2

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OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

TXR No.: 0052146

DATE: November 20, 2003

SUBJECT: **1-Naphthaleneacetic Acid (Including Esters and Salts):** HED Toxicology Chapter for the Reassessment Eligibility Decision (RED)
PC Code 056001, 056002, 056007, 056008,
Registration Case #: 0379

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TASK ID: DP Code D293237

Attached is the Toxicology Chapter for 1-naphthaleneacetic acid to support the Reassessment Eligibility Decision (RED).

1-Naphthaleneacetic Acid

PC Code: 056001, 056002, 056007, 056008

Toxicology Disciplinary Chapter for the Reassessment Eligibility Decision (RED) (or Registration Support) Document

Date completed:
November 20, 2003

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah , Date November 20, 2003
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TABLE OF CONTENTS

1.0 HAZARD CHARACTERIZATION

1- Naphthaleneacetic acid including its sodium and potassium salts, its acetamide and its ethyl ester (referred to hereafter as the NAA group) are growth regulators used to reduce pre-harvest drop of fruit, fruit thinning, induce flowering, prevent fruiting of ornamentals, and control resprouting (sucker pruning). Target crops are apples, pears, citrus, olives, prunes, cherries, pomegranates and ornamental woody plants.

The toxicology data base is adequate to characterize the toxicity of the NAA group. NAA has low acute oral toxicity (Toxicity Category III), inhalation (Category IV), and dermal (Category III) routes of exposure. NAA is not a skin irritant (Category IV). It is not a dermal sensitizer. The NAA acid and its sodium salt were found to be irritating to the eye, but not the NAA ethyl ester (Category IV). The NAA acetamide was found to be an eye irritant in one test and a non-eye irritant in another test. Acute oral doses of 1000 mg/kg and above of NAA or its derivatives produced a number of acute signs including 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 and anal areas.

The registration standard for *NAA, its salts, ester, and acetamide* of July 1981, stated that all the compounds are combined...because they are structurally related and because the Agency has determined that long term toxicity testing should serve for all members of this group of chemicals. The metabolism studies of the acid and its acetamide and the ethyl ester in animals provide supporting evidence that the toxicity of these various forms of NAA would be expected to be similar since all are metabolized to the acid form and eliminated from the body within 36 to 48 hours after exposure as glycine and glucuronic acid conjugates. Repeated exposure oral toxicity studies primarily resulted in decreased body weights and body weight gains accompanied by decreased food consumption. These occurred generally at doses of 200 mg/kg/day and above in both subchronic and chronic oral feeding studies. The major target organs of repeated oral exposure were the liver (enlarged liver, increased liver weight with histopathological changes: vacuolation of the periportal hepatocytes, pericholangitis, sinusoidal histiocytosis in dogs) stomach (mucosal gland dilation), lung (focal alveolar macrophages). Repeated oral exposure at doses of 75 mg/kg/day and above also resulted in decreased hematocrit and hemoglobin along with reduced RBC count in rats and dogs and hypocellularity of the bone marrow in dogs. An increased incidence of uterine endometrial stromal polyps occurred in female rats at 303 mg/kg/day dietary feeding for two years. These are considered to be benign proliferative lesions of no carcinogenic concern. There was no developmental toxicity at highest doses tested of 250 mg/kg/day in the rat or 150 mg/kg/ day of NAA in the rabbit administered by gavage during the critical gestation period of pregnancy. Reproductive effects of NAA sodium salt occurred at 210 mg/kg/day and were limited to reduced litter survival and pup weight throughout lactation in both generations of offspring in a two generation reproduction study. Parental effects (reduced body weight gain and reduced food consumption) occurred at the same dose. NAA and its

acetamide and the ethyl ester were tested for mutagenic effects in a gene mutation bacterial assay, mouse lymphoma assay and mouse erythrocyte micronucleus assay and were not mutagenic. Additionally NAA was tested for mitotic gene conversion and dominant lethality in rats and found to be negative.

2.0 REQUIREMENTS . The requirements (CFR 158.690) for NAA are in the following table. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data Requirements for Naphthaleneacetic Acid Group

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (Rodent)	yes	yes
870.3150 Oral Subchronic (Non-Rodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	yes	yes*
870.3465 28-Day Inhalation	yes	no
870.3700a Developmental Toxicity (Rodent)	yes	yes
870.3700b Developmental Toxicity(Non-rodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (Rodent)	yes	yes
870.4100b Chronic Toxicity (Non-rodent)	yes	yes
870.4200a Oncogenicity (Rat)	yes	yes
870.4200b Oncogenicity (Mouse)	yes	yes**
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5395 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5450 Mutagenicity—Dominant Lethal Assay	yes	yes
870.5575 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.6100a Acute Delayed Neurotox. (Hen)	no	not applicable
870.6100b 90-Day Neurotoxicity Hen)	no	not applicable
870.6200a Acute Neurotoxicity. Screening Battery (Rat)	no	not applicable
870.6200b 90 Day Neurotoxicity Screening Battery (Rat)	no	not applicable
870.6300 Develop. Neurotoxicity	no	not applicable
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	not applicable
Special Studies for Ocular Effects	no	not applicable

* the 21-day dermal satisfies this requirement. ** a NCI published study satisfies this requirement

3.0 DATA GAP(S)

The toxicological data base for NAA is adequate for hazard characterization except for a 28-day or a 90-day inhalation toxicity study.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for NAA acute toxicity is considered complete (Table 2). No additional studies are required at this time.

Table 2: Acute Toxicity Data of NAA

Guideline No.	Test Chemical	MRID #(S).	Results	Toxicity Category
870.1100 Acute Oral	NAA	00103128	LD_{50} = 2520 mg/kg	III
	NAA acetamide	43495901	LD_{50} = >5000 mg/kg	IV
	NAA Na Salt	00108829	LD_{50} = 933-1350 mg/kg	III
	NAA Ethyl Ester	43494101	LD_{50} = 2186 mg/kg	III
870.1200 Acute Dermal	NAA	00103129	LD_{50} = > 2000 mg/kg	III
	NAA acetamide	43495902	LD_{50} = > 2000 mg/kg	III
	NAA Na Salt	00108829	LD_{50} = > 2000 mg/kg	III
	NAA Ethyl Ester	43494102	LD_{50} = > 2000 mg/kg	III
870.1300 Acute Inhalation	NAA	--	--	--
	NAA acetamide	43495903	LC_{50} = > 2.17 mg/L	IV
	NAA Na Salt	--	--	--
	NAA Ethyl Ester	43494103	LC_{50} = > 2.13 mg/L	IV
870.2400 Primary Eye Irritation	NAA	00103127	corrosive	I
	NAA acetamide	00103051	corrosive	I
	NAA acetamide	43495904	minimally irritating	IV
	NAA Na Salt	00108829	corrosive	I
	NAA Ethyl Ester	43494104	minimally irritating	IV
870.2500 Primary Skin Irritation*	NAA	00103127	not a skin irritant	IV
	NAA acetamide	--	--	--
	NAA Na Salt	00108829	not a skin irritant	IV
	NAA Ethyl Ester	00103053	not a skin irritant	IV
870.2600 Dermal Sensitization	NAA	00153217	not a skin sensitizer	NA
	NAA acetamide	43495905	not a skin sensitizer	NA
	NAA Na Salt	--	--	--
	NAA Ethyl Ester	43494105	not a skin sensitizer	NA

NAA has low to moderate toxicity in experimental animals by the oral (Category III), dermal (Category III) and inhalation routes (Category IV). It is not a skin irritant (Category IV) and is

not a skin sensitizer either. However the majority of test indicate that it is corrosive to the eyes (Category I)

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete except for a 28-day or a 90-day inhalation toxicity study.

870.3100: 90-Day Oral Toxicity - Rat

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 rats survived except for one death in the control group. No abnormal behavior or toxic effects were observed in the treated rats. Fluctuations in food consumption occurred in control and 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.

