3-Methylcyclohexen-1-one (MCH) - Human Health and Ecological Risk Assessment FINAL REPORT

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USDA, Forest Service

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

a.e.	acid equivalents
a.i.	active ingredient
AEL	adverse-effect level
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
cm	centimeter
EAFUS	Everything Added to Food in the United States
EC_{50}	concentration causing 50% inhibition of a process
EC_{100}	concentration causing complete inhibition of a process
EIS	environmental impact statement
F	female
F_1	first filial generation
FDA	Food and Drug Administration
FS	Forest Service
g	gram
GC	gas chromatography
GRAS	generally recognized as safe
HQ	hazard quotient
IARC	International Agency for Research on Cancer
i.p.	intraperitoneal
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% mortality
LD_{50}	lethal dose, 50% mortality
LD_{95}	lethal dose, 95% mortality
LOAEL	lowest-observed-adverse-effect level
m	meter
M	male
MCH	3-methyl-2-cyclohexen-1-one
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
MW	molecular weight
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
PAFA	Priority-based Assessment of Food Additives
ppm	parts per million

RBC	red blood cells
RfD	reference dose
UF	uncertainty factor
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency
USDA	United States Department of Agriculture
>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
=	equal to
≃	approximately equal to

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8C°+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556F°-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
hectares (ha)	square meters	10,000
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($µg/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
$1 \cdot 10^{-10}$	0.0000000001	One in ten billion
$1 \cdot 10^{-9}$	0.000000001	One in one billion
$1 \cdot 10^{-8}$	0.00000001	One in one hundred million
$1 \cdot 10^{-7}$	0.0000001	One in ten million
$1 \cdot 10^{-6}$	0.000001	One in one million
$1 \cdot 10^{-5}$	0.00001	One in one hundred thousand
$1 \cdot 10^{-4}$	0.0001	One in ten thousand
$1 \cdot 10^{-3}$	0.001	One in one thousand
$1 \cdot 10^{-2}$	0.01	One in one hundred
$1 \cdot 10^{-1}$	0.1	One in ten
$1 \cdot 10^{0}$	1	One
$1 \cdot 10^{1}$	10	Ten
$1 \cdot 10^{2}$	100	One hundred
$1 \cdot 10^{3}$	1,000	One thousand
$1 \cdot 10^{4}$	10,000	Ten thousand
$1 \cdot 10^{5}$	100,000	One hundred thousand
$1 \cdot 10^{6}$	1,000,000	One million
$1 \cdot 10^{7}$	10,000,000	Ten million
$1 \cdot 10^{8}$	100,000,000	One hundred million
$1 \cdot 10^{9}$	1,000,000,000	One billion
$1 \cdot 10^{10}$	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

Introduction

3-Methyl-2-cyclohexen-1-one (MCH) is a relatively common chemical. It is produced by some animals *in vivo*, is found in a variety of foods, and is approved by the FDA as a food additive. In addition, MCH is a compound that can be used to disrupt the behavior of some forest insect pests, such as the Douglas-fir beetle, in a manner that inhibits infestations. The U.S. EPA is currently reviewing a request to register MCH as an insect control agent. This risk assessment document on human health effects and ecological effects was prepared to support an appraisal of the environmental consequences of using MCH in Forest Service programs.

This document has four chapters: the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections: an identification of the potential hazards associated with the commercial formulation of MCH, an assessment of potential exposure to these products, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure.

There is considerably little information regarding the toxicology and environmental fate of MCH. The most relevant information comes from unpublished studies conducted and submitted to the U.S. EPA in support of product registration. Because of the lack of a detailed recent review and the preponderance of unpublished relevant data in U.S. EPA files, a complete search of the EPA files was conducted. Full text copies of all relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs.

Program Description

The Forest Service anticipates using MCH as a pheromone to disrupt infestations of the Douglas-fir beetle. Pheromones are naturally occurring chemicals involved in the transmission of messages (i.e., chemical communication) within a species. The efficacy of MCH in disrupting infestations of the Douglas-fir beetle is well documented in the published and unpublished literature.

Currently, the Forest Service is considering only one potential formulation of MCH, known as the MCH bubble cap. Each bubble cap contains about 390 mg of MCH in a device that releases ≈4 mg/day over a 100- to 150-day period. Because MCH bubble caps are not used by the Forest Service, except in experimental applications, there is no standard practice regarding application rates or methods. The application under consideration by the Forest Service is 42 g a.i./acre or approximately 108 bubble caps per acre. Each bubble cap would be manually fixed to a tree. No broadcast or aerial applications are planned.

