

FMC Corporation

1735 Market Street
Philadelphia Pennsylvania 19103
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8EHQ-0501-14384

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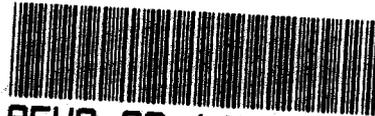
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U.S. Environmental Protection Agency
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ATTN: Section 8(e)

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Re: 8EHQ-0299-14384



89010000168

Dear Sirs:

FMC Corporation makes no claims of TSCA business confidentiality in this submission to the Agency.

On March 23, 2001 EPA sent a letter to FMC Corporation requesting use and exposure information on 7-benzofuranol, 2,3-dihydro-2,2-dimethyl- (commonly referred to as "7-hydroxy"). This request was prompted by a TSCA 8(e) submission FMC had made in February 1999 regarding effects observed in an oral teratology study conducted with this chemical.

In response to your request for use and exposure information, FMC is hereby providing the Agency with the following: (1) a copy of a study entitled *Toxicological Evaluation of 2,3-Dihydro-2,2-dimethyl-7-benzofuranol* ("7-Hydroxy") conducted by Environmental Toxicology International, Inc; (2) a copy of an interoffice memorandum from Susan Gilson, the Baltimore plant's Industrial Hygienist, to me regarding 7-Hydroxy PPE and Exposure Potential at the plant; and finally (3) another interoffice memorandum from Amy Haztenbuhler, an Industrial Hygienist, to Forson, et. al. regarding Plant 4 Monitoring for 7-Hydroxy and several other chemicals.

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7-hydroxy is used exclusively as an intermediate in the manufacture of carbofuran, a FIFRA registered pesticide. The manufacturing facility at Baltimore, MD is the only location at which FMC produces 7-hydroxy. In 2000, of the 7-hydroxy manufactured 83.7% was utilized by FMC at the Baltimore facility in making carbofuran. The remaining 16.3% of our production was sold to international customers; there are no domestic sales of 7-hydroxy.

In December 2000, FMC submitted test plans and summaries of toxicity data on 7-hydroxy to EPA as part of the High Production Volume Chemicals Challenge program. This information should be available on the EPA HPV internet website. The test plan did not cover uses of 7-hydroxy or personal protective precautions. We believe that information can best be derived from the material we are enclosing.

If you have additional questions or concerns, please feel free to contact me at 215/299-6133.

Sincerely yours,

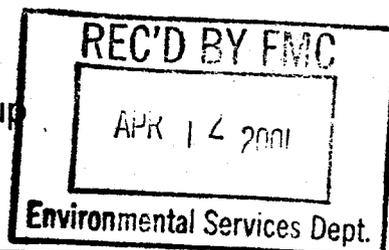
A handwritten signature in cursive script that reads "Linda M. Clark".

Linda M. Clark
Manager, Product Regulatory Affairs

Enc.



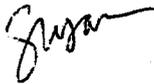
Agricultural Products Group
Baltimore



Interoffice

To: Linda Clark

Date: April 5, 2001

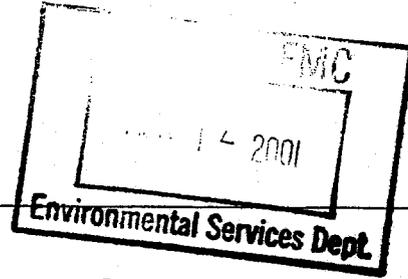
From: Susan Gilson 

cc:

Subject: 7 HYDROXY PPE AND EXPOSURE POTENTIAL

Exposures to 7 hydroxy are possible during two tasks – sample taking and drumming. The operators in the plant take one sample (takes 2 minutes) every batch, averaging every 16 hours, which would be done by an “outside” operator. The outside operator assignment happens approximately 2 shifts per week for each plant 4 operator. There are sixteen operators total, and for each shift, two work outside in the plant and two work inside at the control panel. Drumming is periodic, based on orders. Hydroxy is drummed at 40 degrees C as often as every day or as infrequently as once in two months, usually for a period of up to three hours for any given outside operator with the next shift continuing on. Personal protective equipment is goggles and neoprene gloves.

IH sampling in the plant has generally focused on the more toxic and volatile materials such as MAC, MIBK and MOP. However, we do have IH data on exposures to a mechanic entering a distillation column which were lower than the plant exposure guideline. We also have photoionization detector data for the drumming operation which showed between 1 and 3 meter units in the breathing zone. This may have been primarily picking up the solvents, not the hydroxy, we need to conduct more sampling with the correct media. The 2001 monitoring plan includes measuring the drumming operation, this information can be available in the 2nd quarter.



Interoffice

To R. Forson, G. MacDonald, J. Coxon

Date November 19, 1992

From Amy M. Haztenbuhler

cc S. Gilson
K. Beach
E. Snyder
M. Garrison

Subject

PLANT 4, COLUMN C-4421 DISTRIBUTION TRAY REMOVAL --
MONITORING FOR 7-HYDROXY, MOP, MAC\ICC AND SOLVENT EXPOSURE

There is a need for characterization and documentation of plant based maintenance task exposure, particularly for tasks that may be conducted during the annual plant outage. Industrial hygiene monitoring of these tasks can improve evaluation and control of potential hazards to the maintenance department employees, and the health and safety policy for similar non-routine tasks in the future.

During the recent plant outage, the distribution tray of column C-4421 was removed for inspection. The removal of the distribution tray required the system be "blanked" and that a maintenance mechanic enter the top of the column. There was potential for MAC\ICC and solvent exposure throughout the plant while blanking the system and potential for 7-hydroxy and MOP exposure while in the column. The mechanics followed the existing procedures for blanking the system and for confined space entry. The maintenance mechanic (J. Coxon) who blanked the system and entered the column wore a half-face respirator with organic vapors and acid cartridges for respiratory protection, goggles for eye protection, tyvek paper suit and uniform for dermal protection, safety boots and hard hat per plant safety policies.

Industrial hygiene monitoring results for MAC\ICC and solvent exposure were below detectable levels for TBC, MIBK, and toluene and 0.02 ppm for MAC/ICC and 0.11 ppm for xylenes (details of results attached). These sampling results are well within OSHA and FMC internal guidelines for exposure. The plant had been down for the outage for several days, and as expected ambient solvent concentrations in the area were low. However, the maintenance mechanic did comment that solvent odors were strong on the second level of the plant where some time was spent "blanking" the system.

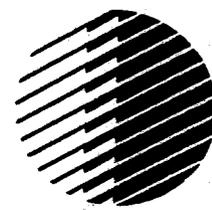
Industrial hygiene monitoring results for 7-Hydroxy and MOP exposure to the maintenance mechanic while in the column were < 90 ppb and , 0.1 ppb, respectively (details of results attached). Again, these results are well within FMC internal guidelines. The column had been open and "cleaned" several days prior to the entry and removal of the distribution tray, which should have adequately ventilated the area.

RESULTS

Results are reported in parts per million (ppm) or parts per billion (ppb) as an estimate of an 8-hour time weighted average (TWA) exposure calculated from actual exposure periods which are less than 8 hours.

<u>Sample #</u>	<u>Date</u>	<u>Type</u>	<u>Time (min)</u>	<u>Concentration</u>	<u>Exposure Limit (OSHA PEL or FMC internal limit)</u>
7-Hydroxy 182-051	9/24/92	personal	122	90.4 ppb	3.5 ppm (or 3500 ppb)
MOP 182-051	9/24/92	personal	122	0.1 ppb	4.9 ppm (or 4900 ppb)
TBC 182-052	9/24/92	personal	300	ND	1.0 ppm
MAC/ICC 182-052	9/24/92	personal	300	0.02 ppm	1.0 ppm
MIBK 182-052	9/24/92	personal	300	ND	50 ppm
Toluene 182-052	9/24/92	personal	300	ND	100 ppm
Xylenes 182-052	9/24/92	personal	300	0.07 ppm	100 ppm

ND - non detectable



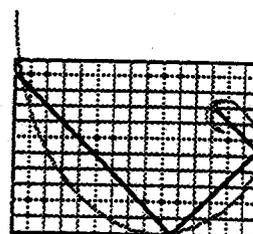
**Toxicological Evaluation of 2,3-Dihydro-
2,2-Dimethyl-7 Benzofuranol
("7-Hydroxy")**

by

**Environmental Toxicology International, Inc.
Seattle**

A Member of ERM Group of Companies

May 12, 1994



ERM

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1. EXECUTIVE SUMMARY

The purpose of this document is to present a summary of the available toxicological literature for 2,3-dihydro-2,2-dimethyl-7-benzofuranol, referred to as "7-hydroxy." 7-Hydroxy is a chemical intermediate used in the manufacture of carbofuran, a carbamate insecticide. It is not used for any purpose other than making this product.