In a subchronic toxicity study (MRID 43896001), **1-Naphthaleneacetamide** (Lot # I940415; 98.7% a.i.) was administered to CRL:CD BR rats (10/sex/dose) by feeding at dose levels of 0, 250, 1,000, or 4,000 ppm (mean measured concentrations of 0, 19.1, 73.8, or 292.1 mg/kg/day for males and 0, 20.4, 81.5, or 313.5 mg/kg/day for females) for 90 days. In the 4,000 ppm treatment groups, mean body weights were lower for males (10-15%) and females (9-12%) throughout the study, compared to controls. Final mean body weight gains were lower for males (14%) and females (20%). In addition, food consumption was consistently

reduced for males (11-28%) and females (2-20%) throughout the study. Mean relative liver weights were significantly increased in both 4,000 ppm males (14%; $p \leq 0.05$) and females (32%; $p \leq 0.01$) with accompanying histopathological changes consisting of enlarged (hypertrophied) centrilobular hepatocytes with an abundance of fine granular eosinophilic cytoplasm. No rats died during the study. No treatment-related differences in clinical appearance, ophthalmology, hematology, clinical blood chemistry or urinalysis parameter or gross pathology were observed in any treatment group. No neoplastic tissue was observed in any of the treatment groups. The **LOAEL** is 4,000 ppm (292.1 mg/kg/day), based on decreased body weight, reduced body weight gain, reduced food consumption, and increased relative liver weights with histopathological changes in both sexes. The **NOAEL** is 1,000 ppm (73.8 mg/kg/day).

In a 90 day oral (diet) toxicity study (MRID 42932601), male and female Crl:CDBR (Sprague-Dawley) rats (10/group/sex) received **1-Napthaleneacetic Acid Sodium Salt** (Lot # 214001; 96.44% purity) either 0, 200, 2000, or 8000 ppm (equivalent to 13.9, 136.6, and 564.9 mg/kg/day for males and 15.2, 149.3, and 583.4 mg/kg/day for females, respectively) for 13 weeks. Dose levels were based on a 14-day dietary study with 1-Na-NAA, no information was provided. No clinical toxicity or mortality related to the treatment was reported in any of the groups. The absolute body weights for both sexes in the high dose groups were statistically significantly different from control from day 7 for males and day 14 for females, approximately 18 to 20 % lower than control for both sexes at the end of 90 days. Systemic toxicity was noted at 2000 ppm and above based on statistically significant ($p<0.05$ -$p<0.01$) decreased hematocrit and hemoglobin, increased liver weights and vacuolation of the periportal hepatocytes along with hypertrophy of the cells of the adrenal cortex zona glomerulosa in females and increased kidney weights in males. Further, at the 8000 ppm dose group there were decreased body weight gains (25-30% decrease), decreased food consumption and decreased food efficiency along with decreased red blood cell parameters, platelet counts, total serum protein and albumin. The liver and kidney weights (absolute and relative to body weight) were increased in high dose males and females along with hepatocellular hypertrophy (4/10 in high dose males and females) and vacuolation of the periportal hepatocytes (10/10 in mid and high dose females) and hypertrophy of the cells of the adrenal cortex zona glomerulosa (6/10 in the mid dose females and 7/10 in the high dose females, and 3/10 in high dose males) and urinary bladder mucosa (9/10 in high dose males and 7/10 in high dose females). The **LOAEL** for systemic toxicity is 2000 ppm (136.6 mg/kg/day for males and 149.3 mg/kg/day for females) with a **NOAEL** for systemic toxicity of 200 ppm (13.9 mg/kg/day for males and 15.2 mg/kg/day for females) based on decreased hematocrit and hemoglobin, increased liver weights and vacuolation of the periportal hepatocytes along with hypertrophy of the cells of the adrenal cortex zona glomerulosa.

In a subchronic oral toxicity study (MRID 43896002), **1-naphthaleneacetic acid, ethyl ester** (Lot # AM 315002; 100% ai) was administered, in the diet, to CRL:CD BR rats (10/sex/dose) at dose levels of 400, 2000 or 8000 ppm for 13 weeks. The actual average doses at the end of the study were 19-25 mg/kg/day for the 400 ppm group, 92-123 mg/kg/day for the 2000 ppm

group, and 388 - 519 mg/kg/day for the 8000 ppm group, for males and females, respectively. Lower body weight, body weight gain, food consumption and food efficiency were observed for the 8000 ppm males and females compared to the controls. Body weights for the males were 7-13% lower and for the females were 9-21% lower than the corresponding controls throughout the study. Body weight gains were significantly reduced for both sexes at various weekly intervals throughout the study, and by the end of the study, were 18 and 38% lower for males and females, respectively, than the control gains. Mean food consumption by the males and females was 5-11 and 15-22 lower, respectively, than the control values for most weekly intervals; decreased food efficiency for both sexes was observed at most weekly intervals. Increased relative and/or absolute liver and kidney weights were observed for the 2000 and 8000 ppm treatment groups. Relative liver weights were 21% higher for the 2000 ppm females and 20 and 58% higher for the 8000 ppm males and females, respectively, compared to the control weights. Absolute liver weights were 13 and 24% higher for the 2000 and 8000 ppm females, respectively, compared to the controls. Relative kidney weights were higher for both sexes from the 2000 ppm (11% higher) and 8000 ppm (17-23% higher) treatment groups. Absolute kidney weight for the 2000 ppm males was 16% higher than the controls but was not increased for the 8000 ppm males. No associated macroscopic or microscopic changes were observed in the livers and kidneys of rats from any treatment group. Decreased red blood cell counts, hemoglobin, and hematocrits for both sexes from the 2000 and 8000 ppm groups were not considered clinically significant, but appeared to be treatment-related since they were dose-dependent. The 8000 ppm males and females also exhibited increased total bilirubin (19-21% higher) in conjunction with reduced red blood cell counts, hemoglobin, and hematocrits. No other treatment-related effects were observed during the study. No rats died during the study. No differences in clinical signs, ophthalmology, macroscopic or microscopic pathology were observed between any of the treatment and control groups. Decreased urine protein in the 2000 and 8000 ppm males was not observed in the corresponding females. The **LOAEL** for this study is 8000 ppm (594 mg/kg/day) for male and female rats, based on lower body weight, suppressed body weight gain, and reduced food consumption as compared to the controls. Absolute and/or relative liver and kidney weights for both sexes were seen at this dose but were not accompanied by any macroscopic or microscopic changes, however, males and females at this dose also exhibited increased total bilirubin (19-21% higher) in conjunction with reduced red blood cell counts, hemoglobin, and hematocrits. The **NOAEL** is 2000 ppm (144 mg/kg/day) for both sexes.

870.3150: 90-Day Oral Toxicity - Dog

In a subchronic oral toxicity study (MRID 00136446), **1-naphthaleneacetic acid**, technical (Lot # 16388; purity not reported) 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.

In a subchronic toxicity study (MRID 43895901), **1-Naphthaleneacetamide** (Lot/Batch # I940415; 98.7% a.i.) was administered via capsule to four beagle dogs/sex/dose at dose levels of 0, 30, 100, or 300 mg/kg/day for 13 weeks. In the 300 mg/kg/day treatment group, all livers contained accumulations of a hemosiderin-containing pigment in the reticuloendothelial cells and bilirubin in the intracanicular spaces. The spleens of 3/4 males and 2/4 females also contained hemosiderin and hematopoiesis was increased in the bone marrow in 3/4 animals of both sexes. Decreases in red blood cell counts, hematocrit, and hemoglobin occurred in both sexes. Platelet

counts and mean corpuscular volumes were increased in both sexes. Total bilirubin was increased in 1/4 males and 3/4 females, but the increases were significant ($p<0.05$ or 0.01) only for females. Body weights were reduced in males only. Clinical signs of toxicity in both sexes were soft or liquid feces. No treatment-related effects were observed in the 30 or 100 mg/kg/day treatment groups. No dogs died during the study. No treatment-related differences in clinical appearance, food consumption, ophthalmology, urinalysis parameters, organ weights, or gross pathology were observed in any treatment group. No neoplastic tissue was observed in any of the treatment groups. The **LOAEL** is 300 mg/kg/day, based on increased platelet count, decreased red cell parameters, and increased mean corpuscular volume which correlate with histopathological changes observed in the liver, spleen, and bone marrow in both sexes.