Human Health Risk Assessment

Hazard Identification

MCH is an approved food additive. Nonetheless, the toxicity data on MCH are very limited. Acute toxicity information is sparse and relatively poor, and there are no chronic or subchronic toxicity studies on MCH. While the classification given to MCH by the FDA as an approved food

additive is recognized and is incorporated into the hazard identification of this compound, the lack of information on the toxicity of this compound is also recognized. Notwithstanding the FDA classification of MCH as an approved food additive, the paucity of information on the toxicity of MCH to humans and other mammalian species is a predominant factor in the uncertainty in the risk characterization of this compound.

Exposure Assessment

Many chemicals used by the Forest Service may be applied by a relatively standard set of methods including aerial broadcast, ground broadcast/mechanical, or backpack. In such instances a relatively consistent set of exposure scenarios is used to assess exposure to workers as well as members of the general public. Most of these exposure scenarios and methods for estimating exposure are not relevant to the application method proposed for MCH. Consequently, only two exposure scenarios are considered quantitatively in this risk assessment: inadvertent dermal contact during placement of the MCH bubble cap by workers and imprudent handling of the bubble cap by a child.

Under typical conditions of placing the MCH bubble cap, workers should not be exposed to substantial levels of MCH. The MCH is encased in a plastic matrix that releases only very small quantities of MCH per unit time. The details of the packaging of MCH are treated as proprietary. Nonetheless, it can be assumed that the entire MCH bubble cap is encased in a packing material that is impermeable to MCH; otherwise, the bubble cap formulation would have an unacceptably short shelf life. Consequently, the only exposure scenario developed for workers involves accidental dermal contamination of the hands with MCH. The exposure scenario postulates that the bubble cap is ruptured in some way either during the removal of the bubble cap from the packing material or during the placement of the bubble cap on a tree. Based on the assumption that both hands are contaminated with MCH for 1 minute, estimates of absorbed dose do not exceed 2.1 mg/kg. The worst case exposure scenario, which may be highly implausible, assumes that the worker does not clean the contaminated hands for 1 hour. In this rather extreme exposure scenario, exposure is not likely to exceed 5.6 mg/kg. The dose estimate is limited not by the dermal absorption rate but by the amount of MCH contained in a single bubble cap.

Under normal conditions, members of the general public should not be exposed to substantial levels of MCH. Nonetheless, as a worst case scenario, it is assumed that a child encounters a bubble cap that was accidently dropped on to the ground or removed somehow from a tree. In this scenario, both dermal and oral exposure could occur through imprudent handling of the bubble cap. The maximum absorbed dose is estimated as 30 mg/kg.

Dose-Response Assessment

Except for a few acute toxicity studies, there is no information regarding dose-response relationships for MCH in humans or experimental mammals. MCH is similar to other compounds for which better data are available; however, the usefulness of these data for assessing the likely effects from exposure to MCH is limited. One acute toxicity study in rats suggests that doses as low as 500 mg/kg, the lowest dose tested, may be lethal and that death is most likely to be delayed for 2-7 days after exposure.

Other than the classification of MCH as an approved food additive, no existing guidelines or standards for MCH were found in the literature. Based on the information available during the preparation of this risk assessment, an estimated safe level for human exposure cannot be inferred from the approval of MCH as a food additive, except to indicate that the FDA judges that MCH poses no unreasonable risk at the levels in which it is present in foods. Neither the U.S. EPA nor the Agency for Toxic Substances and Disease Registry (ATSDR) derived an acceptable level of exposure forMCH.

Risk Characterization

This risk assessment is dominated by uncertainty because of the lack of adequate data regarding the toxicity of MCH. In the absence of adequate data, the characterization of risk must be conservative. The fact that MCH is an approved food additive and may be harmless at levels found in foods is of limited relevance to the characterization of risk for the use of MCH in bubble cap formulations.

MCH will be encased in a plastic matrix and released at a very slow rate into the open air, where concentrations should drop below levels that are likely to cause adverse health effects. Thus, under foreseeable conditions of normal application and use, there is no reasonable basis for asserting that the use of MCH proposed by the Forest Service poses substantial risk to human health, either for workers or members of the general public.

The potential hazards associated with accidental exposures, misuse, or misapplication are much more difficult to assess because of the limited nature of the available toxicity data on MCH. Because of these uncertainties, a conservative interpretation of risk is prudent. For workers, there is no plausible basis for anticipating overt health effects. The possibility of covert health effects cannot be characterized. For members of the general public, admittedly conservative scenarios lead to levels of exposure for which some concern for overt adverse effects is reasonable. In the absence of additional toxicity data, this component of the risk characterization cannot be further elaborated.

