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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

**MEMORANDUM**

March 30, 2004

**SUBJECT:** **Naphthalene Acetates** HED Risk Assessment for Reregistration Eligibility Document (RED) PC Codes:0 56001, 056002, 056003, 056004, 056007, 056008; DP Barcode No: 293881 Reregistration Case 0379

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Attached is Health Effects Division's (HED's) risk assessment of naphthalene acetates for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This document was reviewed by the Lower Risk Pesticide Focus Group, an expedited process used for lower risk pesticide chemicals. The document has been revised in response to Focus Group comments. This document has also been revised to address comments submitted by AMVAC dated February 22, 2004. This is a screening level risk assessment in which high-end assumptions were used for most key parameters. HED is confident that this analysis does not underestimate the risk associated with exposure to naphthalene acetates.

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## 1.0 EXECUTIVE SUMMARY

This assessment provides information to support the issuance of a Reregistration Eligibility Decision Document for naphthalene acetates. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996.

The toxicology data base is adequate to characterize the toxicity of the naphthalene acetates (1-Naphthaleneacetic acid (NAA), its salts, ester, and acetamide). All six chemicals that comprise the naphthalene acetates are combined for the toxicity assessment for this RED because they are structurally related and are metabolized to the acid form and eliminated from the body as glycine and glucuronic acid conjugates within 48 hours after exposure. Analyses of dietary, drinking water, residential and occupational exposure pathways were included in the naphthalene acetates risk assessment. An aggregate assessment of risk from the combined food and drinking water pathways was also conducted. Sources of dietary exposure include food crops to which naphthalene acetates are applied as a plant growth regulator. Drinking water exposure may occur due to run-off from both agricultural and non-agricultural uses of naphthalene acetates to regulate plant growth. There is limited residential use of naphthalene acetates on ornamentals. Occupational exposure may occur through use on agricultural fruit and ornamental plants. A cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity has not been conducted for this RED. HED has not made a common mechanism of toxicity finding as to the naphthalene acetates and any other substances, and the naphthalene acetates do not appear to produce a toxic metabolite produced by other substances.

This assessment concludes that exposure estimates are below HED's level of concern for all exposure pathways evaluated. HED is concerned when estimated dietary risk exceeds 100% of the population adjusted dose (PAD). Based on analyses of estimated dietary risks for the general U.S. population and various population subgroups, the acute and chronic dietary exposure estimates for naphthalene acetates are significantly below HED's level of concern for all supported commodities. The 95$^{th}$ percentile acute dietary exposure estimate for the highest exposed population subgroup, children 1-2, was 10% of the acute dietary exposure PAD. The chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, was 8% of the chronic PAD.

A target Margin of Exposure (MOE) of 100 for the dermal and inhalation routes is considered adequate for both occupational and residential exposure estimates. The MOEs estimated for the occupational and residential exposure scenarios showed no dermal or inhalation risks of concern, i.e., all dermal and inhalation MOEs are greater than the target MOE of 100.

Estimated dermal and inhalation MOEs for residential exposure to naphthalene acetates are 3800 and 58000 respectively. For occupational scenarios, estimated dermal MOEs are ≥ 130 and inhalation MOEs are ≥ 22000 for all handler and post-application activities assessed.

The aggregate risk assessment integrates the assessments conducted for dietary, drinking water, and residential exposure. For the aggregate exposure assessment, Drinking Water Levels of Comparison (DWLOCs) associated with acute and chronic exposure to naphthalene acetates in drinking water were calculated and compared with the modeled drinking water concentration estimates of naphthalene acetates in ground water and surface water (Estimated Drinking Water Concentrations or EDWCs). Both acute and chronic DWLOCs for both surface water and groundwater significantly exceed the peak and average EDWCs for all populations indicating that aggregate exposure to naphthalene acetates in food and water do not present risks of concern. Calculated acute DWLOCs are ≥ 3000 ug/L versus peak surface and groundwater EDWCs of 13 and 0.0008 ug/L respectively. Calculated chronic DWLOCs are ≥ 1400 ug/L versus peak surface and groundwater EDWCs of 0.7 and 0.0008 ug/L respectively.

This is a highly conservative risk assessment in which high-end assumptions were used for most key parameters. It is likely to overestimate risks associated with exposure to naphthalene acetates.