Environmental Toxicology International (ETI) reviewed available toxicological literature with an emphasis on the potential human and environmental effects that may result from exposure. We reviewed data from independent laboratories and scientific studies published in the literature. Most animal studies, done by independent laboratories, were acute studies with the main goal of defining LD₅₀ values. A 90-day gavage and inhalation rat study were also reviewed. The published literature was found by computerized search.

Based on the literature reviewed, 7-hydroxy has a relatively low toxicity. The LD₅₀ value in rats ranges from 1800 to 3000 mg/kg with signs suggesting that depression of the central nervous system is the predecessor to death. Rabbits treated by the Draize method demonstrated reversible corneal opacity. Dermal exposure to intact skin of rats and rabbits did not produce any adverse reactions, including hypersensitivity reactions. No adverse health effects in rats were noted after 90 days at the highest dose administered by gavage. There were no reports of cancer; only weak mutagenic activity was reported in nearly all bacterial assays and this was at high doses.

Occupational exposure data was reviewed for 15 employees of the FMC Corporation, Baltimore facility. The highest reported exposure was 0.130 mg/m³ after 6.5 hours of exposure. Signs or symptoms after exposure to 7-hydroxy were not reported with these data. This value was almost 2 magnitudes of order lower than values derived from an inhalation study in rats that were exposed for 6 hours. There were no observable effects in these rats at that concentration.

The U.S. Environmental Protection Agency has developed surrogate threshold values of toxicity called the reference dose (RfD). This is defined as the amount of a substance that can be taken in food or water daily without causing adverse health effects. The RfD is derived by data generated from good scientific practice, a dose with no observable effect level (NOAEL), and uncertainty factors to extrapolate data generated from animals to humans, acute to chronic studies, and intraspecies variations. Using data from the 90-day rat study cited above, we estimate an oral RfD to be 2.1 mg/kg-day. Data from acute studies are not inconsistent with this value.

Information on the environmental fate of this compound is scarce. Our conclusion — based on review of available information and best professional judgment — is that 7-hydroxy should not pose a chronic threat to the environment if accidentally released.

7-Hydroxy should not cause adverse health or environmental effects at levels seen under typical occupational operating conditions. In the event of an accidental spill, (as with all chemicals released in great quantities), individuals should wear personal protective gear, although no adverse health effect would be expected.

2. INTRODUCTION

7-Hydroxy is the chemical used to make carbofuran, a carbamate insecticide. Carbamates (e.g., Carbofuran, Sevin, Temik) are a general class of insecticides that are nonchlorinated selective central nervous system (CNS) agents. Carbofuran acts as a reversible inhibitor of acetylcholinesterase. They are considered less toxic than organo-phosphates and organo-chlorine insecticides.

Structurally, 7-hydroxy belongs to the phenol family. According to its molecular structure, 7-hydroxy possesses phenol's typical functional groups and appears to react similarly to phenol in forming covalent bonds with other chemicals. It is more reactive in organic solvents than in water.

When a chemical substance is released from a plant (such as an industrial plant), or a container, (such as a drum or bottle), it enters the environment. This release can — but does not always — lead to exposure. A person can only be exposed to a substance by coming into contact with it. Possible paths of exposure are by breathing, eating, or drinking substances containing the chemical or by skin contact. Once exposed, the chemical must enter the body by some pathway and be in great enough quantity (dose) to cause a toxic response. Other factors are important in determining whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the duration of exposure, exposure to other chemicals, and individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

We reviewed industrial studies and studies published in the medical/toxicological literature, most of which were found by computer searches. Many, but not all, of the animal studies were funded by FMC Corporation and conducted by an independent laboratory. We often found that computer searches for "7-hydroxy" or its synonyms resulted in information on the end product, carbofuran. One must carefully read these studies because 7-hydroxy is a much different chemical with properties different from carbofuran. Studies were evaluated for the quality of the experimental design and data produced. Toxicological information shows that the 7-hydroxy's LD₅₀ value ranges from 1800 to 3000 mg/kg body weight (bw) for rats. LD₅₀ values for rats for phenol and carbofuran are approximately 530 mg/kg and 6 to 13 mg/kg bw, respectively, making them more toxic.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The purpose of this chapter is to provide an overall summary of the toxicology of 7-hydroxy. It contains descriptions of toxicological studies done on 7-hydroxy and provides information on the compound's possible effects on public health.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

The information in this section is organized by route of exposure — inhalation, oral, and dermal. Information within each route of exposure is organized by health effect — death, systemic, immunologic, neurological, reproductive, developmental, genotoxic, and carcinogenic effects.

Levels of significant exposure for each route are presented in tables, except for those by inhalation exposure, for which only 2 studies were located. Data in these tables consist of no-observed-adverse-effect-levels (NOAEL), lowest-observed-adverse-effect-levels (LOAEL), median lethal doses (LD_{50}) and median lethal concentrations (LC_{50}). LOAELs have been classified into serious or less serious effects. Serious effects are those that evoke failure in a biological system leading to morbidity, including possibly mortality. Less serious LOAELs are those effects that cause significant dysfunction.

There were no human studies specifically evaluating the health effects of exposure to 7-hydroxy. However, ETI reviewed exposure data for 15 employees at the FMC Corporation's Baltimore plant. These data are summarized in section 5.5, *General Population and Occupational Exposure*.

Most studies reviewed in this section are rodent studies. The largest number of studies use forced oral ingestion (gavage). There are only a few that evaluate the toxicity of 7-hydroxy via inhalation and dermal exposure. The goal of most of the studies was to determine the LD_{50} or LC_{50} . (Tables 3.1 to 3.3).

3.2.1 INHALATION EXPOSURE

No studies were located regarding lethal effects in humans after inhalation exposure to 7-hydroxy. Two studies that exposed animals to 7-hydroxy were obtained and reviewed.

3.2.1.1 DEATH

Six male albino rats (strain and weight not given) were exposed to 7-hydroxy in an exposure chamber for 1 hour. The compound was passed through an atomizer with compressed air resulting in a chamber flow rate of 2.5 L/min (Fogelman, 1974, NCT 610.01). The LC_{50} was determined to be 167,000 mg/m³. Altered states of activity, tearing, and salivation followed exposure. Gross necropsy of deceased subjects revealed blanched kidneys in exposed animals. This study did not include a control group.

3.2.1.2 SYSTEMIC EFFECTS

No studies were located regarding effects in the cardiovascular, gastrointestinal, hematological, musculoskeletal, or hepatic systems in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.2.1 Dermal/Ocular Effects

No studies were located regarding systemic dermal or ocular effects in humans after inhalation exposure to 7-hydroxy.

A group of 5 male and 5 female Sprague-Dawley rats (weights ranging from 252 to 290 grams for males and 225 to 257 grams for females) were exposed to 121 mg/m³ of 7-hydroxy for 6 hours in a whole-body exposure chamber. There were no deaths or signs of toxicity during the exposure and for 14 days thereafter (Freeman, 1987, A85-1662). The only definitive sign observed was red periocular fur in 1 rat in the test group. All rats gained weight and no differences were observed between control and test groups. No gross lesions were observed in between test and control animals at necropsy.

3.2.1.2.2 Renal Effects

No studies were located regarding systemic renal effects in humans after inhalation exposure to 7-hydroxy.

As reported in section 3.2.1.1, 1 study showed that white albino rats exposed via inhalation to an LC_{50} dose (167,000 mg/m³) of 7-hydroxy had blanched kidneys (Fogelman, 1974, NCT 610.01), which may be a generalized sign of CNS failure (i.e., control of blood flow) rather than the direct toxicity of 7-hydroxy. The study did not provide further information regarding other possible effects.

3.2.1.3 IMMUNOLOGICAL EFFECTS

No studies were located regarding immunologic effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.4 NEUROLOGICAL EFFECTS

No studies were located regarding specific neurological effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.5 REPRODUCTIVE EFFECTS

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.6 DEVELOPMENTAL EFFECTS

No studies were located regarding developmental effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.7 GENOTOXIC EFFECTS

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.1.8 CARCINOGENIC EFFECTS

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to 7-hydroxy.

3.2.2 ORAL EXPOSURE

3.2.2.1 DEATH

No studies were located regarding lethal effects in humans after oral exposure to 7-hydroxy.

