee comparable in all groups. There were no visible macroscopic lesions in male rats except for one control male with enlarged spleen and liver and red, depressed areas in the stomach. In the females clear fluid in the uterus (hydrometra) was noted in 3 controls, 2 low dose, 7 mid dose and 5 high dose. These and other lesions (ovarian cyst in one mid dose female, focal omental fat necrosis in one high dose female, one nenocortical cyst in another high dose female) observed were considered not be compound induced. The absolute and relative liver weight in the high dose females appeared to be significantly increased with no histopathological findings.

It was concluded that the **LOAEL** for toxic effects in this study is 300 mg/kg/day based on decreased body weight in both sexes and enlarged liver weights in females. The **NOAEL** is 150 mg/kg/day.

This subchronic toxicity study in the rat was conducted prior to the current testing guidelines. However, the information generated in this study is adequate and it is classified as **Acceptable/Guideline** to satisfy the guideline requirement for a subchronic study in the rat.

COMPLIANCE: This study predates the GLP guidelines.

Supplement to HED Document No. 004110 - DER for MRID: 00136446 Naphthalene Acetic Acid - Subchronic (6-month) Toxicity Study - Dog. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. Date August 4, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. Date 9/9/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Subchronic (6-month) Oral (Gavage) Toxicity - Dogs; OPPTS 870.3150 [§82-1b] (non-rodents); OECD 409.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (98.55%).

SYNONYMS: NAA

CITATION: Morita, D.; Hepler, D.; Beck, L.; et al. (1979) Six Month Oral Toxicity Study of Naphthalene Acetic Acid in Beagle Dogs: Project No. 1395. Elars Bioresearch Laboratories. Unpublished Study. May 3, 1979. MRID 00136446.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a subchronic oral toxicity study (MRID 00136446), 1-naphthaleneacetic acid, technical (Lot # 16388; 98.55% purity) was fed (gelatin capsules) to beagle dogs (4/sex/dose) at dose levels of 0, 50, 150, or 300 mg/kg/day for 180 consecutive days.

Clinical signs of toxicity were evident in the high dose group. These included anorexia lasting several days, tenderness in the mouth while dosing, icteric and pale mucous membranes, steady loss in weight, lethargy, an uncoordinated gait, dark urine, and dark stools. Two of four males and all the females showed some or all of these effects at the end of the study. One dog had a great amount of edema in the hind legs progressing over 3 days until its legs were swollen to approximately the coxo femoral joint. This dog was sacrificed on day 126 of the study. Urine collected from this dog prior to sacrifice showed large amounts of bilirubin,

urobilinogen and a small amount of RBC and blood. These effects are considered to treatment-related.

The mean body weight and body weight gain was significantly depressed in the high dose females ($p < 0.01$) at 2, 3, 4,5 and 6 months in comparison to the control dogs. The male dogs had also reduced body weight and body weight gain during the last two months of the study. Hematological parameters were within reference limits for the four groups. The hematology of the dog that was sacrificed showed slightly increased WBC count with a relative and absolute neutrophilia and lymphopenia which may be compound related. The clinical chemistry analysis showed that alanine amino transferase (SGPT) were elevated at 4 months (slightly) and 6 months (2x the normal value) for the high dose females. The clinical chemistry of the male dog that was sacrificed in moribund condition showed lower protein, cholesterol and glucose and greatly elevated levels of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate amino transferase (SGOT) and SGPT.

Dose-related increases in relative weights of kidneys occurred in both males and females of the high dose group. Dose-related weight increases in liver, adrenals, brain and heart occurred in high dose females. The low dose group males had increased relative kidney weights and the mid dose group females had an increase in relative heart weights. Histopathologisal examination revealed very slight evidence of pericholangistis in the low dose group (2/8), very slight to moderate degree of hepatic insult in the mid dose group (7/8)and slight to severe degree of hepatic insult in the high dose group (8/8). This hepatic insult was characterized by pericholangistis, toxic degenration of hepatocytes and hepatocellular hypertrophy in the mid dose group and additionally centrilobular necrosis, periportal fibrosis in the high dose group and hyperplastic nodule in the male dog that was sacrificed moribund. There was also evidence of squamoid metaplasi in the tracheal epithelium of 2/8 dogs and a slight degree of myocarditis (1/8) in the high dose group. Hyperkeratosis of the skin at the thoroacolumbar junction was seen in 2/8 dogs of the mid dose and 4/8 dogs of the high dose groups.