Ecological Risk Assessment

Hazard Identification

As is the case with the human health risk assessment, there is considerably little toxicity data relevant to the preparation of an ecological risk assessment on MCH. The acute toxicity of MCH was determined in rats, certain species of birds, and some aquatic species. There is very little additional information about MCH toxicity. As is true for the human health risk assessment, the lack of information on the toxicity of MCH is mitigated somewhat by the limited use of the product proposed by the Forest Service. Furthermore, the lack of information on several groups of organisms typically considered in an ecological risk assessment is generally not a severe limitation because of the proposed limited use of MCH.

One possible exception, however, involves the potential for MCH to act as a pheromone, either attractant or disaggregant, in non-target species. There is some information to suggest qualitatively that this activity may occur: compounds similar in structure to MCH act as repellents

in bees and are endogenous in cockroaches. Some of the same compounds act like MCH to repel the Douglas-fir beetle.

Exposure Assessment

For the ecological risk assessment, like the human health risk assessment, there is a set of relatively consistent exposure scenarios developed for terrestrial and aquatic animals and plants. These scenarios are typically used for chemicals that are applied by aerial broadcast, ground broadcast/mechanical, or backpack spray. Because of the limited manner in which MCH will be used by the Forest Service, however, most of these exposure scenarios are not relevant to this risk assessment.

The only exposure scenarios generated for quantitative use in the risk characterization involve the consumption of MCH in a bubble cap by a terrestrial animal. Given the availability of the bubble cap formulation to terrestrial species, this scenario is plausible.

No quantitative exposure scenarios for aquatic species are developed because no plausible basis for such a scenario is apparent. Nevertheless, the low levels that might be found in water are discussed briefly.

By the very nature of the bubble cap dispenser, many organisms will be exposed to MCH in air. The levels of MCH in air, however, will be extremely low and not likely to be toxicologically significant. Nonetheless, if MCH can act as a pheromone in non-target species, some effects are be possible. This possibility is given further consideration in the risk characterization

Dose-Response Assessment

Dose-response relationships for acute toxic effects can be characterized for rats, two species of birds, and various aquatic organisms. No toxicity data are available on plants, microorganisms, or terrestrial invertebrates. As discussed in the human health risk assessment, the one available rat study reports mortality at doses as low as 500 mg/kg after gavage administration. Studies in birds clearly indicate that gavage dosing, placing the chemical directly into the stomach of the animal by intubation, is more hazardous than dietary administration. With gavage administrations to birds, doses less than 500 mg/kg did not cause death. Gavage doses approximately equal to or greater than 800 mg/kg, however, caused death in all treated birds. Based on the available data, rats appear to be somewhat less sensitive than birds to MCH. But the data supporting this generalization are extremely limited (i.e., one gavage study in rats and one gavage study in quail), and the magnitude of the differences is not substantial.

The acute toxicity of MCH to aquatic species is relatively well characterized, with 96-hour LC_{50} values ranging from about 1 to about 50 mg/L. Given the proposed use of MCH and the implausibility of the contamination of ambient water, these data have no substantial impact on this risk assessment.

Risk-Characterization
Given the limited use of MCH proposed by the Forest Service, two exposure scenarios are plausible: tampering with a bubble cap and exposure to very low levels of MCH in the air.

If an animal were to tamper with a bubble cap, the amount of MCH that could be consumed or otherwise absorbed ranges from negligible to approximately 0.39 g or 390 mg (the total amount of MCH in a bubble cap). The consequences of such an event will vary depending on the size of the animal. If a small mammal, such as a mouse, shrew or rat, consumes 390 mg of MCH, it will probably die. Similarly, a small bird will probably die. Somewhat larger animals about the size of small racoons, crows, or gulls, are likely to become ill but less likely to die. Still larger animals, like large racoons or large birds, will probably not show signs of adverse effects.

The probability of any wildlife species consuming lethal amounts of MCH cannot be assessed, based on the available data. The MCH would clearly be available. Nonetheless, numerous field studies were conducted on the efficacy of MCH, including MCH in bubble cap formulations. If wildlife species commonly consume MCH, it is likely to be reported in these publications. In fact, Forest Service workers involved in the efficacy studies on MCH found no indication that wildlife consume or otherwise tamper with MCH in either bubble cap or granular formulations. Despite the potential risk to an individual animal that consumed MCH, it is unlikely that such an event would have a detectable or substantial impact on the population of any species.

Given the manner in which the Forest Service proposes to use MCH, the exposure of numerous species to low levels of airborne MCH is virtually certain to occur. Nonetheless, the such low levels of exposure are not likely to cause toxicological effects, as indicated by the available toxicity data on MCH and its widespread use in food products

On the other hand, the potential for MCH to act as a pheromone in other species is of some concern. The available data indicate that both MCH and other related compounds, like methylcyclohexanone can act as an antiaggregant to the Douglas-fir beetle. Methylcyclohexanone also acts as a repellent to bees. This information suggests a potential for MCH to act as a repellent in bees and perhaps other species as well.