## 2.0 USE PROFILE

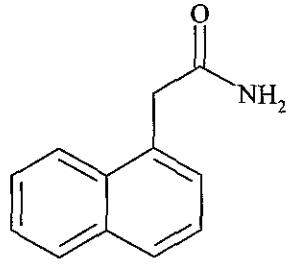
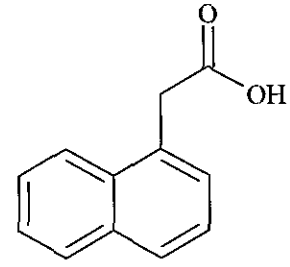
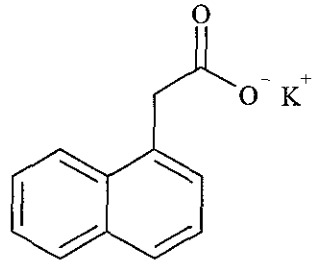
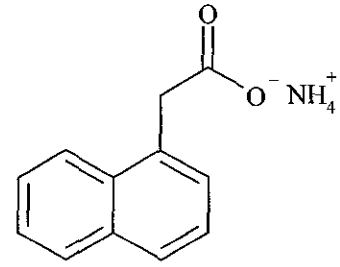
1-Naphthaleneacetic acid, its salts, ester, and acetamide are plant growth regulators which are collectively referred to as naphthalene acetates. They are currently registered for use on various orchard and fruit crops and ornamentals. Naphthalene acetates currently have tolerances in/on the following raw agricultural commodities; apple, cherry, olive, orange, pear, tangelo, and tangerine. They are used to stimulate growth, delay flower induction and leaf drop, prevent preharvest fruit drop, thin fruit, and control sprout formation. The registered formulation classes of naphthalene acetates include dust, wettable powder, flowable concentrate, emulsifiable concentrate, soluble concentrate, and liquid ready-to-use. Thinning and stop drop formulations containing NAA or its ammonium, potassium, or sodium salts are applied using ground spray or aerial equipment. Sprout formation control formulations containing the acetamide of NAA are applied by hand held sprayer and paint brush. NAA containing products are used to stimulate root growth are applied as a dilute root dip or soil drench. The plant growth regulating activity of naphthalene acetates is due to structural similarity to the natural plant hormone indole acetic acid (IAA), the most common naturally occurring auxin. IAA promotes growth in excised plant organs, induces adventitious roots, inhibits axillary bud growth, and regulates gravitropism.

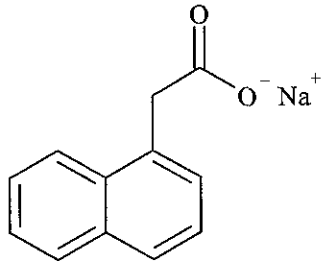
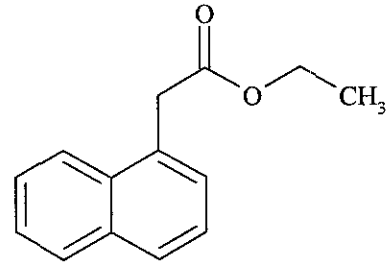
A screening level estimate of naphthalene acetates usage performed by HED's Biological and Economical Analysis Division (BEAD) indicates that the highest usage of naphthalene acetates is on pears (50 % crop treated) and apples (30% CT) with all other uses at ≤ 5% CT.

## 3.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The nomenclature and physicochemical properties of NAA and its salts, ester, and acetamide are provided in Table 1.

Table 1. Naphthalene Acetates Nomenclature and Physical/Chemical Properties

| *Common name* | NAA acetamide (NAAm) | NAA |
|---|---|---|
| Chemical structure |  |  |
| Molecular Formula | $C_{12}H_{11}NO$ | $C_{12}H_{10}O_2$ |
| Molecular Weight | 185.23 | 186.20 |
| IUPAC name | 2-(1-naphthyl)acetamide | 2-(1-naphthyl)acetic acid |
| *CAS name* | 1-naphthaleneacetamide | 1-naphthaleneacetic acid |
| CAS # | 86-86-2 | 86-87-3 |
| *PC Code* | 056001 | 056002 |
| Melting point/range | 182-184 C | 130 C |
| pH of 1% aqueous susp | 5.1 | 3.45 |
| Density or specific gravity | 0.221 g/cm$^3$ | 0.45 g/mL |
| Water solubility (20˚C) | not available | 0.042 g/100 mL |
| Solvent solubility (20˚C) | not available | xylene 5.5 g/100 mL<br>$CCl_4$ 1.06 g/100 mL<br>freely soluble in acetone, ether, and chloroform |
| Vapor pressure at 20˚C | not available | 0.3 mm Hg at 26 C |
| Dissociation constant ($pK_a$) | not available | $3.16 \times 10^{-4}$ |
| *Octanol/water partition coefficient* ($K_{ow}$) | not available | not applicable; polar compound |
| UV/vis absorption spectrum | not available | not available |
| *Common name* | NAA potassium salt | NAA ammonium salt |
| Chemical structure |  |  |
| Molecular Formula | $C_{12}H_{10}O_2K$ | $C_{12}H_{13}NO_2$ |