Several animal studies were conducted to determine the lethal oral dose of 7-hydroxy; these are summarized in Table 3.1. The first 3 studies reveal LD₅₀s that are considerably lower than those discussed in other studies covered in this section. As a subgroup, the studies were completed in the same facility in 1965, subjects were younger in age, and probably did not conform to FDA or EPA Good Laboratory Practice Standards. A possible explanation of these data would be that the facility administered a contaminated or incorrectly formulated "7-hydroxy," which was more

toxic than the other agents. This is supported by the fact that in 1967 the same testing facility administered 7-hydroxy using the same protocol and the same small sample size; they then determined the LD₅₀ to be much higher and comparable to the LD₅₀ in the majority of later studies. These three studies (Palazzolo, 1965, NCT 111.01; Palazzolo, 1965, NCT 98.01; Palazzolo, 1965, 111.02), summarized below, present a complete set of the data we reviewed. Because of these concerns, however, the data from the three 1965 studies were judged to be highly uncertain, and were not used for further evaluation.

In an acute toxicity study, an LD₅₀ of 24 mg/kg bw was determined. Four groups of 2 male and 2 female albino Sprague-Dawley rats, with an average body weight of 165 grams, were given doses ranging from 12 to 40 mg/kg bw of 7-hydroxy in a 0.1% (w/v) propylene glycol solution directly into the stomach using a hypodermic syringe equipped with a ball-tipped intubating needle (Palazzolo, 1965, NCT 111.01). Necropsy of the animals that died as well as animals sacrificed at the end of the 14-day observation did not reveal any significant gross pathological alterations in the tissues and organs. Toxic signs that followed oral administration included muscular weakness, sedation, loss of righting reflex, diarrhea, and analgesia in all treated groups.

In another study using the same procedure, doses of 7-hydroxy in a 1% (w/v) solution in corn oil ranging from 178 mg/kg bw to 600 mg/kg bw were administered to 2 male and 2 female young albino Sprague-Dawley rats (average body weight of 135 grams). An acute oral LD₅₀ was determined to be 400 mg/kg bw. Toxic signs that followed oral administration include muscular weakness, sedation, loss of righting reflex, diarrhea, and analgesia in all groups. Necropsy of the animals that died did not show any significant gross pathologic alterations in the tissues or organs.

In another acute toxicity study, the LD₅₀ was determined to be 33 mg/kg bw. Two male and 2 female albino Sprague-Dawley rats (average body weight of 185 grams) were administered 18 to 60 mg/kg bw doses of 7-hydroxy in 0.1% (w/v) propylene solution via stomach intubation (Palazzolo, 1965, NCT 98.01). No significant gross pathologies were seen in any of the test animals. Reactions following dosing included ataxia, muscular weakness, hypoactivity, and salivation. Reactions occurred 2 to 10 minutes after dosing and persisted up to 6 hours.

The following studies demonstrate LD₅₀ values and toxic signs that are comparable from study to study.

Two male and 2 female Sprague-Dawley rats with a body weight range of 140 to 180 grams were administered via stomach intubation 7-hydroxy by itself and in 2 other

solutions: 25% (w/v) solution in corn oil and 75% (w/v) solution in propylene glycol. Actual doses of 7-hydroxy ranged from 900 mg/kg bw to 3000 mg/kg bw. The acute LD₅₀s for the undiluted, corn oil, and propylene glycol vehicles were 2200 mg/kg, 1800 mg/kg, and 1800 mg/kg, respectively (Schoenig, 1967, NCT 142.01). Signs of toxicity following administration of the mixtures were no different than noted before. Ataxia, salivation, hyperapnea, bloody nasal discharges, muscular weakness, hypoactivity, sedation, and prostration were noted 20 minutes after administration for all animals in all groups. Free blood in urine and tremors were noted 3 to 5 hours after dosing in the same animals. Animals receiving 3000 mg/kg bw of 7-hydroxy also exhibited intermittent tonic convulsions 3 hours after dosing. All reactions subsided 22 hours after dosing, except hypoactivity and muscular weakness persisting 2 to 4 days or until death. No gross pathological changes were noted in tissues and organs of animals that died during the study or those sacrificed at the end of the 14-day period.

Young male albino Charles River strain rats (approximate average body weight of 200 grams) were given doses of 7-hydroxy ranging from 400 to 10250 mg/kg bw by gavage (Kretchmar, 1971 NCT 437.01). A corresponding acute oral LD₅₀ greater than 3038 mg/kg bw was determined. Necropsy did not reveal any gross pathologic alterations among the animals that died or were sacrificed after 14 days. Toxic signs following administration include hypoactivity, ruffed fur, muscular weakness, and diarrhea.

In another gavage study (Freeman, 1984, A83-1133), the dose of undiluted 7-hydroxy ranged from 1800 to 3000 mg/kg bw for males and 1000 to 2300 mg/kg bw for female Sprague-Dawley rats. Male body weights ranged from 208 to 285 grams and female body weights ranged from 200 to 246 grams. The corresponding acute oral LD₅₀ were 2450 mg/kg bw for males and 1743 mg/kg bw for females. Predominant signs observed in all exposed groups, which began approximately 30 minutes after dosing and subsided within the first 24 to 48 hours, were lacrimation, decreased locomotion, oral discharge, tremors, and prostration. All signs of toxicity had subsided by the third day, at which time surviving animals had returned to normal.

In another study (Freeman, 1985, A84-1535), groups of 10 male and/or 10 female Sprague-Dawley rats were exposed to 7-hydroxy by gavage. Male body weights ranged from 229 to 278 grams and females ranged from 204 to 253 grams. The test material was administered as a 25% (w/v) solution in corn oil. The doses ranged from 2100 mg/kg to 3200 mg/kg bw. The acute oral LD₅₀ was determined to be 2,675 mg/kg bw. Predominant signs observed in all exposed groups, which began approximately 30 minutes after dosing, were abdominogenital staining, lacrimation, decreased locomotion, nasal discharge, oral discharge, and prostration. Most signs of toxicity subsided by day 7 for all doses and all surviving animals gained weight

by day 14. Necropsy of deceased animals showed the presence of blood in the stomach and intestine, petechial hemorrhages on the stomach, clear fluid in the thoracic cavity, and red fluid in the bladder. Surviving animals were sacrificed on day 14 and appeared normal when necropsied.

3.2.2.2 SYSTEMIC EFFECTS

No human or animal studies were located regarding cardiovascular, hematological, and dermal/ocular effects following oral exposure of 7-hydroxy. In general, the acute toxicity studies described above provide some information on systemic effects, but the purpose of the studies was to determine a lethal dose value and not to critically evaluate systemic effects. Some information regarding systemic effects from the above studies is provided under this heading for completeness.

3.2.2.2.1 Gastrointestinal Effects

No studies were located regarding gastrointestinal effects in humans following oral exposure to 7-hydroxy.

Two studies show that diarrhea was a common gastrointestinal sign for animals exposed to lethal doses of 7-hydroxy via gavage (Kretchmar, 1971, NCT 437.01). Necropsy of animals sacrificed or those that died did not show any significant gross pathologic alterations in the gastrointestinal tract. In another study, histopathological examination of animals that died following exposures ranging from 1350 to 3038 mg/kg bw of 7-hydroxy showed gastrointestinal bleeding (Harrison, 1976, ACT 12.01). In a similar study, histopathological examinations of animals that died showed blood and hemorrhages in stomachs and intestines in animals exposed to 7-hydroxy at levels ranging from 2100 to 3200 mg/kg bw (Freeman, 1985, A84-1535). It was not clear from the laboratory reports what caused the bleeding.

3.2.2.2.2 Musculoskeletal Effects

No studies were located regarding musculoskeletal effects in humans following oral exposure to 7-hydroxy.

One of the most common signs exhibited by animals exposed to 7-hydroxy at all levels of exposure is muscular weakness (Kretchmar, 1971, NCT 437.01; Harrison, 1976, ACT 12.01; Schoenig, 1967, NCT 142.01). The duration of the reaction increases at higher treatment levels until animals succumb to death at the highest treatment levels. This sign supports a general CNS effect rather than toxicity to skeletal muscle.

3.2.2.2.3. *Renal Effects*

No studies were located regarding renal effects in humans following oral exposure to 7-hydroxy.

Effects of 7-hydroxy on the kidneys and other urinary system structures were sparse. Typically, gross signs (free blood in urine, blood in urinary bladder, and pale and discolored kidneys) were noted in 1 to 2 subjects (sample size: 40 rats, 10 per treatment level, 5 males, 5 females). These signs were atypical and inconsistent among treatment groups and were not thought to be reflective of 7-hydroxy intoxication. Pale and discolored kidneys were observed in animals exposed to 7-hydroxy in doses ranging from 1350 to 3038 mg/kg bw (Harrison, 1976, ACT 12.01). In the same study, blood was found in the urinary bladder in 1 animal exposed to 2025 mg/kg bw. In another study, red fluid was found in the bladder of some animals exposed to 2300 and 3200 mg/kg bw. Free blood in the urine was observed in animals exposed to 900 to 3000 mg/kg bw (Schoenig, 1976, NCT 142.01).