1. INTRODUCTION

3-Methyl-2-cyclohexen-1-one (MCH) is a relatively common chemical. It is produced by some animals *in vivo*, can be found in a variety of foods, and is approved by the FDA as a food additive. In addition, MCH is an antiaggregation pheromone for the Douglas-fir beetle and perhaps other insects. In other words, MCH is a compound that can be used to disrupt the behavior of some forest insect pests, such as the Douglas-fir beetle, in a manner that inhibits infestations. The U.S. EPA is currently reviewing a request to register MCH as an insect control agent. The human health and ecological risk assessments in this document were prepared to support an appraisal of the environmental consequences of using MCH in Forest Service programs.

This document has four chapters: the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections: an identification of the potential hazards associated with the commercial formulation of MCH, an assessment of potential exposure to these products, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in as plain a language as possible in a separate document (SERA 1998). In addition, these terms are defined in the glossary to this risk assessment. Moreover, some of the more complicated terms and concepts are defined, as necessary, in the text.

Information regarding the toxicology or environmental fate of MCH is not readily available. The most relevant information comes from unpublished studies conducted and submitted to the U.S. EPA in support of the registration of MCH. Consequently, given the preponderance of unpublished relevant data in U.S. EPA files and the lack of recent review on MCH, a complete search of the U.S. EPA files was conducted. Full-text copies of all relevant studies were kindly provided by the U.S. EPA Office of Pesticide Programs. These studies were reviewed, and synopses of the most relevant studies are provided in the appendices to this document. The information presented in the appendices and discussed in sections 2, 3, and 4 of this risk assessment is intended to be sufficiently detailed to support an independent review of the risk analyses; however, it is not intended to be as detailed as the information generally presented in Chemical Background documents.

For the most part, the risk assessment methods used in this document are similar to those used in risk assessments conducted previously by the Forest Service as well as in risk assessments conducted by other government agencies. Details regarding the specific health risk assessment

methods used in this document are provided in SERA (1998). More detailed explanations of specific methods used to estimate occupational exposure are provided in Rubin et al. (1998). Similar documentation for methods of assessing dermal absorption is provided in Durkin et al. (1998).

Risk assessments are usually expressed with numbers; however, the numbers are far from exact. *Variability* and *uncertainty* may be dominant factors in any risk assessment and these factors should be expressed. Within the context of a risk assessment, the terms *variability* and *uncertainty* signify different conditions.

Variability reflects the knowledge of how things may change. Variability may take several forms. For this risk assessment, three types of variability are distinguished: *statistical, situational,* and *arbitrary*. *Statistical variability* reflects at least apparently random patterns in data. For example, various types of estimates used in this risk assessment involve relationships of certain physical properties to certain biological properties. In such cases, best or maximum likelihood estimates can be calculated as well as upper and lower confidence intervals that reflect the statistical variability in the relationships. *Situational variability* describes variations depending on known circumstances. For example, the application rate or the applied concentration of a herbicide will vary according to local conditions and goals. As discussed in the following section, the limits on this variability are known and there is some information to indicate what the variations are. In other words, *situational variability* is not random. *Arbitrary variability*, as the name implies, represents an attempt to describe changes that cannot be characterized statistically or by a given set of conditions that can be adequately described. This type of variability dominates certain spill scenarios involving either a chemical spilled onto the surface of the skin or spilled into water. In either case, exposure depends on the amount of chemical spilled and the area of skin or volume of water that is contaminated.

Variability reflects a knowledge or at least an explicit assumption about how things may change, *uncertainty* reflects a lack of knowledge. For example, the focus of the human health dose-response assessment is to estimate an "acceptable" or "no adverse effect" dose level for human exposure. For MCH and for most other chemicals, however, this estimate for humans must be based on data from studies on experimental mammals, which cover only a limited number of effects. The methods used for making this assessment are, for the most part, based on judgment rather than analytical methods. Although the judgments may reflect a consensus (i.e., be used by many groups in a reasonably consistent manner), the resulting estimates cannot be proven analytically. In other words, the estimates regarding risk involve uncertainty. The primary functional distinction between variability and uncertainty is that the variability is expressed quantitatively while uncertainty is expressed qualitatively.

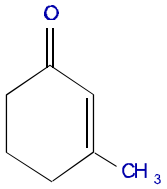
In considering different forms of variability, practically no estimate of risk presented in this document is given as a single number. Typically, risk is expressed as a central estimate and a range. Sometimes these ranges can be very large. Because of the need to encompass many different types of exposures as well as the need to express the uncertainties in the assessment, this

risk assessment involves numerous calculations. Because of the nature of the proposed application of MCH, most of these calculations are extremely simple and are presented directly in the text. A few of the calculations, however, are cumbersome. For those calculations, a set of worksheets, which provide the details for the estimates cited in the body of the document, are included as an attachment. The worksheets are divided into the following sections: general data and assumptions, chemical specific data and assumptions, and exposure assessments for workers.