| Table 1. Naphthalene Acetates Nomenclature and Physical/Chemical Properties | | |
|---|---|---|
| *Molecular Weight* | 224.31 | 203.24 |
| IUPAC name | potassium-2(1naphthyl)acetate | ammonium-2(1naphthyl)acetate |
| CAS name | 1-naphthalene acetic acid, potassium salt | 1-naphthaleneacetic acid, ammonium salt |
| CAS # | 15165-79-4 | 25545-89-5 |
| PC Code | 056003 | 056004 |
| No physicochemical properties information was available concerning the NAA potassium and ammonium salts. | | |
| Common name | NAA sodium salt | NAA ethyl ester (NAA-OEt) |
| Chemical structure |  |  |
| Molecular Formula | $C_{12}H_{10}O_2Na$ | $C_{14}H_{14}O_2$ |
| Molecular Weight | 208.2 | 214.26 |
| IUPAC name | sodium-2(1naphthyl)acetate | ethyl-2(1naphthyl)acetate |
| CAS name | 1-Naphthaleneacetic acid, sodium salt | 1-Naphthaleneacetic acid, ethyl ester |
| CAS # | 61-31-4 | 2122-70-5 |
| PC Code | 056007 | 056008 |
| Melting point/range | >300 C | >150 C |
| pH of 1% aqueous suspension | 9.1 | not available |
| Density or specific gravity | 0.46 g/mL | 1.11 at 20 C |
| Water solubility (26˚C) | 340 g/100 mL | insoluble |
| Solvent solubility (26˚C) | insoluble in nonpolar solvents | soluble in xylene, toluene, ethanol, acetone, and methyl ethyl ketone |
| Vapor pressure at 20˚C | not available | not available |
| Dissociation constant ($pK_a$) | $3.16 \times 10^{-4}$ | not available |
| Octanol/water partition coefficient ($K_{ow}$) | not applicable; polar compound | not available |
| UV/vis absorption spectrum | not available | not available |

## 4.0 HAZARD ASSESSMENT

### 4.1 Hazard Profile

The toxicology data base is adequate to characterize the toxicity of NAA including its sodium and potassium salts, its acetamide derivative and its ethyl ester (TXR No.0052146, A. Khasawinah, November 20, 2003 - See Appended Table 3 for the Toxicology Profile for Naphthaleneacetic Acid Group Chemicals). Naphthalene acetates have low acute toxicity via the

oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. NAA is not a skin irritant (Toxicity 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 old test and a non-eye irritant in another recent study conducted on the currently produced material.

The July 1981 registration standard for naphthalene acetates stated that all forms of NAA 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 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.

Maternal decreased body weight gain during gestation was observed shortly after oral administration of doses of 250 mg/kg/day and above in developmental rat studies. Repeated exposure oral toxicity studies (subchronic and chronic) in rats and dogs primarily resulted in decreased body weights and body weight gains accompanied by decreased food consumption at doses of 150 mg/kg/day and above. The major target organs of repeated oral exposure were the liver, stomach and lung. 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.

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.

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. A published NCI carcinogenicity study of NAA acetamide in mice and a guideline chronic/oncogenicity of NAA salts 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.

The toxicology database for NAA is adequate for FQPA considerations. There is low concern (and no residual uncertainty) for pre- and/or postnatal toxicity resulting from exposure to the 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 naphthalene acetates 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. 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.

## 4.2 Dose Response Assessment

The toxicology assessment for the naphthalene acetates RED identified the following toxicological endpoints of concern for naphthalene acetates. A summary of the endpoints selected by HED toxicologists is provided below and in Table 2.

### 4.2.1 Toxicological Endpoints for Dietary Exposure

For acute dietary exposure for all populations, the toxicity endpoint was selected from a developmental study in the rat which in which the No Observed Adverse Effect Level (NOAEL) was 50 mg/kg/day and the Lowest Observed Adverse Effect Level (LOAEL) was 250 mg/kg/day based on decreased body weight gain during the gestation period. This is a conservative endpoint in that it assumes that decreased maternal weight gain during gestation is attributable to a single dose. For chronic dietary exposure, the toxicity endpoint was based on a one year NAA sodium salt oral feeding study in dogs. The NOAEL from this study was 15 mg/kg/day and the LOAEL 75 mg/kg/day based on stomach lesions in 75% of the males and by slight sinusoidal histiocytosis in the liver of 50% of the males. An uncertainty factor of 100 (10X for interspecies extrapolation and 10x for intraspecies extrapolation) is applied to both the acute and chronic toxicity endpoints resulting in acute and chronic reference doses (RfDs) of 0.5 and 0.15 mg/kg/day respectively.