3.2.2.2.4 *Hepatic Effects*

No studies were located regarding hepatic effects in humans following oral exposure to 7-hydroxy.

Gross pathological assessment of internal organs revealed a very pale and discolored liver in only 1 rat exposed to 2025 mg/kg bw and 2 rats exposed to 3038 mg/kg bw of 7-hydroxy (Harrison, 1976, ACT 12.01). This was an inconsistent sign and therefore not considered a specific effect of 7-hydroxy toxicity.

3.2.2.2.5 *90 Day Exposure in the Rat*

The following study used good experimental design and examined several systemic and histologic variables. The study was limited by insufficient doses to produce an adverse effect. Nevertheless, the doses in this study can be compared favorably to those used in other studies reviewed in this document.

In a 90-day feeding study, groups of albino Charles River strain rats were given 7-hydroxy at levels of 300, 1,000 and 3,000 mg/kg diet (Reyna, 1972, NCT 481.31). Examination of animals did not reveal significant differences between the control and experimental animals for body weight gain, food consumption, and survival at the 3,000 mg/kg diet treatment level, resulting in a NOAEL of 208 mg/kg-day bw. Blood values were not different between groups (total leukocyte, erythrocyte, hemoglobin, hematocrit, lymphocyte, neutrophils, monocytes, eosinophils, basophils, serum alkaline phosphatase, serum glutamic-pyruvic transaminase activity, blood urea, fasted blood glucose). There was no effect on urine (glucose,

albumin, pH) chemistry. There were no significant differences between controls and test animals for erythrocyte, plasma, cholinesterase, and brain cholinesterase activities. Gross and microscopic studies (including organ weights) of gastrointestinal tract, liver, kidneys, spleen, pancreas, urinary bladder, pituitary gland, adrenal gland, testes, seminal vesicle, ovaries, bone marrow, thyroid and parathyroid glands, salivary gland, prostate, heart, aorta, lung, lymph node, skeletal muscle, peripheral nerve, femur, spinal cord, uterus, trachea, eye, optic nerve, and brain revealed no differences between control and treated animals.

3.2.2.2.6 Other

In a study using a mixture of 3 phenolic metabolites of 7-hydroxy (Harrison, 1976, ACT 12.01), 4 groups of 10 young albino Sprague-Dawley rats (5 male and 5 female, with approximate average body weight of 210 grams) were exposed by gavage. The 3 metabolites were 20.75 grams of FMC 10272 Technical, 9.39 grams of FMC 16497 Technical, and 15.36 grams of FMC 16490 Technical. Doses administered in 15% (w/v) corn oil suspension ranged from 900 mg/kg bw to 3038 mg/kg bw. The acute oral LD₅₀ was determined to be 2,300 mg/kg bw. Signs exhibited by 2 of 8 animals, post-oral administration at the 900 mg/kg bw dose level, included hypoactivity and muscular weakness subsiding after 22 hours. Signs exhibited by all exposed animals in the highest test group (3,038 mg/kg bw) persisting for 6 days or until death include hypoactivity, muscular weakness, labored breathing, ptosis, prostration, salivation, lacrimation, convulsions, and ruffed fur. Histopathological examination of animals that died during the experiment revealed red, discolored lungs, gastrointestinal hemorrhages, and pale, discolored kidneys (Harrison, 1976, ACT 12.01) In addition, blood was found in the urinary bladder of 1 animal and very pale and discolored livers were seen in 3 other animals exposed to 2025 and 3038 mg/kg bw. Examination of survivors did not show any gross pathology of organs or tissues.

The following studies administer metabolites of carbofuran (one of which is 7-hydroxy) to hens and dairy cows. No adverse health effects are seen, but the studies suffer from not administering a dose that demonstrates such effects. The cow study is more helpful than the hen study because of the higher doses, 200 mg/kg diet for a relatively long period, at 18 days. The cows were lactating (a sensitive physiological parameter).

Three groups of 4 lactating Holstein dairy cows (Reno, 1973, NCT 507.52) were fed a diet containing premixed equal parts of 3 phenolic metabolites of Carbofuran (2,2-dimethyl-3,7-dihydroxy-2,3-dihydro-benzofuran, 2,3-dihydro-7-hydroxy-2,2-dimethyl-3-oxobenzofuran, and 2,3-dihydro-2,-dimethyl-7-hydroxy-benzofuran) at concentrations ranging from 20 to 200 mg/kg diet (i.e., 6.67 to 66.7 mg for each metabolite) for 28 days. A fourth group of animals served as controls and received a

diet free of 7-hydroxy metabolites throughout the study. Observed signs included altered states of activity (not specified), tearing, and salivation. After 28 days, 2 animals from each group were sacrificed. Surviving animals were given the diet free of 7-hydroxy for an additional 15-day period after which all surviving animals were sacrificed. For all doses, treated animals were normal in appearance and behavior when compared with controls. A NOAEL of 1.84 mg/kg-day bw was derived from the highest dose group. Mastitis (inflammation of the mammary gland) was observed in 1 animal from each of 2 highest treatment groups (60 and 200 mg/kg diet) and 1 in the control group. This does not appear to be related to chemical exposure. Animals generally showed body weight gain during the test periods with corresponding increases in milk production. There was no evidence of gross tissue alterations among the sacrificed control and treated cows.

Three groups of 10 laying hens each received test diets which contained premixed equal parts of 3 metabolites of carbofuran at concentrations ranging from 2 to 20 mg/kg diet (i.e., 6.67 to 66.7 mg. for each metabolite) for 28 days (Reno, 1973, NCT 508.52). A fourth group of 10 hens served as controls and received a diet free of 7-hydroxy throughout the study. After 28 days, 5 hens from each group were sacrificed; all surviving hens in the 4 groups were returned to the diet free of 7-hydroxy for a 15-day recovery period. After the recovery period, all remaining birds were sacrificed. A NOAEL of 0.35 mg/kg-day bw was derived from the highest treatment group. Test hens were normal in appearance and behavior when compared with controls. Body weight changes, food consumption, and egg production in tested animals were similar to the controls. There was no evidence of gross tissue (liver, gizzard, skin, fat, and kidneys) alterations among the sacrificed control and test hens.

3.2.2.3 IMMUNOLOGICAL EFFECTS

No studies were located regarding immunologic effects in humans or animals following oral exposure of 7-hydroxy.

3.2.2.4 NEUROLOGICAL EFFECTS

No studies were located regarding specific neurological effects in humans or animal studies following oral exposure of 7-hydroxy.

Some of the most common signs following oral exposure to 7-hydroxy are neurologically based and include hypoactivity, ataxia, loss of righting reflex, tremors, and convulsions. Hypoactivity and ataxia are observed in all treated animal groups. The duration of these signs tends to correspond directly with the level of exposure (Schoenig, 1967, NCT 142.01; Kretchmar, 1971, NCT 437.01; Harrison, 1976, ACT 12.01; Freeman, 1985, A84-1535; Freeman, 1984, A83-1133). Tremors and

convulsions were observed in treated animals at the 2300 and 3038 mg/kg of 7-hydroxy levels (Freeman, 1984, A83-1133; Freeman, 1985, A84-1535).

3.2.2.5 REPRODUCTIVE EFFECTS

No studies were located regarding reproductive effects in humans or animals following oral exposure of 7-hydroxy.

3.2.2.6 DEVELOPMENTAL EFFECTS

No studies were located regarding developmental effects in humans or animals following oral exposure of 7-hydroxy.

3.2.2.7 GENOTOXIC EFFECTS

No studies were located regarding genotoxic effects in humans following oral exposure of 7-hydroxy.

Two studies tested the mutagenic activity (the induction of sex-linked recessive lethal mutations) of 7-hydroxy in *Drosophila melanogaster* (Valencia, 1983, A83-1047; Valencia, 1983, A83-1020). One thousand ppm of the compound was administered to adult male flies in a feeding solution containing 10% ethanol and 5% sucrose in water. It was shown that the compound does not induce mutations in *Drosophila melanogaster* when administered to male flies orally.