2. PROGRAM DESCRIPTION

2.1. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

MCH is an abbreviation for 3-methyl-2-cyclohexen-1-one:



Selected chemical and physical properties of MCH are summarized in Table 2-1. The information on MCH that is quantitatively used in this risk assessment is summarized in worksheet 07.

The Forest Service anticipates using MCH as a pheromone to disrupt infestations of the Douglas-fir beetle. Pheromones are naturally occurring chemicals involved in the transmission of messages (i.e., chemical communication) within a species. Some pheromones, like Disparlure, are attractants. Others, like MCH, have the opposite effect, causing the organism to be repelled or dispersed. The chief characteristics of pheromones are that they are effective at very low levels and are highly species specific (Daterman 1977).

The efficacy of MCH is well documented in both the published and unpublished literature. Much of this literature was reviewed by the USDA Forest Service and submitted to the U.S. EPA as part of the registration process. A variety of experimental formulations were tested by the USDA/Forest Service, including liquid and granular formulations that can be applied aerially or by hand broadcast. In studies conducted during the 1970s, the optimum application rate was about 1 g released per acre per day from open vials attached to trees (appendix 1). Aerial broadcast applications of 4.1 lbs/acre substantially reduced (≈95%) Douglas-fir beetle infestations (USDA/FS, no date, MRID 00157016/470151-038).

Currently, however, only MCH Bubble Cap, is being considered for use by the Forest Service. This formulation is being developed by Phero Tech Inc, and the formulation specifications have been submitted to the U.S. EPA (Phero Tech Inc. 1996). Specific information regarding the formulation is proprietary under FIFRA Section 10(d)(1)(A). The proprietary information was submitted to the U.S. EPA as a FIFRA CBI (Confidential Business Information) appendix (Lafontaine and Wakarchuk 1996). Although the CBI appendix was reviewed in the preparation of this risk assessment, the contents cannot be discussed in this risk assessment, except to state that the CBI appendix does not contain information that would have a substantial impact on the risk assessment. The non-CBI information regarding product chemistry (Phero Tech Inc. 1996) includes all of the information that is required for the assessment of risk.

Table 2-1. Selected physical and chemical properties of MCH.

Synonyms	3-methyl-2-cyclohexen-1-one, SEUDENONE (Phero Tech. Inc. 1996)
CAS Number	1193-18-6 (Clydsdale 1997)
Molecular weight	110.16 (Clydsdale 1997)
Specific gravity	0.971 (Phero Tech. Inc. 1996)
GRAS Number	6 (Clydsdale 1997)
Appearance, ambient	yellow liquid (Phero Tech. Inc. 1996)
IOFI Classification	Flavor identical to natural flavor from aromatic raw materials or chemically identical synthesized materials (Clydsdale 1997).
FDA Classification	Approved food additive: Fully up-to-date toxicology information available (FDA 1998).
FDA/PAFA estimate of daily exposure from foods	0.0001 mg/kg (Clydsdale 1997).
FDA/PAFA status (Priority-based assessment of food additives)	No toxicity data available. [See Section 3.1.1 for discussion.]
Solubility	Soluble in all organic solvents; sparigly soluble in water (Phero Tech. Inc. 1996)
K_{ow}	56.2 (SRC 1998)
Soil adsorption K_d	N/A
Foliar half-life (days)	N/A
Soil half-life (days)	N/A
Water half-life (days)	N/A
Air half-life (days)	N/A

As reported in Phero Tech. Inc. (1996), each MCH Bubble Cap contains 0.39 g ± 0.02 g of the active ingredient, 3-methyl-2-cyclohexen-1-one, in a device that releases ≈4 mg/day for a period of 100-150 days. MCH comprises about 20% of the product (w/w). The remaining material is classified as *inert* (i.e., it has no effect on the insect). Although the identity and nature of the inerts cannot be specified, they are characterized as a *solid inert plastic polymer* in the non-CBI portion of the product chemistry data (Phero Tech. Inc. 1996, p.9). To be sure, the CBI portion of this submission indicates that this is an accurate description of the inerts. Based on gravimetric analyses, the release rate of MCH from the carrier matrix is relatively constant at moderate temperatures (i.e., 20°C or ≈70°F). At higher temperatures—30°C or 86°F—the initial release rate is about 16-18 mg/day and decreases in a linear fashion to near zero release at approximately 40 days.