It was concluded that there was no **NOAEL** derived from this study. The **LOAEL** was 50 mg/kg/day, the lowest dose tested, based on hepatic liver changes (pericholangistis).

This subchronic toxicity study in the dog was conducted prior to the current testing guidelines. However, the information generated in this test is adequate and it is classified as **Acceptable/Guideline** to satisfy the guideline requirement for a subchronic study in the dog.

COMPLIANCE: This study predates the GLP guidelines.

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Supplement to HED Document No. 004110 - DER for MRID: 00042765; Naphthalene Acetic Acid - Prenatal Developmental Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 10, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 10/10/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid technical (purity not reported, white powder).

SYNONYMS: NAA

CITATION: Miller, T.J.; McElroy, K. (1977) Teratology Study with NAA acid(Technical) by Gavage in the Albino Rat. Huntingdon Research Center: HRC # R-4216-4 (1-350). Prepared by Pharmakon Laboratories, Unpublished Study. January 14, 1977 MRID 00042765.

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a prenatal developmental study (MRID 00042765), NAA technical (Lot # NAA 73323G; purity not reported, white powder) was administered by gastric intubation to groups (24/group) of healthy timed pregnant albino CD rats at dose levels of 0, 10, 50 or 250 mg/kg/day in 0.05% sodium carboxymethylcellulose from days 6 through 15 of gestation. The dams were observed daily for signs of toxicity and weighed on day 1, 3, 6-15, 17 and 20 of gestation. On day 20 of gestation the dams were euthanized with ether and the ovaries and uterine contents were immediately examined for viable and nonviable fetuses, resorptions, number of implantations, and number of corpora lutea. Fetuses were examined for visceral and skeletal anomalies using proper techniques.

No deaths or toxic symptoms were reported at any dose level. There was a statistically significant decrease in the mean body weight gain in the 250 mg/kg/day rats with the onset of the compound administration. The dams in the 10 and 50 mg/kg/day groups did not show significant decrease in body weight gain during compound administration but showed a decrease compared to the controls from days 17-20. Litter size and fetal loss were not affected by the treatment. A slight decrease (statistically insignificant) in mean litter size (9.3, 9.3, 8.8 and 7.9 in the control, low-, mid-, and high-dose groups, respectively) was considered unrelated to treatment. There was a statistically increased ($p<0.05$) mean preimplantation loss in the mid- and high dose groups (38.1-42.6%) in comparison to the control animals (20.6%). However the means were within the range of the individual values of the control animals and were considered not treatment related. The incidence of major malformations and minor anomalies were comparable in all groups. It was concluded that NAA is not teratogenic in pregnant rats at 250 mg/kg/day, the highest dose tested. Therefor the developmental **LOAEL** is >250 mg/k/day and the **NOAEL** is 250 mg/kg/day. The maternal toxicity **LOAEL** 250 mg/kg/day based on decreased body weight gain during the compound administration and the **NOAEL** for maternal toxicity is 50 mg/kg/day.

The study report did not provide the purity of the test material, otherwise the study is adequately conducted. The current reviewer agrees with the earlier review (HED 004110) and considers this study **Acceptable/Guideline** to satisfy the guideline requirement for a developmental study in the rat.

COMPLIANCE: This study predates the GLP guidelines.

Supplement to HED Document No. 003864 - DER for MRID: 00137821, 00137822; Naphthalene Acetic Acid - Prenatal Developmental Study - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. Date Sept. 10, 2003
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. Date 9/10/03
Reregistration Branch 4, Health Effects Division (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700a [§83-3b]; OECD 414.

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (98.55%).

SYNONYMS: NAA

CITATION: Schardein, J.; Cuddeback, B.; Aldridge, D.; et al. (1983) Range-Finding Teratology Study in Rabbits: (Naphthalene Acetic Acid): 369-111. International Research and Development Corp., Unpublished Study. October 28, 1983. MRID 00 137821

Schardein, J.; Miller, L.; Allen, S.; et al. (1983) Teratology Study in Rabbits: (Naphthalene Acetic Acid): 369-105. International Research and Development Corp., Unpublished Study. November 28, 1983 MRID 00137822