### 4.2.2 Toxicological Endpoints for Occupational and Residential Exposure

A NOAEL of 300 mg/kg/day was selected for short-term dermal exposure based on a subchronic dermal toxicity in rats which showed reduced body weight gain and food efficiency at the LOAEL of 1000 mg/kg/day. Due to a lack of inhalation studies, an endpoint from an oral prenatal developmental study in rats was selected for inhalation risk assessments; a NOAEL for maternal toxicity of 50 mg/kg/day was selected for short-term inhalation exposure based on decreased body weight gain during the compound administration at 250 mg/kg/day. An absorption factor of 100% is applied for inhalation exposures. The target margin of exposure (MOE) for dermal and inhalation exposures is 100 based on uncertainty factors of 10x for intraspecies variability and 10x for interspecies sensitivity. For short-term exposure risk assessments, the dermal and inhalation exposure routes can be combined due to the common toxicity endpoint (reduced body weight gain) via the dermal and inhalation (oral equivalent) routes.

| Table 2. Toxicology Endpoints for Naphthalene Acetates | | | |
|---|---|---|---|
| **Exposure Scenario** | **Dose (mg/kg/day)** | **FQPA Safety Factor and Level of Concern for Risk Assessment** | **Endpoint for Risk Assessment** |
| **Dietary Risk Assessments** | | | |
| **Acute Dietary** all populations | NOAEL = **50** UF = 100 **Acute RfD** = 0.5 | **FQPA SF = 1** | **Developmental - Rat: NAA** LOAEL = 250 mg/kg/day based on **decreased BW gain during gestation period.** |
| **Chronic Dietary** all populations | NOAEL= **15** UF = 100 **Chronic RfD = 0.15** | **FQPA SF = 1** | **Chronic Dog: NAA Na salt** LOAEL = **75** mg/kg/day based on **emesis, corpuscular regurgitation incidences, gross and histopathological changes in stomachs and sinusoidal histiocytosis in livers in males** |
| **Non-Dietary Risk Assessments** | | | |
| **Incidental Oral** Not Applicable | | | |
| **Dermal** Short-Term (1 - 30 days) | Dermal study NOAEL= **300** | **FQPA SF = 1** **LOC for MOE** = 100 | **21- day dermal - Rat: NAA Na salt** LOAEL = **1000** mg/kg/day based on **reduced body weight gain and food efficiency** |
| **Dermal** Intermediate-Term (1 - 6 Months) and Long-Term (> 6 Months) Not Applicable | | | |
| **Inhalation** Short-Term (1 - 30 days) | Oral study NOAEL= **50*** | **FQPA SF = 1** **LOC for MOE** = 100 | **Developmental - Rat: NAA** LOAEL = **150** mg/kg/day based on **[decreased BW gain during gestation period.** |
| **Inhalation** Intermediate-Term (1 - 6 Months) and Long-Term (> 6 Months) Not Applicable | | | |
| **Cancer** | Bioassay in rats and mice not carcinogenic. Not mutagenic. | | |

* Inhalation absorption rate = 100%

## 5.0 EXPOSURE ASSESSMENT

## 5.1 Dietary Exposure and Risk

### 5.1.1 Summary of Registered Food Uses

Tolerances are established under 40 CFR §180.155 (a) for residues of 1-naphthaleneacetic acid in/on several plant commodities including apple at 1.0 ppm, cherry at 0.1 ppm, olive at 0.1 ppm, oranges at 0.1 ppm, pear at 1.0 ppm, pineapple at 0.05 ppm, quince at 1.0 ppm, and tangerine at 0.1 ppm. Tolerances are established under 40 CFR §180.155 (b) for residues of the ethyl ester of 1-naphthaleneacetic acid in/on apple at 1.0 ppm, pear at 1.0 ppm, and olive at 0.1 ppm. Tolerances are established under 40 CFR §180.309 for residues of α-naphthaleneacetamide and its metabolite α-naphthaleneacetic acid (calculated as α-naphthaleneacetic acid) in/on apple and pear at 0.1 ppm each. For commodities having

tolerances for both naphthaleneacetic acid and the acetamide of NAA, the total amount of residues calculated as NAA shall not exceed the higher of the two tolerances (40 CFR §180.3(d)(7)). No tolerances have been established for animal commodities.

HED is now recommending that the current NAA tolerance expressions listed in 40 CFR §180.155 (a), 40 CFR §180.155 (b), 40 CFR §180.309, and 40 CFR §180.3(d)(7) be combined into a new single tolerance expression in order to reflect the terminal residues of concern. The tolerance should be expressed in terms of the combined residues of 1-naphthaleneacetic acid and its conjugates, calculated as 1-naphthaleneacetic acid, from the application of 1-naphthaleneacetic acid, its ammonium, sodium or potassium salts, ethyl ester, and acetamide.

5.1.2 Residue Profile

The qualitative nature of the residue in plants and ruminants resulting from registered uses of naphthalene acetates is adequately understood. The terminal residues of concern in plants and ruminants are the parent compounds, NAA and its conjugates, based on apple, olive, and goat metabolism studies (*D293239, G. Otakie, November 18, 2003*).