In a 13 week oral toxicity study (MRID 42983801), 6-month old beagle dogs (4/group/sex) received by capsule either 0, 25, 150, or 450 mg/kg/day 1-Naphthaleneacetic Acid Sodium Salt (Lot# 214001, Purity - 96.44% 1-NAA & 1.79% 2-NAA). Due to inappetence at the high dose, the feeding regimen was altered for several high dose animals to reduce excessive weight loss. Dose levels were based on a previous 6 month study with Naphthalene Acetic Acid (MRID 00136446) where male and female dogs receiving 50, 150, or 300 mg/kg/day experienced severe toxicity at the 300 mg/kg/day dose. These included depressed body weight and body weight gain, histopathological changes and mortality. In the current study with NAA sodium salt, none of the animals died. Regurgitation of intact or partially digested capsules and emesis were the most common treatment- related clinical sign and was toxicologically significant at the high dose. Body weight gain was significantly reduced in the high dose males (15% of controls, $p<0.05$) and females (29% of controls, $p<0.05$) accompanied by decreased food consumption and food efficiency. There were statistically significant increases in relative organ weight for the liver, adrenals, thyroids/parathyroids, kidneys and brain and a decrease in gonad absolute and relative weights for the high dose males. The high dose females only showed a statistically significant increase in relative kidney weights, although the relative weights for other organs did show a tendency towards an increase. Gross examination of the genital tract revealed small prostates, small testes and epididymides in all high dose males. Microscopic examination in these males revealed an increased incidence of hypospermatogenesis, characterized by less spermatogonia and spermatocytes and were associated with aspermia in the epididymides. These may be secondary effects to the condition of the animals, but deserve further examination. Systemic toxicity was noted at 150 mg/kg/day and above based on lesions of the gastrointestinal tract (ulcerative duodenitis and acute or erosive gastritis), hypocellularity of the bone marrow along with changes in liver enzymes (increased alkaline phosphatase in the high dose group), increased relative liver weights, histopathological changes of the liver (single cell necrosis, centrilobular necrosis, pigment accumulation, extramedullary hematopoiesis and mononuclear or mixed cell infiltration), depression in erythrocyte parameters (red blood cell count, hemoglobin and hematocrit levels in high dose females with a slight similar effect in males), decreased body weight gains, food consumption and food efficiency, inappetence and emesis in the high dose group. The **NOAEL for systemic toxicity is 25 mg/kg/day with a LOAEL for systemic toxicity of 150 mg/kg/day** based on lesions of the gastrointestinal tract and hypocellularity of the

bone marrow.

In a subchronic oral toxicity study (MRID 43914901), **1-naphthaleneacetic acid, ethyl ester** (Lot/Batch # AM 315002; 97.75% ai) was fed (gelatin capsules) to beagle dogs (4/sex/dose) at dose levels of 0, 40, 125, or 400 mg/kg/day for 13 weeks. All dogs survived the treatment. Treatment-related clinical signs were limited to soft or liquid feces particularly in males and to a lesser extent in females at the high dose of 400 mg/kg/day. Male dogs in the 40, 125, or 400 mg/kg/day treatment groups had a 4- to 5.5-fold increase in soft/liquid feces (maximum 65 instances during 13 weeks in the 400 mg/kg/day group) compared to the control group. For females, there was one incident of soft/liquid feces in the control group, five in the 40 mg/kg/day group, eight in the 125 mg/kg/day group, and 19 in the 400 mg/kg/day group during the 13-week study. A treatment-related lower body weight gain (20% less than the control) was seen in the males and females of the high dose group. Males in the 40 or 125 mg/kg/day treatment group were 25-29% heavier, and males in the 400 mg/kg/day treatment group were 20% lighter than males in the control group; all three groups consumed 19% more food than the control during the study. Female dogs in the 400 mg/kg/day treatment groups consumed 11% less food over the course of the study. Male dogs in the 40, 125, or 400 mg/kg/day treatment groups had significantly ($p < 0.05$ or 0.01) lower red blood cell, hemoglobin, and hematocrit levels, and lower mean platelet volumes (MPV) than the controls throughout the study. In the high dose males at 12 weeks, these were 18%, 17%, 17% and 22% lower than the controls for RBC, hemoglobin, hematocrit and MPV levels, respectively. Although , these parameters were within the historical range values for this dog type, they were at the lower end of the range and may suggest anemic affects caused by the administration of this material at this dose. Low white blood cell counts in female dogs in the 125 or 400 mg/kg/day treatment groups after 12 weeks of treatment were also within expected biological ranges. No other treatment-related responses were observed during the study. No differences were observed in clinical blood chemistry, ophthalmology, urine volume or chemistry, organ weights, or macroscopic or microscopic organ morphology between dogs in the treated and the control groups. No neoplastic tissue was observed. The **LOAEL** for this study is 400 mg/kg/day, based on soft/liquid feces and the depressed body weight gains of male and female dogs at this treatment level. Additionally some blood parameters (RBC, hemoglobin, hematocrit and mean platelet volume) were all depressed in the male dogs at this level. The **NOAEL** was 125 mg/kg/day.

870.3200: 21/28-Day Dermal Toxicity – Rat

In a repeated dose dermal toxicity study (MRID 43581001), **1-Naphthaleneacetamide** (Lot # I940415; 98.71% ai) was applied to the shaved skin of Crl:CD BR rats (5/sex/dose) at dose levels of 0, 100, 300, or 1000 mg/kg for 6-6.5 hours/day, 5 days/week, for 3 weeks. No treatment-related effects were observed at any dose level. There were no clinical signs of toxicity, and body weights, body weight gains, and food consumption were similar between the treated and control groups. No differences were observed in hematology parameters or clinical blood chemistry. Skin irritations occurred at similar rates in rats in all groups. Although males in the

1000 mg/kg treatment group had absolute liver weight which was 16.4% heavier ($p < 0.05$) than the control, no accompanying anatomical or functional changes were observed, and the mean liver weights of females in the 1000 mg/kg treatment group were lower than the control. No other differences in the organ weights, and no differences in macroscopic or microscopic organ morphology were observed between rats in the treated and the control groups. No neoplastic tissue was observed at any dose level. Ophthalmoscopic examinations and urinalysis were not performed during the study. No **LOAEL** was established. The **NOAEL** was the highest treatment level, 1000 mg/kg body weight.

In a 21 day dermal toxicity study (MRID# 43134701), male and female Crl:CDBR rats (5/group/sex) received either 0, 100, 300, or 1000 mg/kg/day **1-Naphthaleneacetic Acid Sodium Salt** (96.44% 1-NAA & 1.79% 2-NAA) applied to clipped, unabraded dorsal surface of the skin, 5days/week for 3 weeks. Doses were based on a 7-day dermal range finding study in rats where no overt signs of toxicity or dermal irritation was noted at doses of 250, 500 and 1000 mg/kg/day. No treatment-related or clinical signs of toxicity were observed in any of the animals. Systemic toxicity was noted in the high dose group as reduced body weight gain (76.3% of the controls in the males and 71.5% of the controls in females) and reduced food efficiency. Dermal toxicity was noted in the high dose group as microscopic changes of the skin of the treated areas. These changes included minimal to slight hyperplasia of the sebaceous gland and minimal to slight hyperplasia and hyperkeratosis of the epidermis. The **Systemic Toxicity LOAEL** is 1000 mg/kg and the **Systemic Toxicity NOAEL** is 300 mg/kg based on reduced body weight gain and food efficiency. The **Dermal Toxicity LOAEL** is 1000 mg/kg and the **Dermal Toxicity NOAEL** is 300 mg/kg based on microscopic changes in the skin.

In a repeated dose dermal toxicity study (MRID 43581002), **1-naphthaleneacetic acid, ethyl ester** (Lot # 315002; 97.75% ai) was applied to the shaved skin of Crl:CD BR rats (5/sex/dose) at dose levels of 0, 100, 300, or 1000 mg/kg for 6-6.5 hours/day, 5 days/week, for 3 weeks. For all treatment groups, there were no clinical signs of toxicity, and body weights, body weight gains, and food consumption were similar to the controls. There were no differences in hematology parameters, clinical blood chemistry, organ weights, or macroscopic or microscopic organ morphology between rats in the treated and the control groups. No neoplastic tissue was observed. Ophthalmoscopic examinations and urinalysis were not performed during the study. Treatment-related dermal irritation was seen in the treated skin of all animals exposed to 1-Naphthaleneacetic acid ethyl ester. As the dose level was increased, the incidence and/or severity of epidermal hyperplasia and hyperkeratosis, sebaceous gland hyperplasia, and dermal inflammation in skin from the treated areas increased in the treated rats compared to the controls. In general, the severity of the reactions increased from minimal/slight to slight/moderate with increasing dose rate. No systemic responses were observed. Therefore, the **LOAEL** for systemic toxicity is >1000 mg/kg/day and the **NOAEL** for systemic toxicity is 1000 mg/kg/day. The **LOAEL** for dermal irritation is 100 mg/kg, based on the presence of treatment-related dermal irritation in the treated skin of rats in the 100, 300, and 1000 mg/kg treatment groups. No **NOAEL** for dermal irritation was established.