SPONSOR: Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a prenatal developmental study (MRID 00137822), NAA (Lot # RTS2846AC; 98.55% purity) was administered by oral gavage to groups (16/group) of artificially inseminated Dutch Belted rabbits (4 ½ to 5 months old) at dose levels of 0, 37.5, 75, or 150 mg/kg/day from days 6 through 27 of gestation. These doses were selected on the basis of a range finding study (MRID 00137821) where groups (5 rabbits/group) were dosed NAA once daily by gavage at dose levels of 0, 28, 80 or 240 mg/kg/day from days 6 through 27 of gestation. Animals were observed twice

daily for mortality and once daily for toxic signs during the dosing period. Animals that died were necropsied. Body weights were taken on days 0, 6, 12, 18, 24 and 28. Surviving animals were sacrificed on day 28 and the uterus and ovaries were examined for viable and nonviable fetuses, resorptions, number of implantations, and number of corpora lutea.

One animal in the range finding study dosed at 240 mg/kg/day aborted on GD 28 following signs of toxicity consisting of hair loss, decreased feces and significant weight loss. In the main study, one low dose animal died on GD 25 and three high dose gravid animals died during the study on GD 20, 22 and 27. Only two of the high dose animals showed signs of toxicity (hair loss on the forelimbs, clear or white nasal discharge with dried material around the nose, decreased defecation and dry red material, presumably died blood, beneath the cage) prior to death. Necropsy observations of the dead animals showed foamy fluid or congested lining in the trachea, congested lungs, fluid in the thoracic and/or abdominal cavities., reddening and/or erosions on the stomach mucosa, mucoid material or fluid in the intestines and pale liver or pitted kidneys. Weights of the pregnant animals varied over the gestation period with some indication of treatment related loss in the high dose. No compound-related abnormalities were observed in the pregnant animals at necropsy. No compound-related effect was observed on implantation or fetal viability. However, in the range finding study, an increase in the mean preimplantaion loss (23.2% at the low dose to 42.1% at the high dose compared to 11.4% in the concurrent control) occurred at all doses in the treated animals and appeared to be treatment related. However, this increased preimplantation loss was considered problematic by the EPA reviewer since historical control data on 343 animals showed a preimplantaion loss of 30.8%. Examination of the fetuses derived from the main study did not reveal any teratogenic effects.

It was concluded that the maternal toxicity **NOAEL** is 75 mg/kg/day based on lethality at the **LOAEL** of 150 mg/kg/day. The teratogenic and fetotoxic **NOAEL** was 150 mg/kg/day based on lack of developmental and fetoxic effects at the highest dose of 150 mg/kg/day tested.

This developmental toxicity study in the rabbit is considered **acceptable/guideline** and it satisfies the guideline requirement for a developmental study in the rat (OPPTS 870.3700b [§83-3a]; OECD 414) .

COMPLIANCE: Signed and dated Quality Assurance statement was provided. Confidentiality and flagging statement were not provided.

Supplement to HED Document No. 004110 - DER for MRID No.00042762 - Naphthalene Acetic Acid- Bacterial Gene Mutation Assay. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4 (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: - ***In vitro* Bacterial Gene Mutation** *Salmonella typhimurium*/ mammalian activation gene mutation assay; OPPTS 870.5100 [§84-2]; OECD 471

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (purity not reported, white powder)

SYNONYMS: NAA

CITATION: Matthews, R.J.; Naismith, R.W.; Hoffman, P.A. (1978) Summary Data: Ames Salmonella/Microsome Plate Test (with and without Metabolic Activation) on: Amchem 1-Naphthalene acetic acid, Lot GN-2095, Millmaster Onyx. Pharmakon Laboratories. May 11, 1978. MRID 00042762.

SPONSOR: Union Carbide Agricultural Products Co., Inc., (Aventis), Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a microbial/mammalian microsome plate incorporation mutagenicity study (MRID 00042764), *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to 1-naphthaleneacetic acid, (Lot # GN-2095; purity not reported but described as a white powder) 0.5, 2, 8, 40, 200, 1000 or 5000 µg/plate with and without S9 rat liver microsomal activation system. The test material was delivered to the test system in DMSO. In preliminary toxicity screen, strain TA100 showed partial inhibition at 5000 and 1000 µg/plate with very slight inhibition at 200 µg/plate. Strain TA1535 showed partial inhibition at 200 µg/plate and very slight inhibition at 1000 µg/plate. Appropriate positive controls were used in the test system.