Based on requested apple and citrus processing studies, HED has tentatively determined that NAA is a Category 3 pesticide (i.e., no reasonable expectations of finite residues of concern in meat and milk). Pending submission of an additional required citrus processing study (for oil and juice), the Agency will re-evaluate NAA's Category 3 determination based on recalculated dietary burden. However, the dietary burden is not likely to increase sufficiently to produce residues of concern. There are no poultry feeds associated with the currently registered food/feed uses of naphthalene acetates so a poultry feeding study is not required for reregistration and tolerances for the eggs and edible tissues of poultry need not be established. The naphthalene acetates are not registered for direct use on water and aquatic food and feed crops so no residue chemistry data are required under these guideline topics. Confined and field rotational crop studies are not required for orchard crops. Adequate storage stability data are available to support the storage intervals and conditions of treated samples of raw agricultural commodities (RACs) used for tolerance reassessment. Storage stability data on the processed commodities of apples (or citrus fruits) and olives is still required.

The current residue analytical methods listed in the Pesticide Analytical Methods (PAM) Volume II for the analysis of α-naphthaleneacetic acid and 1-naphthaleneacetamide in/on plant commodities are unacceptable because the methods use benzene, which poses safety concerns. The registrant has submitted a new HPLC method using fluorescence detection (Method NAA-AM-001) for determination of NAA in plant commodities. This method incorporates a basic hydrolysis step to release bound residues. It has been subjected to a successful independent laboratory validation and, pending validation at BEAD's Analytical Chemistry Laboratory, the method may be a suitable replacement for existing enforcement methods. Multiresidue Methods Guidelines have been satisfied through testing and subsequent determination that terminal residues of concern would not be recovered using Multiresidue Protocols.

### 5.1.3 Dietary Exposure and Risk Analysis

Acute and chronic dietary naphthalene acetates exposure and risk estimates resulting from food intake were determined for the general U.S. population and various population subgroups. The naphthalene acetates acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The dietary risk assessment incorporates both exposure and toxicity of naphthalene acetates. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the Reference Dose (RfD) divided by the special FQPA Safety Factor. HED is concerned when estimated dietary risk exceeds 100% of the PAD.

The acute and chronic dietary exposure/risk analyses for all supported naphthalene acetates food uses were conducted using conservative, Tier 1 exposure assessments. The Tier I analyses assume tolerance level residues for all registered uses, 100% crop treated for all commodities with existing tolerances, and default processing factors. Based on analyses of estimated dietary risks for the general U.S. population and various population subgroups, the acute and chronic dietary exposure estimates for naphthalene acetates are significantly below HED's level of concern for all supported commodities. The 95$^{th}$ percentile acute dietary exposure estimate for the highest exposed population subgroup, children 1-2, is 0.05 mg/kg/day or 10% of the aPAD. The chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 0.01 mg/kg/day or 8% of the cPAD. (D293241, B. Daiss, 11/20/03).

Acute and chronic dietary risks were also estimated using the Lifeline model (version 2.0). The Lifeline model estimated acute exposure based on the acute 1-day dietary dose drawn randomly from an age-specific seasonal exposure profile of 1000 individuals. The Lifeline chronic dietary exposure estimate is based on an average daily exposure from a profile of 1000 individuals over a one year period. Results of the Lifeline analysis are fully consistent with DEEM results. The Lifeline model estimate for the 95$^{th}$ percentile acute dietary exposure for children 1-2 years old is 10% of the aPAD. The Lifeline chronic dietary exposure estimate for 1-2 year olds is 8% of the cPAD.

### 5.1.4 Uncertainties and Risk Characterization

The conservative acute and chronic Tier 1 dietary exposure assessments for naphthalene acetates could be refined for more realistic dietary exposure estimates using percent crop treated and market share estimates, field trial, and processing data. However, conservative estimates of risk from dietary exposure naphthalene acetates are not of concern and do not require refinements at this time.

## 5.2 Estimated Drinking Water Environmental Concentrations

The Environmental Fate and Effects Division (EFED) calculated conservative, Tier I Estimated Drinking Water Concentrations (EDWCs) of naphthalene acetates in ground water and surface water for use in the human health risk assessment. EDWCs for 1-naphthaleneacetic acid were calculated using FIRST (surface water) and SCIGROW (ground water) drinking water models. These values generally represent upper-bound estimates of the concentrations of 1-naphthaleneacetic acid equivalents that might be found in surface and ground water due to the use of 1-naphthaleneacetic acid on apples, which represents the highest use rate scenario. Both models provide estimates suitable for screening purposes. Modeled EDWCs for peak and average concentrations of naphthalene acetates in surface water are 13 and 0.0008 ppb respectively. The modeled peak and average EDWCs for groundwater are 0.7 and 0.0008 ppb respectively. (D293886, J.L. Melendez, 9/25/03)