870.3465: 90-Day Inhalation Toxicity – Rat

There are no studies available regrading the subchronic inhalation toxicity of the NAA class of chemicals. Therefore this study is considered a data gap.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. There was no evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure. No developmental effects occurred at doses that exceeded maternally toxic doses.

870.3700a: 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. 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.

870.3700b: 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. 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.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. There was no increased qualitative or quantitative offspring toxicity in a 2-generation reproduction study with the 1-naphthaleneacetic acid, sodium salt. Parental and offspring toxicity occurred at similar doses. No additional studies are required at this time.

870.3800: Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 43796301) **1-Na-NAA** (Lot # 214001; 96.44% a.i.)

was administered to 35 Crl:CD®BR, rats/sex/group in diet at dose levels of 0, 100, 1000 and 3000 ppm [0, 7, 69 and 210 mg/kg/day for males and 0, 8, 81 and 239 mg/kg/day for females, respectively]. The dose levels were selected on the basis of previous toxicity studies in rats. At 3000 ppm (HDT), treatment-related decreases in body weight gain and food consumption were observed in the P_1 and P_2 females during premating and gestation periods and decrease in body weight gain in P_2 males during the premating period. Reductions in P_2 male and female premating body weight gain, although appearing systemic in nature, may have been secondary to developmental toxicity in these animals. Reduced survival and growth were observed in both F_1 and F_2 offspring. No adverse effects were noted at ≤1000 ppm. **Systemic and reproductive/developmental LOAEL** = 3000 ppm (210 mg/kg/day for males, 239 mg/kg/day for females), based upon reduced body weight gain and food consumption in parental animals and reduced litter survival, and pup weight throughout lactation in both generations of offspring. **Systemic and reproductive/developmental NOAEL** = 1000 ppm (69 mg/kg/day for males, 81 mg/kg/day for females).

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. The chronic toxicity of 1-naphthaleneacetic acid, sodium salt was investigated in rats and dogs.

870.4100a: Chronic Toxicity – Rat

In a combined chronic toxicity/oncogenicity study (MRID 44157501), **1- Naphthaleneacetic acid sodium salt** (1-Na-NAA) (96.44% 1-NAA; 1.79% 2-NAA w/w; Lot no. 214001) was administered to Crl:CD® BR rats (80/sex/dose) in the diet at concentrations of 0, 100, 1000, or 5000 ppm (corresponding to 0, 4.4, 43.8, and 224.5 mg/kg/day for males and 0, 5.6, 55.8, and 303.6 mg/kg/day for females). An interim sacrifice was performed at 12 months on 20 rats/sex/dose; terminal sacrifice (main study) was after 20.5-23 months due to the high mortality and poor health in the treated and control groups. There were no treatment-related effects on survival or clinical observations. High-dose females had lower mortality than the controls ($p \leq 0.05$). Weekly body weights of the high-dose males were significantly lower for days 14-119 and 238-259 (≤ 8.8%; $p \leq 0.05$ or 0.01), but their overall weight gain was similar to that of the controls. The low- and mid-dose females' weekly body weights and overall weight gains were within 7.4% and 14% of controls, respectively ($p \leq 0.05$ or 0.01). High-dose females, however, had lowered weekly body weights (≤ 35%; $p \leq 0.01$), total weight gain (61% of controls), and overall food consumption and efficiency (15% and 36% lower than controls, respectively). Serum triglyceride levels were about 50% lower than control levels at 6 and 12 months in high-dose males, and were 66-78% lower at 12 and 18 months in high-dose females ($p \leq 0.05$ or 0.01). The urine protein content of high-dose females was decreased from 12 months to terminal sacrifice to only 4.1-6.1% of control values ($p \leq 0.05$ or 0.01). These clinical chemistry changes had no histopathological correlates and their toxicological significance is unknown. High-dose

males and females had a significantly increased incidence and severity of stomach mucosal gland dilation ($p \leq 0.05$). The incidence of focal alveolar macrophages (in some cases accompanied by focal chronic inflammation) was increased in mid- and high-dose females, and was correlated at the high dose with an increased incidence of grossly observed lung nodules ($p \leq 0.05$ or 0.01). The incidence of focal alveolar macrophages was also slightly increased in high-dose males ($p = 0.071$). The **LOAEL** is 5000 ppm (224.5 mg/kg/day for males and 303.6 mg/kg/day for females), based on an increased incidence of stomach (mucosal gland dilation) and lung lesions (focal alveolar macrophages) in both sexes of rats, and on lowered body weight gain and food efficiency in females. The corresponding **NOAEL** is 1000 ppm (43.8 mg/kg/day for males and 55.8 mg/kg/day for females). The only neoplastic finding ($p \leq 0.01$) was an increased incidence of uterine endometrial stromal polyps in high-dose females (2/60, 1/60, 3/60, 13/60 at 0, 100, 1000, 5000 ppm, respectively). The longer survival time of the high-dose females (about 88 days) did not account for the greater incidence of these benign neoplasms. The rats were dosed adequately, judging by the toxicologic findings in both sexes of high-dose rats.

870.4100b: Chronic Toxicity - Dog

In a chronic toxicity study (MRID 43744201), **1-napthaleneacetic acid, sodium salt** (Lot # 214001; 96.44% ai) was administered (gelatin capsules) to beagle dogs (4/sex/dose) at dose levels of 0, 15, 75, or 225 mg/kg/day for 52 weeks. At 225 mg/kg/day, Na-NAA administration resulted in gross pathological changes in the stomach of one male and one female and histopathological changes in the stomachs of four males and one female. The latter were characterized by mucosal atrophy (3) and congestion (1) in males and hemorrhaging in the female. Slight sinusoidal histiocytosis was observed in the livers of four males and three females. Both males and females exhibited a high incidence of emesis and capsule regurgitation at the 225 mg/kg/day dose level. At 75 mg/kg only males exhibited dose-related toxic response to Na-NAA as characterized by stomach lesions in three animals consisting of necrosis of the fundic or pyloric epithelium and by slight sinusoidal histiocytosis in the liver of two males. No other definitive treatment-related changes were noted in organ weights or gross pathological changes. All microscopic tissue abnormalities, other than those mentioned, occurred randomly and sporadically in all study groups. No neoplastic tissue was observed in beagles in the treatment or control groups. No dogs died during the study. No treatment-related differences were observed between the clinical appearance, body weights, food consumption, biochemistry, hematology, urinalysis, or ophthalmology of the treated and control animals. The **LOAEL** is 75 mg/kg/day in males and 225 mg/kg/day in females, based on emesis, capsular regurgitation incidences, gross and histopathologic changes in stomachs, and sinusoidal histiocytosis in livers. The **NOAEL** is 15 mg/kg/day in males and 75 mg/kg/day in females.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: A guideline study for the oncogenicity of NAA in mice is not available. However, a published NCI carcinogenicity study of NAA

acetamide in mice and a guideline chronic/oncogenicity of Na NAA in rats study are considered adequate for the evaluation of the oncogenicity of the NAA group. In these two studies the tested NAA compounds were not carcinogenic in mice or rats.

870.4200a: Carcinogenicity Study - Rat

This study is described above in the chronic studies section. An increased incidence of uterine endometrial stromal polyps occurred in female rats at 303 mg/kg/day dietary feeding of Na NAA for two years. According to HED consulting pathologist, Dr. John Pletcher these are considered to be benign proliferative lesions of no carcinogenic concern (email to Dr. William Burnam of HED on 04/04/2002). Na NAA was not carcinogenic in the rat.

