

Pesticides

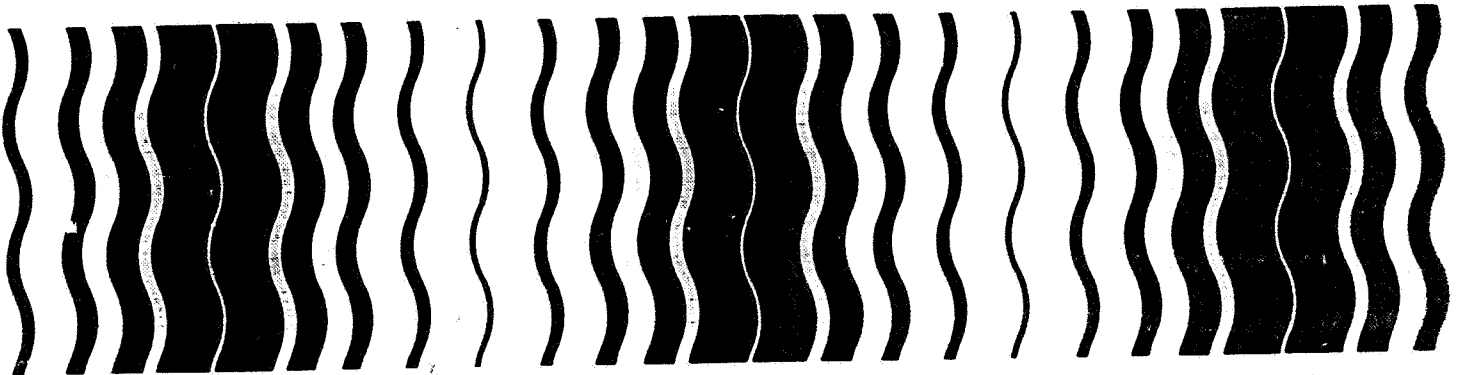


# Naphthalene

587

## Pesticide Registration Standard

Toxicology chapter



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## VI. Toxicology

### A. Toxicology Profile: Technical Naphthalene

No data were available to assess the acute dermal and acute inhalation toxicities of naphthalene.

In a supplementary study\* by Adams (1930, MRID #005015698), 4 rats were given 2.5-3g naphthalene (in paraffin) orally and 1 death was observed. These data suggest that the acute oral toxicity of naphthalene is low; however the study is insufficient to fulfill the acute oral toxicity testing requirement for naphthalene.

No data were available to assess the primary dermal irritation and the dermal sensitization potential of naphthalene.

Insufficient data were available with respect to the eye irritation potential of naphthalene. In a study by D'Asaro Biondo (1973, MRID #005019746), rabbits with partially removed nictitating membranes exhibited severe eye irritation when exposed to the vapors of naphthalene for 3 or 10 minutes. However, the inadequacies in the methodology used in this study precludes the use of the study to assess the primary eye irritation potential for naphthalene.

The subchronic toxicity of naphthalene could not be adequately assessed. In a subchronic oral toxicity study in rats, the maximum tolerated dose (MTD) was estimated to be 200 mg/kg/day, (Battelle Columbus Laboratories, 1980, MRID #GS0022023 and GS0022024). However, subchronic oral toxicity testing is not required for naphthalene since repeated human exposure through the oral route is unlikely with this pesticide.

No subchronic dermal toxicity data were available for naphthalene, and no data were available to assess the subchronic inhalation toxicity of naphthalene. An assessment of the subchronic inhalation data requirement will be made once data for acute inhalation toxicity are available.

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\* "Supplementary" studies and/or "supplementary" data provide some valid information, but do not satisfy a Guideline requirement.

\*\* Acute oral toxicity data may be available from the NCI and these data may satisfy the acute toxicity testing requirement.

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Insufficient data were available to assess the chronic effects of naphthalene. In a study by Schmaehl (1955, MRID #005015285), rats fed 10 to 20 mg of naphthalene in the diet, 6 times per week, for approximately 700 days, or 20 mg of naphthalene given to rats by intraperitoneal or subcutaneous injection once a week for 40 weeks, did not produce toxicity, tumors, or affect the life span. While this study was inadequate to permit an assessment of the chronic toxicity of naphthalene due to deficiencies in reporting and methodology, the data suggested that chronic low dose exposure to naphthalene is well-tolerated in rats.

Naphthalene is scheduled to be tested by the National Toxicology Program for oncogenicity, chronic feeding, and mutagenicity. As of publication of this standard, (September 1981) no data were available to assess the mutagenic potential of naphthalene. When the NTP testing is completed, the Agency will evaluate it to determine if the results satisfy the FIFRA guideline testing requirements for oncogenicity, chronic feeding and mutagenicity.

No data were available to assess the teratological potential or the reproductive toxicity potential of naphthalene. Teratology testing in two mammalian species is required. The reproductive toxicity data requirement is being held in reserve until all of the acute and chronic toxicity data mentioned above as well as teratology data requested from the registrants are available. At that time, a toxicological assessment can be made of the need for a reproductive test.