## 5.3 Occupational and Residential Exposure and Risk

Fifteen exposure scenarios were assessed for naphthalene acetates. These include 14 occupational and one residential exposure scenario. Occupational exposure scenarios include including mixing, loading, and applying naphthalene acetates using liquid spray and paint formulations to fruit and ornamental trees and post-application exposure to workers who reenter treated areas. Residential uses are limited to root dip and sprout inhibition applications. Only short term exposures from inhalation and dermal exposure routes were assessed for all exposure scenarios. Longer term MOEs were not calculated since exposure for more than 30 days is unlikely to occur based on use patterns. Occupational and residential exposure and risk estimates were conducted using maximum application rates and surrogate exposure data from the Pesticide Handlers Exposure Database and the Residential Exposure Assessment SOPs. (D293240, B. Daiss, 11/20/03)

A target Margin of Exposure (MOE) of 100 is considered adequate for occupational and residential exposure via dermal and inhalation routes. The MOEs estimated for the occupational handler and post-application exposure scenarios showed no dermal or inhalation risks of concern, i.e., all dermal and inhalation MOEs are greater than the target MOE of 100. The residential handler scenario assessment indicates no MOEs of concern for residential exposure (i.e., MOEs > 100).

### 5.3.1 Residential Exposure and Risk Analysis

Residential uses are limited to application of NAA to stimulate root growth, and application of the ethyl ester of NAA to control sprouts and sucker growth on fruit and ornamental trees. Only the spray application of naphthalene acetates to control sprout and sucker growth was evaluated for the residential exposure assessment for this RED. Residential exposures from root dip applications are expected to be significantly less than spray applications for sucker growth because of the low concentration of NAA in root dip and soil drench products, and the very short

exposure duration and limited area of exposure associated with use of these products. Only short term exposures are expected for residential applications of naphthalene acetates. No chemical specific exposure data was available for naphthalene acetates. Therefore surrogate dermal and inhalation exposure data from HED's SOP for Residential Exposure Assessments was used to assess residential exposure from aerosol spray application of naphthalene acetates to control tree sprouts. Exposure assumptions for residential exposure included maximum label application rate for aerosol spray application, application of the entire contents (one quart) of sprout inhibitor formulation available for residential use, and no protective clothing. Estimated dermal and inhalation MOEs for residential exposure to naphthalene acetates are 3800 and 58000 respectively. These MOEs are well above the target MOE of 100 and not of concern.

5.3.2 Occupational Exposure and Risk Analysis

Occupational exposures were estimated for handlers (i.e., workers who mix, load, and apply the pesticide product) and workers involved in post-application activities (i.e., individuals who can be exposed to pesticides after entering areas previously treated with pesticides – also often referred to as reentry exposure). Only short-term exposures are expected/assessed for occupational exposure scenarios.

Occupational Handler Exposure and Risk

Twelve handler scenarios covering mixing and loading of spray formulations, spray and paint brush application of liquids, and mixing, loading and applying liquid formulation. Based on actively registered labels, HED assessed the following scenarios for the RED:

- mixing and loading for airblast application aerial sprayer
- mixing and loading for rights of way sprayer
- mixing and loading for aerial sprayer
- aerial application of liquid spray
- application of liquid by air blast sprayer
- application of liquid by rights-of-way sprayer
- paintbrush application of liquid
- spray application with high pressure handwand
- mixing, loading and applying liquids with low pressure handwand;
- mixing, loading and applying liquids with backpack sprayer
- mixing, loading and applying liquids with paintbrush
- flagging for aerial spray application

Exposure assumptions for handler exposure included maximum application rate, based on data provided by the registrant, for airblast and aerial application is 0.11 lb a.i./acre (50 gm a.i./acre), maximum application rate for all other spray applications (0.1 lb a.i/gal), high-end area treated (500 acres/day for aerial and 40 acres/day for airblast spray application) and baseline dermal exposure (long pants, long sleeved shirts, shoes, and socks ). Based on the handler

assessment, both dermal and inhalation MOEs for the occupational handler exposure scenarios are above the target MOE of 100 and not of concern. Dermal MOEs are ≥ 130 for all scenarios and inhalation MOEs are ≥ 22,000 for all scenarios.

Post-application Exposure and Risk

Post-application scenarios assessed covered the activities of irrigation, scouting and weeding, harvesting, pruning, propping, training and thinning of treated trees. Worker post-application activities were assessed for apple and pears, the crops with the highest application rates. Exposure assumption for post-application exposure include maximum application rate for airblast and aerial application (0.11 lb a.i./acre), SOP assumptions for dislodgeable foliar residue (20% of the application rate), high-end dermal transfer coefficients (1000 for irrigation, scouting and weeding, and 3000 for harvesting, pruning, propping and thinning), and exposure estimates for day 0 or the same day the pesticide is applied. Results of the assessment indicate that both dermal MOEs for post-application exposure scenarios are well above the target MOE of 100 and not of concern. Dermal MOEs are ≥ 1000 for post-application activities assessed.