NAA was negative in all strains in this test. The study was considered core-minimum in an earlier review (HED 004110). However, the purity of test material was not reported but

adequately described as a white powder. Therefore, this study in *Salmonella typhimurium* strains is considered **Acceptable/Guideline** and satisfies the guideline requirements OPPTS 870.5100 [§84-2], bacterial reverse mutation.

COMPLIANCE: The study predates the GLP guidelines.

Supplement to HED Document No. 004110 - DER for MRID No.00042763 - Naphthalene Acetic Acid- Micronucleus Assay. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4 (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: - *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice, OPPT 870.5395/ (§84-2) OECD 474

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (purity not reported, white powder)

SYNONYMS: NAA

CITATION: Naismith, R.W.; Matthews, R.J.; Dixon, R.H. (1979) Summary Data: Genetic Toxicology Micronucleus Test (MNT): Study No. PH-309-AM19-NAA. Pharmakon Laboratories. January 30, 1979. MRID 00042763.

SPONSOR: Union Carbide Agricultural Products Co., Inc., (Aventis), Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a mouse micronucleus assay (MRID 00042763), NAA (Lot # GN 2095; purity not reported but described as a white powder) was administered i.p. once daily for two days to groups of four male and four female mice at 60 or 125 mg/kg. The doses selected were based on a preliminary dose range finding study where NAA was administered daily for two days to groups of 10 mice at concentrations of 250 or 125 mg/kg. No overt symptoms or mortality was observed at the 125 mg/kg dose. The test material was delivered to the animals as suspensions prepared in distilled water and administered at 20 ml/kg. Concurrently, triethylenemelamine at 0.5 mg/kg was used as a positive control and water at 20 ml/kg was used as a negative control. All animals were sacrificed by the inhalation of CO_2, six hours after the second dose.

NAA was negative in this micronucleus test. There was no statistical increase in the number of micronuclei per 1000 polychromatic RBC in the treated versus the control animals. The study

report did not provide the purity of the test material, otherwise the test is adequately conducted. Therefore the current reviewer agrees with the earlier review (HED 004110) and considers this study to be **Acceptable/Guideline** and satisfies the guideline requirement Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

COMPLIANCE: The study predates the GLP guidelines.

Supplement to HED Document No. 004110 - DER for MRID No.00042758 - Naphthalene Acetic Acid- Mitotic Gene Conversion - *Saccharomyces cervisiae*. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4 (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: - Mitotic Gene Conversion - *Saccharomyces cervisiae*, OPPTS 870.5575 (§84-2)/OECD none

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (white powder)

SYNONYMS: NAA

CITATION: Naismith, R.W.; Matthews, R.J.; Schneider, C.; et al. (1978) Summary Data: Mitotic Crossing over~Saccharomyces. Pharmakon Laboratories. Unpublished Study. MRID 00042758 & 00042759.

Naismith, R.W.; Matthews, R.J.; Hoffman, P.A. (1978) Summary Data: Mitotic Gene Conversion~Saccharomyces cerevisiae. Pharmakon Laboratories. Unpublished Study. MRID 00042760.

SPONSOR: Union Carbide Agricultural Products Co., Inc., (Aventis), Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a mitotic gene conversion assay (MRID 00042758 &00042759, 00042760) NAA (lot # N-2095, purity not reported: white powder) was tested for mutagenic properties in yeast cells using the D7 strain of *Saccharomyces cerevisiae*. In one test heteroallelic ade 2-40/ade 2-119 diploid strain was used (MRID 00042758). In the second test homoallelic ilv I-292 diploid strain was used (MRID 00042759) and in the third test (MRID 00042760) the heteroallelic diploid trp 5-12/trp 5-27 strain was used. NAA was solubilized in phosphate buffer at pH 7 using DMSO to enhance solubility. In all the tests, NAA was tested in preliminary screen at 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} M. The assay was repeated at the same concentrations.

NAA was not mutagenic in this test system. There was no increase of aberrant cells at any dose over the phosphate buffer control and the DMSO control. The positive control agent NQQ produced significant increase of aberrant cells over the controls. The study was considered **Acceptable** by the original EPA reviewer. However, these assays had several deficiencies (purity of the test material not reported, it was not run with microsomal activation, and it was not run at toxic doses). Therefore these assays are **Unacceptable/Guideline** and do not satisfy the guideline requirements OPPTS 870.5575 [§84-2], for mitotic gene conversion.

COMPLIANCE: The study predates the GLP guidelines.