2.2. APPLICATION METHODS AND RATES

Because MCH Bubble Cap is not currently used by the Forest Service except in experimental applications, there are no standards regarding application rates or methods. Although the Forest Service has experimented with several different application methods and application rates, as

discussed in the previous section, current plans are to apply MCH only in the Phero Tech. bubble cap formulation described in the previous section. The application rate under consideration by the Forest Service is 42 g a.i./acre or approximately 108 bubble caps per acre. Each bubble cap would be manually fixed to a tree. No broadcast or aerial applications are planned.

In the one published study regarding the application of bubble caps, MCH bubble caps were stapled to Douglas fir trees at intervals of 3 m (Lindgren et al. 1988). The bubble caps used in this study were described as releasing MCH at a rate of 3 mg/day, which is somewhat less than the rate of 4 mg/day described in the submissions to the U.S. EPA (Phero Tech Inc. 1996).

In many exposure assessments, the amount of material handled per day is calculated as the product of the application rate (lbs a.i./acre) and the number of acres treated per day (acres/day) by an individual worker (Rubin et al. 1998). There are no estimates regarding the number of acres that an individual worker might treat per day with MCH bubble caps. In general, workers who apply herbicides by hand treat fewer acres per day, compared with workers engaged in other methods of application. The typical range for hand application is 2-10 acres per day. It is not clear whether this range is applicable to workers applying MCH bubble caps. As discussed in the exposure assessment (section 3.2), this uncertainty has a minimal impact on this risk assessment because of the manner in which the bubble caps are applied.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview. MCH is an approved food additive. Nonetheless, the toxicity data on MCH are very limited. Acute toxicity information is sparse and relatively poor, and there are no chronic or subchronic toxicity studies on MCH. Despite its classification by the FDA as an approved food additive, the lack of information regarding the toxicity of MCH is recognized and duly incorporated into the hazard identification for this compound. Furthermore, the paucity of information regarding the toxicity of MCH to humans and other mammalian species figures prominently as a source of uncertainty in the risk characterization of this compound (section 3.4).

3.1.2. Acute Oral Toxicity. There is relatively little information regarding the acute oral toxicity of MCH. As summarized in appendix 2 and discussed further in section 3.3, gavage doses between 500 and 2000 mg/kg bw were lethal to rats (WARF Institute Inc.1976). These are the only data regarding effects in mammals after acute oral exposure to MCH.

Other available information regarding the acute oral toxicity of MCH concerns adverse effects in birds (appendix 3). Although this kind of information generally is not used to identify potential risk to mammals, it is considered here because of the general lack of more relevant data. In birds, the signs associated with acute oral exposure involved a general decrease in activity [i.e., decreased reaction to external stimuli (sound and movement), wing droop, lethargy, and decreased food consumption] (Campbell et al. 1991). Also, decreased activity was observed in rats after acute inhalation exposure to MCH (WARF Institute Inc. 1976) (section 3.1.8).

Central nervous system depression that can lead to narcosis as well as less severe signs of neurological impairment, including numbness, apathy, depression, and decreased activity, are toxic effects commonly associated with acute exposure to various ketones of low molecular weights and related compounds, including cyclohexanone and cyclohexane (ATSDR 1997, U.S. EPA 1994, Snyder and Andrews 1996).

3.1.3. Subchronic or Chronic Systemic Toxic Effects. Information regarding the subchronic or chronic toxicity of MCH was not found in the available literature.

Subchronic and chronic toxic effects can be very difficult to assess by analogy to other chemicals because apparently minor differences in structure can lead to qualitative differences in toxicity. For example, 2,5-hexanedione is a classic neurotoxic agent that causes peripheral neuropathy. Both *n*-hexane as well as 2-methyl-*n*-butyl ketone cause the same effect because they are metabolized to 2,5-hexanedione. Closely related compounds with apparently similar structures (e.g., n-pentane or n-heptane) do not cause this kind of neurotoxicity because their metabolism does not lead to the formation of 2,5-hexanedione (Lande et al. 1976, Anthony et al. 1996).

In light of this major reservation, it is notable that the toxicity of both cyclohexane (U.S. EPA 1994) and cyclohexanone (U.S. EPA 1997) to mammals is characterized by nonspecific chronic toxic effects, like decreased growth and decreased activity.

3.1.4. Reproductive and Teratogenic Effects. Data regarding reproductive or teratogenic effects in humans or animals after exposure to MCH were not located in the available literature..

Structural analogies are of limited use also in assessing the potential reproductive or teratogenic effects of MCH. In the absence of directly relevant data on MCH, however, it is notable that neither cyclohexane (U.S. EPA 1994) nor cyclohexanone (U.S. EPA 1997) caused birth defects or other specific signs of reproductive toxicity at doses that are apparently not toxic to pregnant dams (i.e., do not cause overt signs of toxicity).