The objective of the following genotoxic studies was to evaluate 7-hydroxy for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations. Genotoxic effects in tester strains TA98, TA1537, and TA 1538 of *Salmonella typhimurium* are expressed as reverting from histidine dependence (auxotrophy) to histidine independence (prototrophy) by frame shift mutagens. Tester strains TA100 and TA1535 are reverted by mutagens that cause base substitutions. The *S. typhimurium* strains are all histidine auxotrophs resulting from mutations in the histidine operon. When histidine-dependent cells are grown in a minimal media containing a trace of histidine, only those cells that revert to histidine independence are able to form colonies. The trace amount of histidine allows all cells to undergo a few divisions. When a mutagen is added to this growing media, the mutation frequency is increased 2 to 100-fold. Cells which grow to form colonies are assumed to have reverted to histidine independence. For a test article to be considered positive, it must cause at least a doubling in the mean revertants per plate of at least 1 tester strain. This increase in the mean number of revertants per plate must be associated by a dose response to increasing concentrations of the test compound. *In vitro* genotoxic data are presented in Table 3.2. A review of these studies suggest that 7-hydroxy may exhibit weak genotoxic

effects in some strains of *Salmonella typhimurium*, especially *Salmonella* strain TA1535 in the absence of Aroclor 1254-induced rat liver microsomes. 7-Hydroxy did not induce gene mutations at the TK locus in several bacterial/microsomal assay systems, including *Salmonella* strains TA98, TA100, TA1537, and TA1538 in the absence or the presence of Aroclor 1254-induced rat liver microsome and in 1 yeast study with *Saccharomyces cerevisiae*.

In another study with mouse lymphoma cells (L517YTK+/-), 7-hydroxy induced genetic mutations in the presence and absence of Aroclor-induced rat liver microsome (Kirby *et.al.*, 1983). Genotoxic effects in mouse lymphoma cells (L5178YTK+/-) are expressed as reverting from TK+/- to TK-/- when grown in a restrictive medium (only TK -/- cells will grow in this medium).

Four nonactivated and 2 activated cloned cultures (aroclor-induced rat liver) exhibited mutant frequencies which were significantly greater than the mean mutant frequency of solvent controls. These results indicate that a positive dose response exhibited a mutant frequency at least 2-fold greater than the background level.

3.2.2.7 CARCINOGENIC EFFECTS

No studies were located regarding carcinogenic effects in humans or animal studies following oral exposure of 7-hydroxy. The chronic animal studies reviewed in this document did not report increases in tumors.

3.2.3 DERMAL AND OCULAR EXPOSURE

Five dermal toxicity studies were reviewed for this section and are summarized in Table 3-3. These data demonstrate reversible corneal opacity results after a one-time direct exposure and that 7-hydroxy causes slight erythema, particularly when applied to abraded skin.

3.2.3.1 DEATH

No studies were located regarding lethal effects in humans after dermal exposure to 7-hydroxy.

In an acute dermal toxicity study, 7-hydroxy was topically applied to the shaved backs of 2 groups of 4 adult albino rabbits (strain and weight not given) and the rabbit was left in an impervious cuff for 24 hours. The dosage levels were 1000 and 5000 mg/kg bw (Fogelman, 1974, NCT 610.01). The LD₅₀ is estimated to be greater than 5000 mg/kg since only 1 rabbit died at the 1000 mg/kg bw treatment level, and it "was unrelated to the compound". No other details regarding signs of toxicity were given in this study.

In another study, undiluted 7-hydroxy was applied to the shaved backs of 16 adult albino New Zealand rabbits (8 male and 8 female) with an average body weight of 2.5 kg. (Palazzolo, 1965, 111.02). Dose levels ranged from 3000 to 10,200 mg/kg bw. The exposure site was covered by an impervious wrap and remained in place for 24 hours. The dermal LD₅₀ was determined to be 5,600 mg/kg bw. All animals receiving 6,800 and 10,200 mg/kg bw of 7-hydroxy exhibited bloody rhinitis prior to death. Death occurred 6 to 18 hours following treatment for animals receiving 6,800 and 10,200 mg/kg bw. All test animals exhibited moderate to severe erythema and edema 24 hours following exposure. These reactions subsided and by the end of the 14-day observation period the skin of surviving animals appeared normal. Necropsy of animals that died during the study and those sacrificed did not reveal any significant gross pathological alterations in (unspecified) examined tissues and organs.

3.2.3.1.1 *Ocular Effects*

No studies were located regarding ocular effects in humans after dermal exposure to 7-hydroxy.

Ninety-eight percent pure 7-hydroxy was applied to the eyes of 4 New Zealand white rabbits at a dose of 0.1 ml (Freeman, 1985, A84-1536). The eyes of 2 rabbits were rinsed with 100 ml of tap water 20-30 seconds after treatment while the eyes of the other 2 rabbits remained unwashed. Eyes were assessed for irritation using the Draize method. All eyes in the treatment groups exhibited moderate conjunctivitis and corneal opacity 1 hour after dosing. Conjunctivitis was not observed 7 days after dosing; however corneal opacity was still observed in the unwashed eyes and 1 unwashed eye. All corneal opacity was resolved 13 days after dosing. The test material was considered moderately irritating to both washed and unwashed eyes.

In another study, 8 rabbits (strain and weight not given) were randomly divided into 2 groups. Approximately 100 mg of 7-hydroxy was introduced into the conjunctival sac of 1 eye per rabbit (Fogelman, 1974, NCT 610.01). In Group I, consisting of 5 rabbits, the treated eyes were washed after a 5-minute exposure, while the 3 rabbits in Group II were washed after a 24-hour exposure. Discernible opacity of the cornea, and irritation and swelling of the conjunctiva were observed in all treated animals 1 hour following treatment, persisting 48 hours after exposure. No other details regarding toxic effects were given in this study.

3.2.3.1.2 *Dermal Effects*

No studies were located regarding dermal effects in humans after dermal exposure to 7-hydroxy.

Ten New Zealand rabbits were treated with 20 and 300 mg/kg bw (5 per dosage group) of 7-hydroxy on intact skin for 24 hours under an occlusive wrap (Freeman, 1984, A83-1168). No control treatment group was used in this study. Skins were scored for irritation using the Draize method. All animals remained healthy throughout the study. Most of the animals lost weight by day 14. Desquamation of the skin over the test sites was the only irritation sign observed. At necropsy, no gross lesions were observed. The test material was considered to be non-irritating and practically non-toxic when applied topically under these conditions.

In another study, Technical (0.3 mls of a 50% w/v solution in 80% ethanol) 7-hydroxy was applied topically to hairless left shoulders of 20 Hartley guinea pigs (Freeman, 1987, A87-2274). No control treatment group was used in this study. The test material was applied 3 times, 1 week apart, and was left in contact with the skin for approximately 6 hours each time. Fourteen days after the third induction, the animals were tested with the material at a virgin test site. All animals remained healthy throughout the study. Barely perceptible erythema was noted in 4 of 20 test animals following the initial induction. All animals gained weight throughout the study. Three animals in the test group had slight erythema at challenge. 7-Hydroxy is judged to be non-sensitizing under these conditions.

In a different study, 6 adult albino rabbits (strain and weight not given) were exposed to 7-hydroxy by applying 50mg to each side of each rabbit; 1 side abraded, the other side intact and both covered with an impervious cuff for 24 hours (Fogelman, 1974, NCT 610.01). The only signs of toxicity were slight erythema and/or edema on the abraded skin on 4 of the 6 rabbits exposed to 7-hydroxy. No controls were used in this study.

3.2.3.2 SYSTEMIC EFFECTS

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, musculoskeletal, or renal effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.2.3.3 IMMUNOLOGICAL EFFECTS

No studies were located regarding immunologic effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.2.3.4 NEUROLOGICAL EFFECTS

No studies were located regarding neurological effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.2.3.5 REPRODUCTIVE EFFECTS

No studies were located regarding reproductive effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.2.3.6 DEVELOPMENTAL EFFECTS

No studies were located regarding developmental effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.2.3.7 GENOTOXIC EFFECTS

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 7-hydroxy.

3.2.3.8 CARCINOGENIC EFFECTS

No studies were located regarding carcinogenic effects in humans or animals after dermal or ocular exposure to 7-hydroxy.

3.3 ECOLOGICAL RECEPTORS

Only a few acute toxicity studies were located describing the effects of exposing ecological receptors to 7-hydroxy. Four similar studies evaluated the effects of 7-hydroxy exposure to 2 different daphnid test species (*Daphnia pulex* and *Daphnia magna*). In all studies, the daphnia were exposed to test concentrations of 7-hydroxy ranging from 0.64 mg/L to 50 mg/L (CELS, 1994). Ten daphnia of both species were tested for each treatment. The LC₅₀ for the 2 tests with *Daphnia pulex* (LC₅₀ is defined as the concentration of the chemical in water that causes 50% mortality under a 96-hour interval) were 16.4 and 16.7 mg/L. The LC₅₀s for *Daphnia magna* were 25.1 and 26.0 mg/L. No other signs of toxicity were reported.