Supplement to HED Document No. 004110 - DER for MRID No.00042761 - Naphthalene Acetic Acid- Bacterial DNA Repair - *E. coli polA*. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4 (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: - Bacterial DNA Repair - *E. coli polA*, OPPTS 870.5500 (§84-2)/OECD none

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (purity not reported)

SYNONYMS: NAA

CITATION: Naismith, R.W.; Matthews, R.J.; Hoffman, P.A. (1978) Summary Data: Primary DNA Damage, Escherichia coli Plate Test. Pharmakon Laboratories. July 25, 1978. MRID 00042761.

SPONSOR: Union Carbide Agricultural Products Co., Inc., (Aventis), Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a bacterial DNA repair assay (MRID 00042761) NAA (lot # GN-2095, purity not reported but described as a white powder) was tested for mutagenic properties in *Escherichia coli polA* in the presence and absence of Aroclor 1254 induced rat liver metabolic activation system. Strains W3110 and p3478 were grown to exponential phase and the test material was applied to test wells at concentrations of 1, 2 or 4 mg/ml in distilled water except for the high dose in 10% DMSO. Diethylnitrosoamine and ethylmethanesulfonate were used as positive controls for the activated and non-activated systems, respectively. The solvents (DMSO or water) were included as negative controls. NAA did not produce a zone of inhibition in either strain indicating lack of genetic effects in *E. Coli*. It was concluded that NAA is not mutagenic in this assay.

The study was considered core-minimum in an earlier review (HED 004110). However, the purity of test material was not reported but adequately described as a white powder. Therefore, this study in *E. coli* is considered **Acceptable/Guideline** and satisfies the guideline requirements

OPPTS 870.5500 [§84-2], bacterial DNA repair.

COMPLIANCE: The study predates the GLP guidelines.

Supplement to HED Document No. 004110 - DER for MRID No.00042764 - Naphthalene Acetic Acid- Rodent Dominant Lethal Assay. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date Sept. 4, 2003
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: William Dykstra, Ph.D. W. Dykstra Date 9/9/03
Reregistration Branch 4 (7509C)

TXR # 0052103

DATA EVALUATION RECORD

STUDY TYPE: - Rodent Dominant Lethal Assay, OPPT 870.5450/ (§84-2) OECD none

DP BARCODE: D293238
P.C. CODE: 056002 TOX. CHEM. NO.: 589

TEST MATERIAL (PURITY): Naphthalene Acetic Acid (purity not reported, white powder)

SYNONYMS: NAA

CITATION: Naismith, R.W.; Matthews, R.J.; Panasevich, R.E.; et al. (1979). Dominant Lethal Study (1-Napthalene acetic acid -16388): Study No. PH-307-AM-118 NAA. Final Report. February 28, 1979. MRID 00042764.

SPONSOR: Union Carbide Agricultural Products Co., Inc., (Aventis), Research Triangle Park, NC

EXECUTIVE SUMMARY:

In a dominant lethal assay (MRID 00042764) Sprague Dawley COBS CD (SD) rats (10/group) were administered NAA (lot # 16388; purity not reported, white powder) orally at doses of 125, 250 or 500 mg/kg/day for 5 days. Concurrently, triethylenemelamine (as a positive control), was administered orally to a group of 10 male rats at 0.8 mg/kg/day for 5 days. Another group of 10 male rats received 0.25% methylcellulose at 20 ml/kg/day for 5 days as a negative control. Twenty four hours after the last dose each male was co-housed with two virgin females for 7 days. The matings were repeated weekly with 2 virgin females for a total of 8 weeks. The females were sacrificed 14 days from mid-week lutea and live and dead implants were counted and recorded.

NAA did not produce dominant lethal effects in the male rats at the doses administered as measured by pre-implantation and post-implantation losses. Post implantation fetal deaths were significantly increased after the first four matings in those groups mated to male rats receiving

the positive control substance. It was concluded that NAA is not a dominant lethal chemical in this test. The study report did not provide the purity of the test material, otherwise the test is adequately conducted. Therefore the current reviewer agrees with the earlier review (HED 004110) and considers this study to be **Acceptable/Guideline** and satisfies the guideline requirement Test Guideline OPPTS 870.5450 (§84-2) .

COMPLIANCE: The study predates the GLP guidelines.

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R099724

Chemical:	**1-Naphthaleneacetic acid**
PC Code:	**056002**
HED File Code	**13000 Tox Reviews**
Memo Date:	**01/29/2004**
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