3.1.5. Carcinogenicity and Mutagenicity. MCH bioassays for mutagenicity or carcinogenicity are not available in the published literature or in U.S. EPA or FDA files.

3.1.6. Effects on the Skin and Eyes. There is only one available study regarding the ocular effects of MCH. As part of an acute toxicity screening assay (WARF Institute Inc.1976) (appendix 2), 0.1 mL MCH was applied to one eye of each rabbit, and the animals were observed for 1 week. Conjunctival irritation (i.e., redness, swelling, and discharge) but no effects on the iris or cornea were noted. All effects decreased in severity after 24 hours and no effects were observed 1 week after treatment. There are no studies regarding skin irritation from exposure to MCH.

3.1.7. Systemic Toxic Effects from Dermal Exposure. In general, most occupational exposure scenarios and many of the exposure scenarios for the general public involve the dermal route of exposure. Given the proposed use of MCH, most scenarios involving dermal exposure to MCH are irrelevant (section 3.2). Nonetheless, the potential for dermal absorption is important to the exposure scenarios that are plausible.

There is no available information regarding the dermal toxicity of MCH or the dermal absorption kinetics of MCH. As discussed in Durkin et al. (1995), scenarios involving immersion or prolonged contact with solutions containing a compound use Fick's first law and require an estimate of the permeability coefficient, K_p, expressed in cm/hour. Using the method recommended by U.S. EPA (1992), the estimated dermal permeability coefficient (zero-order) for MCH is 0.0068 cm/hour with a 95% confidence interval of 0.0043-0.011 cm/hour. These estimates are used in all the exposure assessments based on Fick’s first law. The calculations for these estimates are summarized in worksheet 10 and detailed in worksheet 09.

For exposure scenarios like an accidental spill, which involve deposition of the compound on the skin surface, dermal absorption rates (proportion of the deposited dose per unit time) rather than dermal permeability rates are used in the exposure assessment. Using the methods discussed in Durkin et al. (1998), the estimated first-order dermal absorption coefficient is 0.019 $hour^{-1}$ with

95% confidence intervals of 0.0045-0.083 $hour^{-1}$. The calculations for these estimates are summarized in worksheet 10 and detailed in worksheet 08.

3.1.8. Inhalation Exposure. WARF Institute Inc. (1976) conducted an acute inhalation toxicity study as part of an early toxicity screening assay of MCH (appendix 2). When rats were exposed to a concentration of 19.7 mg MCH/L (equal to 19,700 mg MCH/m^3) for 1 hour, the primary effect was hypoactivity (i.e., the animals laid down and closed their eyes, although they were still responsive to tapping on the sides of the chambers). Gross examination of organ tissue from treated animals established no effects that could be attributed to exposure.

3.1.9. Impurities and Metabolites. There is no information available regarding the impurities in MCH or the metabolism of MCH.

Although speculative, suppositions concerning the metabolism of MCH can be made by analogy to related compounds. MCH has a low molecular weight, relative to endogenous chemicals like proteins or fatty acids. In mammals, there are a number of enzymes and enzyme systems involved in the oxidation and reduction of many low molecular weight alcohols, aldehydes, and ketones (Parkinson 1996). The role of these enzymes in the metabolism of methylcyclohexanols and methylcyclohexanones is characterized by Elliot et al. (1969). Occupational monitoring for exposure to cyclohexanone involves urine analyses for cyclohexanol and cyclohexane diols (Lauwerys 1996). These findings support the supposition that MCH might be metabolized to the corresponding alcohol and possibly a diol.

The metabolism of hexobarbital seems to involve the formation of a cyclohexenone-glutathione adduct (Takenoshita et al. 1993). Accordingly, the metabolism of MCH might involve conjugation with glutathione with subsequent elimination in the urine.

The time to death in the acute oral toxicity study by WARF Institute Inc. (1976) may be another important reason for speculating about the potential significance of MCH metabolism. As detailed in appendix 2, all animals died 2-7 days after dosing. As the dose increased, the average time to death in each dose group also increased (i.e., averages of 2 days at 0.5 g/kg; 2.5 days at 1 g/kg; 4.3 days at 2 g/kg). This pattern of delayed death is consistent with the speculation that a metabolite rather than MCH itself was the cause of death. The increasing time to death with increasing dose suggests that a metabolic pathway involved in the generation of the toxic metabolite may be saturated at doses in the range of 0.5 mg/kg bw. Thus, in the higher dose groups, peak blood levels of the presumed toxic metabolite might not be substantially higher than those in the lower dose group at days 1 and 2 after dosing. This assumption is consistent with the observation that one animal in each group died on day 2. The additional deaths in the higher dose groups at later periods would be consistent with the speculation that sufficient amounts of MCH remained in the higher dose group animals for longer periods of time. This would effectively increase the period of exposure to the presumed toxic metabolite and account for the increase in the average time to death as the dose increased.