In 2 similar studies, 10 fathead minnows (*Pimephales promelas*) per treatment were exposed to 7-hydroxy ranging in dosage from 0.64 to 50 mg/L (CELS, 1994). The resulting LC₅₀ values were 29.0 and 29.7 mg/L. No other signs of morbidity were reported in these studies.

In a different toxicity study (Hutchinson, 1972, NCT 476.61), the susceptibility of fish to 7-hydroxy was tested in terms of the 96-hour median tolerance limit (TL₅₀ is defined as the concentration of the chemical in water that causes 50 percent response under the test conditions during a 96-hour interval). The response observed in this study was death. Trout (*Oncorhynchus mykiss*) were supplied by a commercial trout

producer and had a mean weight of 0.8 grams and a mean length of 45 mm. Bluegill (*Lepomis macrochirus*) also came from a commercial producer and had a mean weight of 0.85 grams and a mean length of 40 mm. The bioassays were conducted under static conditions, without aeration, and with a single introduction of toxicant. Ten fish were tested for each treatment. The concentrations in the trout assay ranged from 21 to 75 mg/L and from 32 to 100 mg/L in the bluegill assay. The TL_{50} s after 24 hours were 48.1 mg/L for trout and 55.8 mg/L for bluegill and the corresponding 96-hour TL_{50} s were 32.3 and 39.1 mg/L, respectively. The no observed effect levels (NOEL) for the trout and bluegill were 21 and 32 mg/L, respectively. The behavior of the trout and bluegill dying from exposure to 7-hydroxy was characteristic of chemically poisoned fish. Moribund fish were first observed to become dark, lose equilibrium, and drop to the bottom of the tank where they eventually died.

3.4 INTERACTION WITH OTHER CHEMICALS

No information was located in the scientific literature regarding the potential interaction of 7-hydroxy with other chemicals.

3.5 ESTIMATING A SURROGATE REFERENCE DOSE (RfD).

The U.S. EPA assumes that chemical substances have a threshold value for noncarcinogenic effects, equal to or below which a chemical can be consumed daily without adverse health effects. Above this value the likelihood of adverse health effects increase. The threshold value used by U.S. EPA is the Reference Dose (RfD). It is based on no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) values from toxicology studies and is usually adjusted by uncertainty factors. Uncertainty factors allow for animal data to be extrapolated to human data; extrapolation of data between different species of test animals; use of LOAEL in the absence of NOAEL; and using data derived from acute studies for chronic exposures. The NOAEL represents the highest exposure level not eliciting an adverse effect in rats exposed to 7-hydroxy.

A surrogate oral subchronic RfD of 2.1 mg/kg-day bw for 7-hydroxy was estimated from a 90-day rat feeding study (Reyna, 1972, NCT 481.31). This was calculated using a NOAEL of 208 mg/kg-day bw and adjusting this with an uncertainty factor of 100. The uncertainty factor, applied to the NOAEL, was the product of a value of 10 for extrapolating from animals to humans and 10 for extrapolating to protect sensitive populations (U.S. EPA, 1989). This value may also be considered a chronic oral RfD as a 90-day exposure covers more than 10% of a rat's lifetime (U.S. EPA, 1989).

3.5.1 DISCUSSION

Review of this literature shows that human reactions to 7-hydroxy have not been documented. There are animal studies; most of these are acute toxicity studies using rats. *Salmonella* genotoxicity studies have also been reviewed. One rat study (90-day feeding study) of sound experimental design was evaluated and used to estimate an oral RfD. Acute oral toxicity is defined exclusively for rats, but lacking in other test species. Inhalation data are minimal. Dermal and ocular toxicity data are also reviewed.

Signs associated with acute toxicity included hypoactivity, muscular weakness, disturbed balance, and tearing. Death usually occurred within an hour of administration at the LD₅₀. Those rats receiving a less than lethal dose displayed no signs of toxicity 48 hours after administration.

It was interesting that among the acute toxicity studies, 3 studies report LD₅₀ values ≤ 400 mg/kg bw. Two of these were below 50 mg/kg bw, which is nearly 2 orders of magnitude lower than the majority of the studies reviewed. The discrepancy be due to these old studies not using or following what today would be called standard laboratory practices; it may also indicate that the chemical used may be different than the other 7-hydroxy compounds tested. It could not be exactly determined whether one or more of these reasons explain the low LD₅₀ and as a result, these studies were not used for further evaluation.

It is accepted that a threshold value exists for chronic exposure to chemicals that are not carcinogenic. We estimate a RfD value using data from the 90-day rat feeding study. This study had a satisfactory study design with adequate numbers of subjects per group. The highest doses tested, 208 mg/kg bw (3000 ppm) of 7-hydroxy in diet, did not demonstrate adverse effects over several body systems. Using the uncertainty factor of 100, subchronic and chronic RfD were estimated to be 2.1 mg/kg-day bw. Had the 90-day rodent study exposed rats to higher doses, our RfD may easily have been higher; it is, therefore, a conservative value.

This value is not inconsistent with the results of the rodent, hen, and cow acute studies. For example, using the rodent acute toxicity data, the lowest dose administered as a NOAEL value, and applying uncertainty factors of 10 interspecies, 10 intraspecies, and 10 for extrapolating from an acute to a chronic study, yields an RfD of 0.4 mg/kg-day bw. This is only 5-fold lower, but in the range of the chronic rat studies RfD value. Cows were fed the metabolites of carbofuran at 1.84 mg/kg-day bw for 28 days and no adverse health effects were noted.

In summary, the dose data for rats show that NOAELs range from 400-900 mg/kg bw, less serious LOAELs are approximately 1350 mg/kg bw, more serious LOAELs are 900-1800 mg/kg bw, and LD₅₀ are 1800 - 3000 mg/kg 7-hydroxy, demonstrating a consistent dose-response picture of the rat data.

The sum of data demonstrate that 7-hydroxy acts as a central nervous system depressant, not unlike many common solvents. It can be assumed that human exposure to large quantities of the chemical (i.e. ingestion for suicide) would prove lethal. The data do not demonstrate carcinogenicity, and if 7-hydroxy is mutagenic, it is only weakly so. Exposing the eye to 7-hydroxy may cause some temporary and reversible corneal damage.

The overall adequacy of the 7-hydroxy database is limited. Had this been a compound that was selective for the central nervous system (i.e., it binds to specific receptor class) the database would have been inadequate. More data would be helpful in evaluating the more sensitive body systems (i.e., immunologic, reproductive, neurologic). However, based on information from studies done on similar chemicals, the limited data available should not cause alarm. Occupational data would be helpful for future evaluation; we would expect it to be consistent with the effects seen at corresponding doses in this review.

TABLE 3-1. LEVELS OF SIGNIFICANT EXPOSURE TO 7-HYDROXY - Oral

Species	Route	Exposure Duration/Frequency	System	NOAEL (mg/kg/day)*	LOAEL (mg/kg/day) Less Serious	Serious	LD50 mg/kg	Reference
<i>Acute Exposure</i>								
<i>Death</i>								
Rat	Gavage	Once			2,100	2,675		Freeman, 1985, A84-1535
Rat	Gavage	Once			1,800m 1,000f	2,450m 1,743f		Freeman, 1984, A83-1133
Rat	Gavage	Once		900	1,350	2,300		Harrison, 1976, Act 12.01
Rat	Gavage	Once		400	1,350	>3038 <10250		Kretchmar, 1971 NCT 437.01
Rat	Gavage	Once			900	2,200 (undiluted)		Harrison, 1967 NCT 142.01
					900	1,800 (corn oil)		Schoenig, 1967 NCT 142.01
					900	1,800 (propylene glycol)		Schoenig, 1967 NCT 142.01
Rat ¹	Gavage	Once			267	400		Palazzolo, 1965 NCT117.01
Rat ¹	Gavage	Once		12	18	24		Palazzolo, 1965 NCT 111.01, NCT 111.02

TABLE 3-1. LEVELS OF SIGNIFICANT EXPOSURE TO 7-HYDROXY - Oral

Species	Route	Exposure Duration/Frequency	System	NOAEL (mg/kg/day)*	LOAEL (mg/kg/day) Less Serious	LD50 mg/kg	Reference
Acute Exposure							
Death (continued)							
Rat ¹	Gavage	Once		18	27	33	Palazzolo, 1965, NCT98.01
Intermediate Exposure							
Rat	Diet/Feed	90 days	Body/Organ Weight Gain	208			Reyna, 1972, NCT 481.31
			Hematological	208			Reyna, 1972, NCT 481.31
			Urine	208			Reyna, 1972, NCT 481.31
			Cholinesterase	208			Reyna, 1972, NCT 481.31
Cow	Diet/Feed	28 days	Body Weight Gain	1.84			Reno, 1973, NCT 507.52
Chicken	Diet/Feed	28 days	Body Weight Gain	0.35			Reno, 1973, NCT 508.52
			Egg production	0.35			Reno, 1973, NCT 508.52

* Unless otherwise noted.

m Male

f Female

¹ These studies were not used for analysis. See text for information.