870.4200b: Carcinogenicity (feeding) - Mouse

There is an NCI study published in 1969 where NAA acetamide was tested at one dose (maximum tolerated dose: according to the published article) as part of a testing program of 120 compounds. Only the preliminary results were published (Innes *et al*, Innes JR, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallotta AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, Peters J. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Natl Cancer Inst. 42: 1101-1114). The test materials were administered to two hybrid strains of mice : C57BL/6 x C3H/Anf and C57BL/6 x AKR (18/sex/hybrid strain). The mice were administered NAA acetamide at one week of age by stomach intubation at 464 mg/kg/day until weaning at 4 weeks of age and administered the NAA acetamide in the diet at 1298 ppm (equivalent to 195 mg/kg/day at the conversion rate of 0.15 mg/kg for 1ppm) for approximately 18 months. Gross and hostopathologic examination of the mice at the end of the feeding period did not reveal a significant increase in tumors over the controls.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The 1-naphthaleneacetic acid data base for Mutagenicity is considered adequate.

Gene Mutation

GLN 870.5100, MRID 43581006: NAA Acetamide MRID 00042761: NAA MRID 43581004: NAA Ethyl Ester	No mutagenic effect was noted with or without microsomal activation at concentrations up to the toxic range of 5000 micrograms/plate in the initial tests or in the confirmatory assay.

Chromosomal Aberrations

GLN 870.5395 MRID 43581005 NAA Acetamide MRID 00042763 NAA MRID 43581003 NAA Ethyl Ester	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice. There was no indication that NAA technical or the acetamide or the ethyl ester induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.

GLN 870.5300 MRID 43580202: NAA Acetamide MRID 43580201: NAA Ethyl Ester	*In Vitro* mammalian cell gene mutation - L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay. NAA acetamide was tested up to cytotoxic levels (≥1250 µg/mL -S9 and ≥150 µg/mL +S9). NAA Ethyl ester was tested up to cytotoxic levels (100 µg/mL -S9 and ≥300 µg/mL +S9). Both were non mutagenic without S9 activation system, but positive with S9 activation system at or above 100 ug/mL for the acetamide and 300 ug/mL for the ethyl ester.

GLN 870.5450 MRID 00042764 NAA	Rodent Dominant Lethal Assay. NAA did not produce dominant lethal effects in mice at oral doses of 125, 250 or 500 mg/kg/day as measured by pre implantation and post implantation losses

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: There are no neurotoxicity studies available but the chronic and subchronic studies do not indicate neurotoxic effects by the NAA group of chemicals.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for NAA metabolism is considered to be complete. No additional studies are required at this time.

In a study (MRID 43963301) conducted to examine the metabolism and disposition of **1-naphthaleneacetamide**, five male and five female Sprague-Dawley rats were given either a single 1 or 100 mg/kg bw oral dose, or a 14-day repeated dose (1 mg/kg/day). Groups of male and female rats were subjected to the dosing regimens above using [^{14}C] ring labeled -1-naphthaleneacetamide (Batch No. 94-516-38-10; 99.7% radiochemical purity, specific activity 55.5 mCi/mmol), and nonlabeled test article (Batch No. KP 0100487, chemical purity not available). Excretion, tissue distribution, and metabolite profiles were determined. There were no biologically significant treatment-related effects noted during the course of the study. Overall recovery of administered radioactivity was an excellent 97.2-101%. 1-Naphthaleneacetamide was readily absorbed and excreted within 36 hours following a single 1 mg/kg bw, a 14-day repeat

oral dose of 1 mg/kg bw, or a single 100 mg/kg bw oral dose. Following single or multiple oral low doses (1 mg/kg bw) of [C^{14}]-1-naphthaleneacetamide, urinary excretion accounted for 70.8-74.1% of the administered radioactivity suggesting that a multiple exposure regimen did not affect the absorption/excretion processes. Urinary excretion was unaffected following a single 100 mg/kg dose with 66.2-69.5% of the administered radioactivity excreted in urine. Excretion via the feces accounted for the remainder of the administered radioactivity in all treatment groups (21.6-26.2%). Excretory patterns did not exhibit gender-related variability but reflected delayed absorption in the high-dose group. Because tissue burdens were very low at termination, neither 1-naphthaleneacetamide nor its metabolites appear to undergo significant sequestration. Both urinary and fecal metabolites were quantified by HPLC and most were identified using HPLC and HPLC/MS in conjunction with known standards. Urinary metabolism involved amide cleavage followed by glycine conjugation with the glycine conjugate being the major metabolite of the low and repeat doses (13.7-47.3% of the administered radioactivity). The glucuronide conjugate was also a major metabolite at the low doses (4.5-7.0% of administered). For feces, the major metabolite detected was the dihydrodiol of naphthaleneacetamide (3.6-11.3% of administered. Parent compound was detected at low concentrations (0.7-1.9% of administered) only in feces. Extraction efficiencies appeared to be excellent and most components in the matrices examined (urine and feces) were adequately quantified and characterized. The available data, based upon studies using labeled 1-naphthaleneacetamide, affirmed the metabolism pathway proposed by the investigators.

In another study (MRID 43961701) conducted to examine the metabolism and disposition of **1-naphthaleneacetic acid, ethyl ester**, male and female Sprague-Dawley rats were given a single 1 or 100 mg/kg bw oral dose, or a 14-day repeated dose (1 mg/kg/day). Groups of male and female rats were subjected to the dosing regimens above using [^{14}C] ring labeled -1-naphthaleneacetic acid, ethyl ester (Batch No. CSL-94-516-33-25, 99.3% radiochemical purity, specific acttivity 56.2 mCi/mmol), and nonlabeled test article (Batch No. GAB 69-34-02, chemical purity not available). Excretion, tissue distribution, pharmacokinetic parameters, and metabolite profiles were determined. There were no biologically significant treatment-related effects noted during the course of the study. Overall recovery of administered radioactivity was an excellent 98.6-101.8%. 1-Naphthaleneacetic acid, ethyl ester was readily absorbed and excreted within 36 - 48 hours following a single 1 mg/kg bw, a 14-day repeat oral dose of 1 mg/kg bw, or a single 100 mg/kg bw oral dose. Following single or multiple oral low doses (1 mg/kg bw) of [C^{14}]-1-naphthaleneacetic acid, ethyl ester, urinary excretion accounted for 67.6-85.3% of the administered radioactivity. Urinary excretion was unaffected following a single 100 mg/kg bw dose with 61.8-78% of the administered radioactivity excreted in urine. Excretion via the feces accounted for the remainder of the administered radioactivity excreted by all treatment groups (12.3-35.2%). Excretory patterns did not exhibit gender-related variability for the low dose groups although a minor difference was observed at the high dose. Excretion patterns of the high-dose group reflected delayed absorption. Because tissue burdens were very low at termination, neither 1-naphthaleneacetic acid, ethyl ester nor its metabolites appear to undergo significant sequestration. Both urinary and fecal metabolites were quantified by HPLC,

TLC and most were identified using HPLC, GC/MS, and HPLC/MS in conjunction with known standards. The major pathway of metabolism involved ester cleavage followed by glycine and glucuronide conjugation at the low and low repeat doses. At the high dose, glucuronide conjugation appeared to play a more important role following ester cleavage. Parent compound was detected at low concentrations (0.5-4.7% of administered) only in feces. Extraction efficiencies appeared to be excellent and most components in the matrices examined (urine and feces) were adequately quantified and characterized. The available data, based upon studies using labeled 1-naphthaleneacetic acid, ethyl ester, affirmed the metabolism pathway proposed by the investigators.