A number of investigators have provided supplementary information about the metabolism of naphthalene in rats, rabbits, mice, hamsters, guinea pigs, and humans. Table VI. 1 lists naphthalene metabolites that have been identified in the urine of naphthalene-dosed animals. Adequate data were available to assess the metabolism of radiolabeled naphthalene in rats. In a study by Chen and Dorough (1979, MRID #005020080) it was demonstrated that the metabolism of naphthalene occurs by (at least) a two phase elimination process. In the initial rapid phase, approximately 74% of the naphthalene is eliminated; urinary excretion accounts for approximately 60% of this elimination while fecal excretion accounts for approximately 14%. The major urinary metabolite is N-acetyl-S-(1,2-dihydro-2-hydroxyl-1-naphthyl) cysteine, a premercapturic acid. Tissue accumulation (greater than 20%) accounts for the slow elimination of naphthalene in the second phase. While these and additional in vitro studies indicate the presence of metabolic intermediates of naphthalene which may be of toxicological concern, the full significance of these materials cannot be evaluated until the chronic testing data are available for review.

#### B. Toxicology Profile: End-Use Naphthalene

The Confidential Statements of Formula do not indicate an anticipated change in toxicity due to inert ingredients; see Chapter IV, Introduction, for rationale. Separate discussions or profiles of naphthalene end-use products, therefore, will not be included in this standard.

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TABLE VI.1  
NAPHTHALENE URINARY METABOLITES

Metabolites	Rabbit	Guinea Pig	Mice	Rat	Hamster	Man	Citation
1-naphthol	1,3,5	1	1	1,3,7, 8,10		9	1 = MRID: 005005367 2 = MRID: 005005368
2-naphthol	1,5	1	1	1,7,8		9,11	3 = MRID: 005006213
1,2-dihydro-1,2-dihydroxy naphthalene	1	1	1	1,7,8			4 = MRID: 005006208
1-naphthyl sulfate	1,3,4	1	1	1,3			5 = MRID: 005006209
1-naphthylmercapturic acid	4	1	1	6			6 = MRID: 005007954
1-naphthylglucosiduronic acid	1,3		1	1,3			7 = MRID: 005005671
1,2-dihydro-2-hydroxy-1-naphthyl- glucosiduronic acid	2			1,10			8 = MRID: 005005672
1,2-dihydro-1,2-dihydroxy-1-naphthal sulfate				10			9 = MRID: 005005949
l-acetyl-S-(1,2-dihydro-2-hydroxy- 1-naphthyl)-L-cysteine	5	5	5	5,10	5	5	10 = MRID: 00502080
2-hydroxy-1-naphthyl sulfate	5						11 = MRID: 005012927
1-hydroxy-2-naphthyl sulfate	4						
1,2-dihydroxynaphthalene				3,8			
1,2-naphthaquinone						9	
1,4-naphthaquinone						9	
methylionaphthalene				7,8			

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### C. Human Hazard Assessment: Naphthalene

The use of naphthalene may result in human exposure through the dermal and inhalation routes. However, at present, no adequate exposure or toxicology data are available to perform a human hazard assessment on naphthalene. Supplementary data describing the cataractogenic and hemolytic effects of naphthalene were available. Naphthalene-induced cataracts have been produced experimentally in rats and rabbits; rabbits appear to be the more sensitive species. Single high oral doses of naphthalene (1-3g) have been shown to cause eye damage and/or opacities in rabbits as early as 6 hours to one week following treatment. (Adams, 1930, MRID #005015698 and Pirie, 1968, MRID #0050005197).

In humans, the hemolytic properties of naphthalene have been well documented. Case histories report incidents of acute hemolytic anemia in humans following naphthalene poisoning. Persons with glucose-6-phosphate dehydrogenase deficiencies appear to be more susceptible to this type of toxicity. In addition, naphthalene induced acute hemolytic anemia has been observed experimentally in dogs (Zuelzer and Apt, 1949, MRID #005005235; and Mackell et al., 1951, MRID # 005005949). It should be noted that this effect has generally been observed, following high dose exposure or misuses of the pesticide.

### D. Summary of Data Gaps

The data gaps for technical grade and end-use naphthalene are acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, primary dermal irritation, and dermal sensitization. The data gaps for technical naphthalene are teratogenicity, and subchronic dermal toxicity.

Oncogenicity (in the rat and mouse), chronic feeding, mutagenicity and reproduction data are also insufficient to meet the guidelines requirements and would normally be required. Naphthalene, however, is scheduled to be tested under the National Toxicology Program. This testing will most likely encompass the required oncogenicity, mutagenicity and chronic feeding studies.

Therefore, at this time the Agency will not require oncogenicity, chronic feeding, and mutagenicity studies.\*

In addition, the Agency has decided to reserve its decision to require reproductive testing with naphthalene until the results of all the above cited studies are available, and a toxicological assessment of the need for a reproductive test can be made.

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\* If naphthalene is not tested under the NTP, the registrants may be required to submit the outstanding chronic studies.

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