TABLE 3-2. GENOTOXICITY OF 7 HYDROXY In Vitro

Species (test system)	Concentration mg/plate*	End Point	Results		Reference
			With** Activation	Without*** Activation	
Fungi					
<i>Saccharomyces cerevisiae</i> (D4)	0.01-5 µg / plate	Gene Mutation	-	-	Brusick, 1976, No. 2547
Invertebrate					
<i>Drosophila melanogaster</i>	1000 ppm Feeding Solution	Gene Mutation	NA	-	Valencia, 1983 A83-1047, A83-1020
Animal Cells					
Mouse Lymphoma (L5178YTK +/-)	0.0075-0.24 µg / ml	Gene Mutation	+	+	Kirby <i>et.al.</i> , 1983 A83-961
Bacteria					
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA98, TA1538)	0.01-5 µg / plate	Gene Mutation	-	-	Brusick, 1976, No.2547
<i>S. typhimurium</i> (TA98, TA100, TA595 TA1537, TA1538)	50-5,000	Gene Mutation	-	+(TA1535)	Haworth, <i>et.al.</i> , 1983 A83-927

TABLE 3-2. GENOTOXICITY OF 7 HYDROXY In Vitro (cont)

Species (test system)	Concentration mg/plate*	End Point	Results		Reference
			With** Activation	Without** Activation	
<i>S. typhimurium</i> (TA100, TA1535)	12.5-10,000	Gene Mutation	NA	+ (TA1535)	Haworth, et. al., 1983 A83-999, A83-998
<i>S. typhimurium</i> (TA98, TA100, TA1535)	0.01-20.0 µg / plate	Gene Mutation	-	-	DeGraff, 1983 A38-1038
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	40-6,600	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-1018
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	40-6,000	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-937
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	30-6,000	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-928
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	60-6,000	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-929
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	40 - 7,000	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-930

TABLE 3-2. GENOTOXICITY OF 7 HYDROXY In Vitro (cont)

Species (test system)	Concentration mg/plate*	End Point	Results		Reference
			With** Activation	Without*** Activation	
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	40 - 5,000	Gene Mutation	-	+ (TA1535)	Haworth, et. al., 1983 A83-936
<i>S. typhimurium</i> (TA1535)	2.5-10,000	Gene Mutation	NA	+ (TA1535)	Haworth, et. al., 1938 A83-938
<i>S. typhimurium</i> (TA1535)	2.5-10,000	Gene Mutation	NA	+ (TA1535)	Haworth, et. al., 1983 A83-954, A83-956 A83-959
<i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538)	123.5-3,333	Gene Mutation	-	+ (TA1535)	Farrow, et. al., 1983 A83-911
<i>S. typhimurium</i> (TA1535)	312.5-5,000	Gene Mutation	NA	+ (TA1535)	Haworth, et. al., 1984 A83-1084, A83-1085
<i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538)	61.73-1666.7	Gene Mutation	-	+ (TA1535)	Farrow, et. al., 1984, A83-842
<i>S. typhimurium</i> (TA98, TA100, TA1535 TA1537, TA1538)	61.73-1666.7	Gene Mutation	-	+ (TA1535)	Farrow, et. al., 1984, A83-843

NA: Not Applicable
-: Negative Results

+: Positive Results

*: Unless otherwise stated

** : With activated rat liver microsomes

***: Without activated rat liver microsomes

TABLE 3-3. LEVELS OF SIGNIFICANT EXPOSURE TO 7-HYDROXY - Dermal

Species	Route	Effect	Body System	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)* Less Serious Serious	LD50 mg/kg	Reference
Guinea Pig	Dermal/ 3 weeks/6 hours	Slight Erythema	Skin	3.04M			Freeman, 1987, A87-2274
Rabbits	Dermal/Once	Desquamation	Skin	20			Freeman, 1984, A83-1168
Rabbit	Dermal/Once	none	Skin	1,000	>5,000		Fogelman, 1974 NCT610.01
Rabbit	Dermal/Once Abraded	Erythema/Edema	Skin	50			Fogelman, 1974 NCT610.01
Rabbits	Dermal/Once	Severe Erythema/ edema	Skin		3,000	5,600	Palazzolo, 1965, NCT 111.01, NCT 111.02
Rabbits	Ocular/Once	Conjunctivitis Corneal opacity	Eye	6.56M			Freeman 1985 A84-1536
Rabbit	Ocular/Once	Conjunctivitis Corneal Opacity	Eye		100		Fogleman, 1974 NCT610.01

* unless noted
M Molar

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 7-hydroxy.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of 7-hydroxy.

4.3 DISCUSSION

The data and information on Tables 4-1 and 4-2 show that 7-hydroxy is a colorless to light brown liquid, with a mildly phenolic odor. The compound is stable under room temperature and is slightly soluble in water (less than 1%). Its volatility is low compared with typical volatile and semi-volatile organic compounds. Volatilization data at room temperature are not available. The vapor pressure value at high temperature suggests that 7-hydroxy is a low volatility compound. As the temperature (much above ambient temperatures) increases, volatilization is greater.

Structurally, 7-hydroxy belongs to the phenol family. According to its molecular structure, 7-hydroxy possesses the typical functional groups that other phenols have, and it appears to react as a phenol forming covalent bonds. It is more reactive in organic solvents than in water, which would suggest that binding to soil particles would be possible. This has been observed (Talebi and Walker, 1993, Deuel *et. al.*, 1979, Venkateswarlu, *et. al.*, 1977). Many typical chemical reactions for phenol should be applicable to 7-hydroxy.

It should be noted that computer network searches commonly retrieve information for carbofuran, rather than for carbofuran 7-phenol (i.e., 7-hydroxy). It is very easy to mistake information attributed to carbofuran for that attributed to 7-hydroxy. These two compounds are clearly different. Care must be taken when interpreting toxicological data since 7-hydroxy synonyms have either carbofuran as a prefix or benzofuran as a suffix.

Compared with carbofuran and benzofuran, the physical properties of 7-hydroxy are quite different. Carbofuran is an odorless, white, crystalline solid; benzofuran is an oil compound with an aromatic odor. 7-Hydroxy's chemical-physical parameters (e.g., density, odor, solubility) are characteristic of phenol; however, at room

temperature the physical states for these two compounds are different. 7-Hydroxy is liquid while phenol is solid.

TABLE 4-1. CHEMICAL IDENTITY OF 7-HYDROXY

Property	Value	Reference
Chemical Name	7-Hydroxy	MSDS Sheet
Synonyms	Carbofuran phenol Carbofuran 7-phenol 2,3-Dihydro-2,2-dimethyl-7-benzofuranol 2,3-Dihydro-2,2-dimethyl-7-hydroxybenzofuran	SANSS (also HSDB)
Trade Name	7-Hydroxy	MSDS Sheet
Chemical Formula	C ₁₀ H ₁₂ O ₂	HSDB
Chemical Structure		SANSS
Identification Numbers:		
CAS Registry	1563-38-8	HSDB 1994
RTECS	(a)	
EPA Hazardous Waste	(a)	
OHM-TADS	(a)	
DOT/UN/NA/IMCO shipping	(a)	
HSDB	5839	HSDB
NCI	(a)	
CAS	Chemical Abstracts Service	
NIOSH	National Institute for Occupational Safety and Health	
RTECS	Registry of Toxic Effects of Chemical Substances	
OHM-TADS	Oil and Hazardous Materials/Technical Assistance Data System	
DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code	
NCI	National Cancer Institute	
HSDB	Hazardous Substances Data Bank	
SANSS	Structure and Nomenclature Search System	
(a)	No data located.	

TABLE 4-2. PHYSICAL AND CHEMICAL PROPERTIES OF 7-HYDROXY

Property	Value	Reference
Molecular weight	164.21	MSDS sheet
Color	Colorless to light brown	MSDS sheet
Physical state	Liquid	MSDS sheet
Melting point, °C	(a)	
Boiling point at 1 mmHg, °C	85	MSDS sheet
Density, 25/4	1.0988	MSDS sheet
Odor	Mildly phenolic	MSDS sheet
Odor threshold		
Water	(a)	
Air	(a)	
Solubility		
Water	Less than 1%	MSDS sheet
Organic solvent	(a)	
Partition coefficient		
Log K _{ow}	(a)	
Log K _{oc}	(a)	
Vapor pressure at 124 °C, mmHg	10	MSDS sheet
Henry's law constant	(a)	
Autoignition temperature, °C	(a)	
Flash point	117.5	MSDS sheet
Flammability	(a)	
Stability	Stable	MSDS sheet
Conversion factor		
ppm (v/v) to mg/m ³ at 25 °C in air	1 ppm =	
0.149 mg/m ³	Andur 1991	
(a) - No data located.		