There are two published reports dealing with the metabolism of NAA in animals. In one study (Dixon *et al*, 1977), carboxy -^{14}C-1-naphthylacetic acid (aqueous equivalent NaOH solution) at 100 mg/kg was administered intramuscularly to 6 primate species (rhesus monkey: 1M, 1F; cynomolgus monkey: 1F; squirrel monkey: 2F; capuchin: 2F; marmoset: 1M and bushbaby: 1M, 1F), and intraperitoneally to cats (2F, 1M), rat (3F) and fruit bat (1F, 1M), orally to the rabbit (2F) and orally to 2 human males at 5 mg/individual. Urine was collected for 24 hours and analyzed for radioactivity and metabolites, by liquid scintillation counting, chromatography, radiochromatography scanning, and reverse isotope dilution. In most species tested, 60-100% of the administered radioactivity was excreted in the urine by the end of 48 hours. **The glucuronic acid conjugate** was the major urinary metabolite in man, rhesus monkey, marmoset, rabbit, rat, and fruit bat. In the cat, no glucuronic acid conjugate was detected; turine and glycine conjugates were the major excretion products. The **1-Naphthylacetyl glycine** conjugate was a major urinary metabolite (>20%) in the cat, squirrel and bushbaby monkey and a minor metabolite in rabbit, rat, capuchia and marmoset monkey. **1-Naphthylacetylglutamine** conjugate was formed only in the cynomolgus , squirrel and capuchin monkeys and marmoset in amounts not exceeding 3% of the administered dose. **1-Naphthylacetylturine** was excreted by all species except the rabbit, rat and the fruit bat. It was a major excretion product (>6%) in the squirrel and capuchin monkeys, the marmoset and the cat. In addition, when female rats were administered intraperitoneally doses of 5-500 mg/kg, bile duct cannulation showed that 10-44% of the radioactivity was present in the bile 3 hours after injection, while 0.6-32% was present in the urine. At higher doses, urinary glucuronic acid predominated whereas at the lower doses the glycine conjugates predominated. In the bile, the glucuronic acid conjugate was the major metabolite (>80% of the bile radioactivity), and the glycine conjugate was a minor metabolite (<4% of the bile radioactivity). There was no analysis of the fecal radioactivity reported.

In another study (Lethco and Brouwer, 1966) carboxy -^{14}C-1-naphthylacetic acid metabolism was investigated in male rats. ^{14}C-NAA (neutralized with NaOH) was administered orally by stomach intubation at 0.1, 1.0, 100 and 250 mg/rat (2 rats/dose, weighing 250-280 g). Urine and feces were collected for 3 days. For bile cannulation study, ^{14}C-NAA was administered orally to 8 and 7 rats (weighing 350-435 g) at 0.1 and 100 mg/ rat, respectively, and urine and bile were collected at 2 and 6 hours after administration. Radioactivity was analyzed by liquid scintillation counting, column and paper chromatography and enzymatic analysis. Within 3 days, 71-90% of

the administered ^{14}C was excreted in the urine. At the lower doses (0.1-100 mg/kg) most of the radioactivity was excreted during the first 24 hours, while at the higher dose (250 mg/kg), excretion was highest on the second day. Fecal excretion accounted for 3-10% at the 0.1-1.0 mg/kg doses and 14-21% of the administered dose at the 100 and 259 mg/kg doses. After the third day, no radioactivity was detected in the feces or urine at any dose. Fractionation of the urinary radioactivity by column chromatography and subsequent paper chromatography, UV spectral analysis and B-glucuronidase enzyme hydrolysis, revealed that 70-93% of the urinary radioactivity was **NAA glycine conjugate** and **NAA glucuronic acid conjugate**. The glucuronic acid conjugate predominated at the two high doses and the glycine conjugate predominated at the lower dose. Minor amounts of unchanged NAA and two other minor unidentified metabolites were also detected in the urine. The fecal radioactivity was not characterized. In the bile cannulation experiment, excretion of radioactivity into the bile and urine varied by the administered dose. At the low dose of 0.1 mg/kg radioactivity in the urine was nearly four times the radioactivity detected in the bile after 2 hours, while at the higher dose of 100 mg/kg the ratio was reversed. At the high dose a maximum of 29% of the administered radioactivity was recovered at 6 hours, while a maximum of 54% was recovered at the low dose at 2 hours. At the low dose, the **NAA glycine conjugate** was the major metabolite and the **NAA glucuronic conjugate** was a minor metabolite, while in the bile the preponderance of these two metabolites was reversed. Also unchanged NAA was detected in the bile but not in the urine at both doses. At the high dose the **NAA glucuronic conjugate** was the major metabolite in both urine and bile while the **glycine conjugate** was a minor metabolite.

870.7600: Dermal Absorption - Rat

No studies were available

4.10 Special/Other Studies

a. Published Studies. Two metabolism studies and a tumoreginicity study in mice described above were identified in the published literature.

5.0 HAZARD ENDPOINT SELECTION

a. Acute Reference Dose (aRfD) (General Population). A developmental study in the rat, described above (MRID 00042765) is selected for deriving the aRfD. On the basis of this study, the dose selected is 50 mg/kg/day based on decreased body weight gain at 250 mg/kg/day during the gestation period. This dose and endpoint is protective of the general population and is representative of the exposure duration of concern (effects occurred during administration of NAA during short period of exposure). This was also the only available study on NAA with short exposure duration. An uncertainty factor of 100 (10X for interspecies extrapolation and 10x for intraspecies extrapolation) is applied.

Acute RfD = $\frac{50 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.5 mg/kg**

b. Chronic Reference Dose (cRfD). A one year oral feeding study in dogs, described above (MRID 43744201) is selected for deriving the cRfD. On the basis of this study, the dose selected is 15 mg/kg/day based on stomach lesions in 75% of the males consisting of necrosis of the fundic or pyloric epithelium and by slight sinusoidal histiocytosis in the liver of 50% of the males occurring at 75 mg/kg/day of oral feeding of the NAA sodium salt. The sodium salt also appeared to be the more toxic in subchronic testing among the NAA group of chemicals. A chronic study in rats with NAA sodium salt showed a NOAEL of 44-56 mg/kg/day based on increased incidence of stomach (mucosal gland dilation) and lung lesions (focal alveolar macrophages) in both sexes, and on lowered body weight gain and food efficiency in female rats at 224 - 303 mg/kg/day. Therefore, this dose and endpoint is appropriate for protecting the general population from dietary chronic exposure to NAA group of chemicals. An uncertainty factor of 100 (10X for interspecies extrapolation and 10x for intraspecies extrapolation) is applied.

Chronic RfD = $\frac{15 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.15 mg/kg/day**

c. Short-Term Dermal (1-30 days) Exposure. A 21-day dermal toxicity study (MRID 43134701), described above, is selected for deriving the dermal dose for risk assessment. In this study, the systemic **NOAEL** was 300 mg/kg/day based on reduced body weight gain and food efficiency at the **LOAEL** of 1000 mg/kg/day. Therefore, the dermal dose for risk assessment is 300 mg/kg/day. A margin of Exposure (MOE) of 100 is applied.

Intermediate and long term dermal exposures from the use of this chemical are not applicable, since it is used only during growing seasons.

d. Inhalation Exposure. Only short term (1-30 days) exposure assessment is required, since longer term exposures are not applicable due to the seasonal use of this chemical. For this purpose, the prenatal developmental study (MRID 00042765) in rats, described above, is selected for assessing this type of exposure. In that study, the **NOAEL** for maternal toxicity is 50 mg/kg/day based on decreased body weight gain during the compound administration at 250 mg/kg/day. Therefore, the dose selected for short term inhalation risk assessment is 50 mg/kg/day with an MOE factor of 100. Since this dose is selected from an oral toxicity study, a 100% absorption factor is applied for the inhalation risk assessment.

f. Recommendation for Aggregate Exposure Risk Assessments. Short term dermal and inhalation exposures can be aggregated since the endpoint of concern (reduced body weight gain)

is the same for these exposure routes.

5.1 Endpoint Selection Table.

See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

A dermal absorption factor is not required, since a dermal toxicity study was available to assess dermal exposure risk.

5.3 Classification of Carcinogenic Potential

NAA has not been referred to the HED CARC. A guideline bioassay in rats and a published bioassay in mice do not indicate a carcinogenic concern. NAA is also negative for mutagenicity.

6.0 FQPA CONSIDERATIONS

The toxicology database for NAA is adequate for FQPA considerations.

6.1 Special sensitivity to Infants and Children

There is low concern (and no residual uncertainty) for pre- and/or postnatal toxicity resulting from exposure to NAA group of chemicals. The available data provided no indication of increased susceptibility (quantitative or qualitative) to rats or rabbits to *in utero* exposure to NAA group of chemicals or to pre and post-natal exposure in rat reproduction studies. Therefore, the special FQPA safety factor is **not applied** to risk assessments for this chemical.