5.3.3 Uncertainties and Risk Characterization

The occupational and residential exposure assessment conducted for Naphthalene Acetates RED is a highly conservative assessment intended to encompass all of the major uses throughout the country. Chemical specific exposure studies are unavailable for the handler and post-application exposure so HED default exposure values and assumptions were used. HED default exposure values and assumptions are selected to be realistic and yet provide a reasonable certainty that the exposures are not underestimated. High-end assumptions were used for area treated for handlers. High transfer coefficients were used for post-application activities. Application rates used in handler and post-application occupational assessment are the maximum allowable based on data submitted by the registrant. Baseline exposure assumptions were used for all handler exposure scenarios for this assessment. Most labels require minimum personal protective equipment of coveralls, socks, and waterproof gloves and shoes for handlers. Maximum label application rates were based on data provided by the registrant. Many of the active labels for naphthalene acetates do not provide clear information on application rates. These labels need to be revised to reflect the maximum allowable application rate submitted by the registrant.

## 5.4 Aggregate Exposure

The aggregate risk assessment integrates the assessments conducted for dietary, drinking water, and residential exposure. Since there is potential for concurrent exposure via the food, water and short-term residential exposure pathways, the combined exposures are estimated and compared with modeling-based estimates of drinking water contamination determined by the EFED.

For aggregate exposure assessment, Drinking Water Levels of Comparison (DWLOCs)

associated with acute and chronic exposure to naphthalene acetates in drinking water were calculated and compared with the EDWCs of naphthalene acetates in ground water and surface water. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and residential sources. The acute and chronic DWLOCs for naphthalene acetates include aggregate exposure from food and water only. The short-term DWLOC includes aggregate exposure from food, water and residential uses associated with application of naphthalene acetates and is calculated only if there is a common toxicity endpoint for each route of exposure.

Acute and chronic DWLOCs were calculated based on the acute dietary exposure estimates and default body weights and water consumption figures. To calculate the DWLOC, the acute dietary food exposure was subtracted from the acute population adjusted dose and the chronic dietary food exposure was subtracted from the chronic PAD. Both peak and average modeled concentrations (EDWCs) for both surface water and groundwater are significantly below the acute and chronic DWLOCs for the general U.S. population and all population subgroups indicating that aggregate exposure to naphthalene acetates in food and water do not present risks of concern. Calculated acute DWLOCs are $\geq$ 3000 ug/L versus peak surface and groundwater EDWCs of 13 and 0.0008 ug/L respectively. Calculated chronic DWLOCs are $\geq$ 1400 ug/L versus peak surface and groundwater EDWCs of 0.7 and 0.0008 ug/L respectively. (D293241, B. Daiss, 11/20/03)

Short term aggregate risk cannot be estimated for naphthalene acetates because the toxicity endpoints selected for the chronic dietary/drinking water routes of exposure and those selected for inhalation and dermal routes of exposure are not based on common effects i.e., the chronic dietary endpoint is based on systemic effects and the dermal and inhalation endpoints are based on decreased body weight gain.

## 6.0. CUMULATIVE EXPOSURE

Section 408(b)(2)(D)(v) of FIFRA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide chemical's residues and "other substances that have a common mechanism of toxicity." Unlike other pesticides for which HED has followed a cumulative risk approach based on a common mechanism of toxicity, HED has not made a common mechanism of toxicity finding as to the naphthalene acetates and any other substances. The naphthalene acetates do not appear to produce a toxic metabolite produced by other substances. For the purposes of this risk assessment, therefore, HED has not assumed that the naphthalene acetates have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## 7.0 DATA GAPS

Outstanding data needs include:

- Storage stability data on the processed commodities of apples (or citrus fruits) and olives.
- Data depicting residues of NAA and its conjugates in the processed commodities of citrus (dried pulp, oil, and juice).
- The replenishment of analytical reference standards for all registered NAA acid salts, ester, and acetamide as requested by the Repository.

Maximum label application rates were based on data provided by the registrant. Many of the active labels for naphthalene acetates plant growth regulators do not provide clear information on application rates. These labels need to be revised to clearly reflect the maximum allowable application rate submitted by the registrant.

## ATTACHMENTS

Product & Residue Chemistry Chapter, G. Otakie (D299296, 3/10/04)
Occupational and Residential Exposure Assessment, B. Daiss (D299297, 3/10/04)
Dietary Exposure and Risk Estimates for Tolerance Reassessment, B.Daiss (D293241, 11/20/03)
Review of Naphthaleneacetic Acid Incident Reports, J. Blondell (D293397 10/9/03)
Tier I Estimated Drinking Water Concentrations of 1-Naphthaleneacetic Acid for use in Human Health Risk Assessment, J.L. Melendez (D293886, 9/25/03)
Toxicology Chapter, A. Khasawinah (D293237 TXR No. 0052407, 3/8/04)