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

7-Hydroxy has the potential to be released into the environment during its manufacture, industrial use, and possibly by its disposal. Interestingly, 7-hydroxy is formed as the principal metabolite of degraded carbofuran, following its application as an insecticide. However, due to difficulties associated with incomplete recovery by chemical extraction of the compound in "non-flooded" soils, the identification and quantification of 7-hydroxy has rarely been reported (Talebi and Walker, 1993). In general, research discussed in this section has focused on the effectiveness of carbofuran as an insecticide and less on the effects of its breakdown. Therefore it is important to consider that the presence of 7-hydroxy in the various studies below was due to application of carbofuran, not the release of 7-hydroxy. Where appropriate, information on the potential for human exposure and the environmental behavior of 7-hydroxy was deduced from this research.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 AIR

No data regarding release of 7-hydroxy to the air could be located.

5.2.2 SOIL

7-Hydroxy is formed by the breakdown (presumably by microbes) of the insecticide carbofuran in soils. Although this has not been studied in detail, it is hypothesized that accelerated degradation is attributed to microorganisms that may have adapted or altered their metabolism over time.

5.2.3 WATER

7-Hydroxy as a metabolite may be released to surface waters by the runoff treated crops with carbofuran moved to surface waters (Deuel *et. al.*, 1979). In addition, dependent on percolation depth, carbofuran and its derivatives may reach beyond the root zone, potentially impacting groundwater (Ramanand, *et. al.*, 1988).

5.3 ENVIRONMENTAL FATE

It appears from these limited data and the reactivity of the compound that 7-hydroxy is degraded by microbes in the soil or binds covalently to soil particles. Therefore, the environmental risk, except for large spills, is low.

5.3.1 TRANSPORT AND PARTITIONING

7-Hydroxy apparently moves through soils by percolation. Results of a 1988 study indicate that both carbofuran and 7-hydroxy are more mobile in nonpuddled vs. puddled rice crops (Ramanand *et. al.*, 1988). The residues of carbofuran and its metabolite 7-hydroxy were recovered from leachates at both 15 cm and 30 cm depths of a studied nonpuddled wetland rice field. Percolation of the residues below the root zone may potentially lead to groundwater contamination.

In general, water quality of surface impoundments (H_2O gathered and enclosed for irrigation purposes) and estuaries in the vicinity of rice crops treated with carbofuran could be adversely affected by repeated applications of the insecticide during irrigation return flow processes (Deuel *et. al.*, 1979). How relevant this information is to 7-hydroxy is not known.

Following formation via hydrolysis in soil, 7-hydroxy is reported to bind rapidly to organic components of soil where it is subsequently metabolized by microorganisms (Talebi and Walker, 1993; Deuel *et. al.*, 1979; Venkateswarlu *et. al.*, 1977).

5.3.2 TRANSFORMATION AND DEGRADATION

7-Hydroxy is not volatile at ambient temperatures. It is slightly heavier than water, explaining its tendency to drop through the water column in still water. Mixing would occur, however, with any movement and agitation. Degradation in soil appears to be by nonspecific microbes.

5.3.2.1 AIR

No direct data regarding the transformation and/or degradation of 7-hydroxy in air could be located.

The volatility of carbofuran was found to be negligible in the laboratory environment (Deuel *et. al.*, 1979). This observation is further supported by the only slightly volatile nature of phenol (thought to behave similarly to 7-hydroxy) at ambient temperatures. It is therefore doubtful that significant amounts of carbofuran or its metabolites such as 7-hydroxy would be dissipated from rice paddy water via volatilization.

5.3.2.2 WATER

The decrease of carbofuran and its metabolites, such as 7-hydroxy, from the water of a rice-fish model ecosystem were thought to be attributed to factors such as evaporation, adsorption and/or photodecomposition, uptake by plant and fish, and microbial degradation (Zayed *et. al.*, 1988). 7-Hydroxy was shown to be a main degradation product, following photodecomposition of carbofuran (Metcalf *et. al.*, 1968; Archer, 1976 as cited in Zayed *et. al.*, 1988).

7-Hydroxy may sink as a nonaqueous-phase liquid in still water over time, given its specific gravity of 1.1 at 25° (MSDS).

5.3.2.3 SOIL

7-Hydroxy is the major hydrolytic metabolite of carbofuran. Following hydrolysis, 7-hydroxy is reported to bind rapidly to organic components of soil where it is slowly metabolized by microorganisms (Talebi and Walker, 1993; Deuel *et. al.*, 1979; Venkateswarlu *et. al.*, 1977). 7-Hydroxy is considered the principal metabolite found in flooded soil, but as previously mentioned, it is rarely reported in the literature due to difficulties associated with extraction, and incomplete recovery in non-flooded soil (Talebi and Walker, 1993).

Degradation of carbofuran in soil is reported to be enhanced in soils previously treated with the compound (Talebi and Walker, 1993).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 AIR

No data regarding the concentrations of 7-hydroxy in ambient air were located.

5.4.2 WATER

No data regarding the concentrations of 7-hydroxy in ambient surface or ground waters were located.

In a field study performed in India, designed to investigate leaching of carbofuran, levels of 7-hydroxy recovered in puddled and nonpuddled flood water analyses ranged from 0 to 3.0 (± 0.7) $\mu\text{g}/\text{ml}$ and 0 to 3.0 (± 0.5) $\mu\text{g}/\text{ml}$, respectively (Ramanand *et. al.*, 1988).

5.4.3 SOIL

No data regarding the concentrations of 7-hydroxy in ambient soils were located.

5.4.4 OTHER MEDIA

No data regarding the concentrations of 7-hydroxy in other environmental media could be located.

Data available on the insecticide carbofuran indicate that carbofuran does not seem to accumulate in fish to an appreciable extent (Zayed *et. al.*, 1988).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

No data regarding general population exposures to 7-hydroxy could be located.

ETI reviewed FMC Corporation's *Exposure Monitoring Summaries* for 8 job classes representing 15 employees at the Baltimore plant, where 7-hydroxy is used. Job classes included rigger, maintenance supervisor, pipefitter, welder, machinist, first class operator, shift supervisor, and unknown. Samples were obtained from personal monitoring devices and used to estimate inhalation exposure. Employees were monitored for at least 6 hours. Out of the 27 sample events, 17 analyses were "not detectable". The other 10 analyses had concentrations that ranged from >0.001 mg/m³ (0.1 ppb) to 0.130 mg/m³ (19.3 ppb) of 7-hydroxy. The 2 highest exposures were 0.130 and 0.086 mg/m³, which occurred when one employee removed a pump from operations and another cleaned a 7-hydroxy spill, respectively. Seven exposures ranged from 0.007 to 0.045 mg/m³ (1.0 to 6.7 ppm). These exposures occurred when employees cleaned or performed maintenance in 7-hydroxy operations. This exposure group comprised first class operators. We could not determine if symptoms or signs of chemical exposure were observed at any exposure level.

5.5.1 DISCUSSION

Since this compound is used as a chemical intermediate, employees of facilities producing or storing the compound could be at risk of high exposures. However, the data present evidence that cleaning a 7-hydroxy spill gives rise to only a small occupational exposure. There are no occupational guidelines or values for 7-hydroxy (i.e., American Conference of Governmental Hygienist). FMC Corporation *Exposure Monitoring Summaries* report a "FMC/TLV" limit of 0.013 to 0.033 mg/m³ (2.0 to 4.9 ppm) for occupational exposure. We do not know how this value was derived, but it is clear that exposures in the documents ETI reviewed were well below their limit.

There is only 1 animal study to compare with these occupational data. In that study, rats were given 121 mg/m³ of 7-hydroxy for 6 hours in a whole-body exposure chamber. No deaths or signs of toxicity were observed during or after the exposure, or 14 days later (Freeman, 1987, A85-1662). The highest exposure an employee received was almost 2 magnitudes of order lower (0.130 mg/m³) than the exposures to these rats. Although different species were involved, no adverse effects were reported, providing evidence of no adverse effects at measurable concentrations.

5.6 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No data identifying select human subpopulations as unusually susceptible to 7-hydroxy toxicity were located.

6. **SUMMARY STATEMENT**

Reviewing the studies described herein, and under the typical use patterns of a chemical intermediate, 7-hydroxy would not be expected to produce adverse health or environmental effects.

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