6.2 Recommendation for a Developmental Neurotoxicity Study (DNT)

A developmental neurotoxicity study is not required since there was no evidence of neurotoxicity or neuropathology from the available studies and there is no concern or residual uncertainties for pre/post-natal toxicity.

7.0 OTHER ISSUES: None

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9.0 APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

TOXICOLOGY PROFILE
Naphthaleneacetic Acid Group chemicals , TECHNICAL GRADE
November 20, 2003

pc 056003: K salt No Studies available
pc 056004: NH_4 salt No Studies available

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Acute - oral	**MRID 43495901** LD_{50} > 5050 mg/kg Category III	**MRID 00103128** LD_{50} (95% C.I.) = 2520 mg/kg (2100-3021) .	**MRID 00108829** LD_{50}: Males 1.35 (1.12–1.64) Females 0.933 g/kg (0.631-1.38)	**MRID 43494101** LD_{50} 2186 (1907-2506) mg/kg Category III
Acute - Dermal	**MRID 43495902** LD_{50} > 2020 mg/kg Category III	**MRID 00103129** LD_{50} is greater than 2 g/kg. Category III.	**MRID 00108829** dermal LD_{50} = > 2 g/kg. Category III	**MRID 43494102** LD_{50} > 2020 mg/kg. Category III
Acute - Inhal.	**MRID 43495903** LC_{50} > 2.17 mg/L Category IV			**MRID 43494103** LC_{50} > 2.13 mg/L Category IV
Eye Irritation	**MRID 00103051 corrosive Category I MRID 43495904** minimally irritating Category IV	**MRID 00103127 corrosive Category I**	**MRID 00108829 corrosive Category I**	**MRID 43494104** minimally irritating Category IV
Derm. Irritation		**MRID 00103127** Non-irritating **Category IV**	**MRID 00108829** Non-irritating **Category IV**	**MRID 00103053 & 00103218.** non-irritating **Category IV**
Sensitization	**MRID 43495905** not a skin sensitizer. No positive control. **Unacceptable**	**MRID 00153217** not a skin sensitizer		**MRID 43494105** not a skin sensitizer. No positive control. **Unacceptable**

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
90-day - rat	**MRID 43896001** 0, 250, 1,000, or 4,000 ppm (0, 19.1, 73.8, or 292.1 mg/kg/day for males and 0, 20.4, 81.5, or 313.5 mg/kg/day for females). **LOAEL** is 4,000 ppm (292.1 mg/kg/day) decreased bw , bw gain & food consumption, and increased relative liver weights with adaptive histopathological changes in both sexes. **NOAEL** is 1,000 ppm (73.8 mg/kg/day)	**MRID 00043624** 0, 50, 150, or 300 mg/kg/day to SD rats (20/sex/dose) **LOAEL** for toxic effects 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.	**MRID 42932601** 0, 200, 2000, or 8000 ppm (13.9, 136.6, and 564.9 for males and 15.2, 149.3, and 583.4 mg/kg/day for females). **LOAEL** for systemic toxicity = 2000 ppm (136.6 for males and 149.3 mg/kg/day for females) with a **NOAEL** for systemic toxicity of 200 ppm (13.9 for males and 15.2 mg/kg/day for females) based on decreased hematocrit and hemoglobin, increased liver weights and vacuolation of the periportal hepatocytes along with hypertrophy of the cells of the adrenal cortex zona glomerulosa.	**MRID 43896002** 0, 400, 2000 or 8000 ppm (Average doses at study end were 19-25; 92-123 ; and 388 - 519 mg/kg/day for males-females). **LOAEL**= 8000 ppm (594 mg/kg/day), based on lower bw, bw gain, and food consumption. males and females at this dose also exhibited increased total bilirubin (19-21% higher) in conjunction with reduced RBC counts, hemoglobin, and hematocrits. **NOAEL**= is 2000 ppm (144mg/kg/day).
10-day range finding - rat		**MRID 00043623** 0, 250, 1000 or 4000 mg/kg bw/day by gavage for 10 days (3 rats/sex/dose). Death of all high dose rats, one female in the mid dose and none in the low dose. Dose related depression in body weight gain and food consumption. Discoloration of lungs, liver and kidneys, distended bladder (high dose), blood and gas in the GI tract. The MTD would be 250 mg/kg/day.		

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
90-day - dog	**MRID 43895901** 0, 30, 100, or 300 mg/kg/day for 13 weeks. **LOAEL** is 300 mg/kg/day, based on increased platelet count, decreased red cell parameters, and increased mean corpuscular volume which correlate with histopathological changes observed in the liver, spleen, and bone marrow in both sexes. The **NOAEL** is 100 mg/kg/day.	**MRID 00136446** 0, 50, 150, or 300 mg/kg/day **for 6 months** to beagle dogs (4/sex/dose) by gelatin capsules. The **LOAEL** was 50 mg/kg/day, the lowest dose tested, based on hepatic liver changes (pericholangistis). No **NOAEL** derived from this study.	**MRID 42983801** 0, 25, 150, or 450 mg/kg/day. **LOAEL** for systemic toxicity =150 mg/kg/day based on lesions of the GI tract and hypocellularity of the bone marrow. **NOAEL** for systemic toxicity is 25 mg/kg/day .	**MRID 43914901** 0, 40, 125, or 400 mg/kg/day for 13 weeks. **LOAEL**= 400 mg/kg/day, based on soft/liquid feces and depressed body weight gains of male and female dogs. Blood parameters (RBC, hemoglobin, hematocrit and mean platelet volume) were all depressed in the male dogs at this level. **NOAEL** = 125 mg/kg/day.
21-day - dermal	**MRID 43581001** 0, 100, 300, or 1000 mg/kg for 6-6.5 hours/day, 5 days/week, for 3 weeks. No **LOAEL** was established. The **NOAEL** was the highest treatment level, 1000 mg/kg body weight.		**MRID 43134701** 0, 100, 300, or 1000 mg/kg for 6-6.5 hours/day, 5 days/week, for 3 weeks. **LOAEL** for systemic toxicity is 1000 and **NOAEL** = 300 mg/kg/day based on reduced bw gain and food efficiency. **LOAEL** for dermal toxicity = 1000 mg/kg Dermal Toxicity **NOAEL** = 300 mg/kg based on microscopic changes in the skin.	**MRID 43581002** 0, 100, 300, or 1000 mg/kg for 6-6.5 hours/day, 5 days/week, for 3 weeks. **LOAEL** for systemic toxicity is >1000 mg/kg/day and **NOAEL** =1000 mg/kg/day. **LOAEL** for dermal irritation = 100 mg/kg, based on the presence of treatment-related dermal irritation in the treated ski. No **NOAEL** for dermal irritation was established.
28-day inhal.	Not available			

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Develop.-rat		**MRID 00042765** 0, 10, 50 or 250 mg/kg/day gastric intubation to pregnant rats (24/group). Developmental **LOAEL** is >250 mg/k/day and the **NOAEL** is 250 mg/kg/day. Maternal toxicity **LOAEL** 250 mg/kg/day based on decreased body weight gain during the compound administration and the **NOAEL** is 50 mg/kg/day.		
Develop. - Rabbit		**MRID 00137821, 00137822** doses 0, 37.5, 75 or 150 mg/kg/day maternal toxicity **NOAEL** = 75 mg/kg/day based on lethality at the **LOAEL** of 150 mg/kg/day. The teratogenic and fetotoxic **LOAEL** = >150 mg/kg/day and **NOAEL** = 150 mg/kg/day.		
Reproduction			**MRID 43796301** 0, 100, 1000 or 3000 ppm [0, 7, 69 or 210 and 0, 8, 81 or 239 mg/kg/day for males and females]. **Systemic and repro./develop. LOAEL** = 3000 ppm (210 & 239 mg/kg/day for males & females), based upon reduced bw gain and food consum. in parental animals and reduced litter survival, and pup weight throughout lactation in both generations of offspring. **Systemic and repro./develop. NOAEL** = 1000 ppm (69 & 81 mg/kg/day for males & females)	

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Chronic/Onco - rat			**MRID 44157501** 0, 100, 1000, or 5000 ppm (0, 4.4, 43.8, and 224.5 mg/kg/day for males and 0, 5.6, 55.8, and 303.6 mg/kg/day for females). **LOAEL** = 5000 ppm (224.5 mg/kg/day for males and 303.6 mg/kg/day for females), based on an increased incidence of stomach (mucosal gland dilation) and lung lesions (focal alveolar macrophages) in both sexes, and on lowered bw gain and food efficiency in females. **NOAEL**= 1000 ppm (43.8 mg/kg/day for males and 55.8 mg/kg/day for females). Increased incidence ($p \leq 0.01$) of uterine endometrial stromal polyps in high-dose females (2/60, 1/60, 3/60, 13/60 at 0, 100, 1000, 5000 ppm, respectively).	