# TOXICOLOGY PROFILE
## Naphthaleneacetic Acid Group chemicals , TECHNICAL GRADE

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

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| Study | pc 056001: acetamide | pc 056002: NAA | pc 056007: Na salt | pc 056008: ethyl ester |
| Acute - oral | **MRID 43495901**<br>$LD_{50}$ > 5050 mg/kg<br>Category IV | **MRID 00103128**<br>$LD_{50}$ (95% C.I.) = 2520 mg/kg (2100-3021) .Category III | **MRID 00108829**<br>$LD_{50}$: Males 1.35 (1.12–1.64) Females 0.933 g/kg (0.631-1.38 )Category III | **MRID 43494101**<br>$LD_{50}$ 2300 (2129-2486) mg/kg<br>Category III |
| Acute - Dermal | **MRID 43495902**<br>$LD_{50}$ > 2020 mg/kg<br>Category III | **MRID 00103129**<br>$LD_{50}$ is greater than 2 g/kg.<br>Category III. | **MRID 00108829**<br>dermal $LD_{50}$ = > 2 g/kg.<br>Category III | **MRID 43494102**<br>$LD_{50}$ > 2020 mg/kg. Category III |
| Acute - Inhal. | **MRID 43495903**<br>$LC_{50}$ > 2.17 mg/L<br>Category IV | **MRID 00128256**<br>$LC_{50}$ = 0.45 mg/L<br>Category II | | **MRID 43494103**<br>$LC_{50}$ > 2.13 mg/L<br>Category IV |
| Eye Irritation | **MRID 00103051**<br>**corrosive Category I**<br>**MRID 43495904**<br>minimally irritating<br>Category IV | **MRID 00103127**<br>**corrosive Category I** | **MRID 00108829**<br>**corrosive Category I** | **MRID 43494104**<br>minimally irritating<br>Category IV |
| Derm. Irritation | **MRID 00103050**<br>non-irritant<br>Category IV | **MRID 00103127**<br>Non-irritating **Category IV** | **MRID 00108829**<br>Non-irritating **Category IV** | **MRID 00103053 & 00103218.**<br>non-irritating **Category IV** |
| Sensitization | **MRID 43495905**<br>not a skin sensitizer. No positive control.<br>**Unacceptable** | **MRID 00153217**<br>not a skin sensitizer | | **MRID 43494105**<br>not a skin sensitizer. No positive control.<br>**Unacceptable** |
| 90-day - rat | **MRID 43896001**<br>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**<br>0, 50, 150, or 300 mg/kg/day to SD rats (20/sex/dose) **LOAEL** for toxic effects is 500 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**<br>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**<br>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). |

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| Study | pc 056001: acetamide | pc 056002: NAA | pc 056007: Na salt | pc 056008: ethyl ester |
| 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. | | |
| 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 | | | |

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| 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) | |

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| 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). | |
| 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. | | | |

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| Study | pc 056001: acetamide | pc 056002: NAA | pc 056007: Na salt | pc 056008: ethyl ester |
| Chronic - dog | | | **MRID 43744201**<br>0, 15, 75, or 225 mg/kg/day.<br>**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.<br>**NOAEL**= 15 mg/kg/day in males and 75 mg/kg/day in females. | |
| Gene mutation-bacterial | **MRID 43581006**<br>*Salmonella* five doses 100-5000 ug/plate. No mutagenic effect with or without S9 activation | **MRID 00042761**<br>*Escherichia coli polA*. Strains W3110 and p3478 at 1, 2 or mg/ml. Not mutagenic.<br>**MRID 00042762**<br>*Salmonella*. At 0.5-5000 ug/plate. Not mutagenic: | | **MRID 43581004**<br>five doses 33-5000 ug/plate. No mutagenic effect with or without S9 activation |
| Gene mutation - mammalian: mouse lymphoma cells | **MRID 43580202**<br>-S9: not mutagenic.<br>+S9 mutagenic at 100 ug/mL and above | | | **MRID 43580201**<br>-S9: not mutagenic.<br>+S9 mutagenic at 300 ug/mL and above |
| erythrocyte micronuleus mice | **MRID 43581005**<br>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**<br>ip injections 60 or 125 mg/kg to 4 mice/sex. No overt aymptoms at high dose. Negative. | | **MRID 43581003**<br>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**<br>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**<br>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. | | |

| TOXICOLOGY PROFILE Naphthaleneacetic Acid Group chemicals | | | | |
|---|---|---|---|---|
| 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.<br><br>**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.<br><br>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.<br><br>MRID 43963301. Rats (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 (NAD).** 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. | | | |

13544

# R100567

| | |
|---|---|
| **Chemical:** | **1-Naphthaleneacetamide; 1-Naphthaleneacetic acid; Potassium 1-naphthaleneacetate; Ammonium 1-naphthaleneacetate; Sodium 1-naphthaleneacetate; Ethyl 1-naphthaleneacetate** |
| **PC Code:** | **056001; 056002; 056003; 056004; 056007; 056008** |
| **HED File Code** | **14000 Risk Reviews** |
| **Memo Date:** | **03/30/2004** |
| **File ID:** | **DPD293881** |
| **Accession Number:** | **412-04-0243** |

**HED Records Reference Center**
**07/20/2004**