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Chronic - mouse	**NCI study . (Innes *et al* 1969).** NAA acetamide was tested at one dose (MTD according to the published article) as part of a testing program of 120 chemicals. Only the preliminary results were published. The test materials were administered to two hybrid strains of mice : C57BL/6 x C3H/Anf and C57BL/6 x AKR (18/sex/hybrid strain). The mice were administered NAA acetamide at one week of age by stomach intubation at 464 mg/kg/day until weaning at 4 weeks of age and administered the NAA acetamide in the diet at 1298 ppm for approx. 18 months. Gross and hostopath. examination of the mice at the end of the feeding period did not reveal a significant increase in tumors over the controls.			
Chronic - dog			**MRID 43744201** 0, 15, 75, or 225 mg/kg/day. **LOAEL=** 75 mg/kg/day in males and 225 mg/kg/day in females, based on emesis, capsular regurgitation incidences, gross and histopathologic changes in stomachs, and sinusoidal histiocytosis in livers. **NOAEL=** 15 mg/kg/day in males and 75 mg/kg/day in females.	

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Gene mutation-bacterial	**MRID 43581006** *Salmonella* five doses 100-5000 ug/plate. No mutagenic effect with or without S9 activation	**MRID 00042761** *Escherichia coli polA*. Strains W3110 and p3478 at 1, 2 or mg/ml. Not mutagenic. **MRID 00042762** *Salmonella.* At 0.5-5000 ug/plate. Not mutagenic:		**MRID 43581004** five doses 33-5000 ug/plate. No mutagenic effect with or without S9 activation
Gene mutation - mammalian: mouse lymphoma cells	**MRID 43580202** -S9: not mutagenic. +S9 mutagenic at 100 ug/mL and above			**MRID 43580201** -S9: not mutagenic. +S9 mutagenic at 300 ug/mL and above
erythrocyte micronuleus mice	**MRID 43581005** ip injections 250, 500 or 1000 mg/kg to 5 mice/sex. Lethargy and death at high dose. Did not induce a clastogenic or aneurogenic effect.	**MRID 00042763** ip injections 60 or 125 mg/kg to 4 mice/sex. No overt aymptoms at high dose. Negative.		**MRID 43581003** ip injections 305, 610, or 1220 mg/kg to 5 mice/sex. Lethargy and death (48%) at high dose. Did not induce a clastogenic or aneurogenic effect
Mitotic gene conversion: *Saccharomyces cervisiae*		**MRID 00042758, 00042759, 00042760** NAA was tested at 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} M.. NAA was not mutagenic in this test system. **Unacceptable**. No purity, not run at toxic dose, no S9 activation		
Rodent dominant lethal assay		**MRID 00042764** oral doses of 125, 250, or 500 mg/kg/day to 10 male rats/dose for 5 days. NAA did not produce dominant lethal effects as measured by pre implantation and post implantation losses.		

Study	pc 056001: acetamide	pc 056002: NAA	pc 056007: Na salt	pc 056008: ethyl ester
Metabolism	**Dixon *et al.*1977. NAA ^{14}C as Na salt.** 60-100% of the AD was excreted in the urine by the end of 48 hours. **The glucuronic acid conjugate (GAC)**: major urinary metabolite in man, rhesus monkey, marmoset, rabbit, rat, and fruit bat. In th cat, no **GAC** was detected; but turine and glycine conjugates The **glycine** conjugate was a major urinary metabolite (>20%) in the cat, squirrel and bushbaby monkey and a minor metabolite in rabbit, rat, capuchia and marmoset monkey. **1-NAA glutamine** conjugate was formed only in the cynomolgus , squirrel and capuchin monkeys and marmoset in amounts not exceeding 3% of the AD. **1-NAA turine** was excreted by all species except the rabbit, rat and the fruit bat. It was a major excretion product (>6%) in the squirrel and capuchin monkeys, the marmoset and the cat. When female rats were given ip doses of 5-500 mg/kg, bile duct cannulation showed that 10-44% of the radioactivity was present in the bile 3 hours after injection., while 0.6-32% was present in the urine. At the higher doses urinary GAC predominated whereas at the lower doses the glycine conjugates predominated. In the bile the GAC was the major metabolite (>80% of the bile radioactivity) and the glycine conjugate was a minor metabolite (<4% of the bile radioactivity). There was no analysis of the fecal radioactivity. **Lethco and Brouwer, 1966. carboxy -^{14}C-1- NAA as NA salt** in male rats. Within 3 days, 71-90% of the AD was excreted in the urine. At the lower doses (0.1-100 mg/kg) most of the radioactivity was excreted during the first 24 hours, while at the higher dose (250 mg/kg), excretion was highest on the second day. Fecal excretion was 3-10% at the 0.1-1.0 mg/kg doses and 14-21% of the AD at the 100 and 250 mg/kg doses. After the third day, no radioactivity was detected in the feces or urine at any dose. 70-93% of the urinary radioactivity was **NAA glycine conjugate** and **NAA GAC**. The GAC predominated at the two high doses and the glycine conjugate predominated at the lower dose. Minor amounts of NAA and two other minor unidentified metabolites were detected in the urine. Bile cannulation experiments demonstrated biliary metabolism and excretion of the test material. At the high dose a maximum of 29% of the AD was recovered at 6 hours, while a maximum of 54% was recovered at the low dose at 2 hours. At the low dose, the NAA glycine conjugate was the major urinary metabolite and the NAA GAC was a minor metabolite, while in the bile the preponderance of these two metabolites was reversed. Unchanged NAA was detected in the bile but not in the urine at both doses. At the high dose the NAA GAC was the major metabolite in both urine and bile while the glycine conjugate was a minor metabolite. MRID 43961701. Rats (5/sex) were given a single 1 or 100 mg/kg bw oral dose of [^{14}C] ring labeled -1-naphthaleneacetic acid, ethyl ester, or a 14-day repeated dose (1 mg/kg/day) of unlabeled material followed by a single dose of the labeled material. Overall recovery of AD was 98.6-101.8%. NAA ethyl ester was readily absorbed and excreted within 36 - 48 hours following all exposure regimens (urinary excretion: 67.6-85.3% of the AD at the low dose and 61.8-78% of the AD at the high dose). Fecal excretion was 12.3-35.2% of the AD. Tissue radioactivity was very low. The major pathway of metabolism involved ester cleavage followed by glycine and glucuronide conjugation at the low and low repeat doses. At the high dose, glucuronide conjugation appeared to play a more important role following ester cleavage. Parent compound was detected at low concentrations (0.5-4.7% of administered) only in feces. MRID 43963301. Rrats (5/sex) were given either a single 1 or 100 mg/kg bw oral dose, or a 14-day repeated dose (1 mg/kg/day) using **[^{14}C] ring labeled -1-naphthaleneacetamide (NAAD).** Overall recovery of the AD was 97.2-101%. NAAD was readily absorbed and excreted within 36 hours (urinary excretion: 70.8-74.1% of the AD at the low dose, single or multiple, 66.2-69.5% of the AD excreted in urine at the high dose). Fecal excretion was 21.6-26.2% of the AD. Tissue radioactivity was very low (<0,5% of the AD). Metabolism involved amide cleavage followed by glycine conjugation (13.7-47.3% of the AD) glucuronide conjugation (4.5-7.0% of the AD at the low dose and 12.8-18.1% of the AD at the high dose inthe urine). For feces, the major metabolite detected was the dihydrodiol of naphthaleneacetamide (3.6-11.3% of the AD). Parent compound was detected at low concentrations (0.7-1.9% of administered) only in feces.			

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Chemical:	**1-Naphthaleneacetamide; 1-Naphthaleneacetic acid; Sodium 1-naphthaleneacetate; 2-Methyl-1-naphthaleneacetamide**
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