3.1.10. Toxicological Interactions. No information is available about the toxicological interactions of MCH with other compounds. Speculations regarding potential interactions between MCH and other compounds are made in the risk characterization (section 3.4.5) and based on the limited available data regarding the toxicological action of MCH.

3.1.11. Status of MCH as Food Additive. The approval of food additives is the responsibility of the FDA (Kotsonis et al. 1996), which maintains a database of approved food additives. The "Everything Added to Food in the United States" (EAFUS) database is available at the FDA web site (FDA 1998). EAFUS lists substances that FDA has either approved as food additives or listed or affirmed as GRAS [Generally Recognized as Safe]. The EAFUS database is a subset of FDA's Center for Food Safety and Applied Nutrition's Priority-based Assessment of Food Additives (PAFA) database. The PAFA database includes abstracts of more than 7000 toxicology studies performed on substances added to food. This database is commercially available on CD-ROM (Clydsdale 1997). Both databases were searched during the preparation of this risk assessment.

MCH and seven other cyclohexenones are listed in the EAFUS database as approved food additives (appendix 4). The database indicates that there is *a "fully up-to-date toxicology information"* profile available for MCH (FDA 1998). Essentially the same statement is given in the full PAFA database (Clydsdale 1997). On the other hand, the PAFA database also indicates that there are no toxicity data available on MCH and five of the other cyclohexenones listed in PAFA. For two of the cyclohexenones, PAFA summarizes 90-day feeding studies in rat and indicates that the studies do not meet FDA data quality standards (appendix 4).

The approval of MCH as a food additive is an important fact for consideration in this risk assessment. Nonetheless, the limited nature of the data supporting this classification and the more general context in which FDA approves chemicals as food additives also must be taken into consideration. This issue is discussed further in the risk characterization (section 3.4).

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview. Many chemicals used by the Forest Service are applied by a relatively standard set of methods, including aerial broadcast, ground broadcast/mechanical, or backpack. For those methods of pesticide or herbicide application, a relatively consistent set of exposure scenarios was developed to assess exposure for workers and the general public (Rubin et al. 1998). Most of those exposure scenarios and approaches to exposure assessment are not relevant to the application method proposed for MCH.

In this risk assessment, only two exposure scenarios are considered: inadvertent dermal contact during placement of the MCH bubble cap by workers and imprudent handling of the bubble cap by a child.

Under typical conditions of placing the MCH bubble cap, workers should not be exposed to substantial levels of MCH. The MCH is encased in a plastic matrix that releases only very small

quantities of MCH per unit time. Without violating the proprietary nature of the packaging material, it can be stated that the entire MCH bubble cap is encased in material that is impermeable to MCH. Were this not true, the bubble cap formulation would have an unacceptably short shelf life.

Thus, the only exposure scenario developed for workers involves accidental dermal contamination of the hands after the bubble cap is removed from its packaging (worksheet 11). This scenario postulates that the bubble cap is ruptured in some way during its removal from the packaging material or during its placement on a tree. Based on the assumption that both hands are contaminated with MCH for 1 minute, estimates of absorbed dose do not exceed 2.1 mg/kg. In a worst case and perhaps highly implausible exposure scenario, in which the worker does not clean the contaminated hands for 1 hour, exposure is not likely to exceed 5.6 mg/kg. In this case, the dose estimate is limited not by the dermal absorption rate but by the amount of MCH contained in a single bubble cap.

Like workers, members of the general public usually would not be exposed to substantial levels of MCH. Nonetheless, as a worst case scenario, it is assumed that a child could encounter a bubble cap that was accidently dropped on to the ground or removed in some way from a tree. In this scenario, both dermal and oral exposure could occur through imprudent handling of the bubble cap. The maximum estimated absorbed dose for the scenario is approximately 30 mg/kg.

3.2.2. Workers. Not only are there no studies regarding worker exposure to MCH, but there are no studies regarding worker exposure to other chemicals in "bubble cap" formulations. Under typical conditions of exposure (i.e., stapling the bubble cap to a tree), the risk of toxicologically significant exposure to MCH is unlikely .

Nonetheless, under very conservative and perhaps implausible conditions, any number of exposure scenarios could be developed. For example, as discussed in section 2.3, approximately 108 bubble caps may be applied per acre, each bubble cap will contain 0.00039 kg (0.39 g or 390 mg) of MCH, and workers who apply chemicals by hand may treat 2-10 acres per day. Thus, a worker could handle approximately 0.08-0.4 kg MCH per day:

$$0.00039 \text{ kg MCH/bubble cap} \times 108 \text{ bubble caps/acre} \times 2 \text{ to } 10 \text{ acres} = 0.084\text{-}0.42 \text{ kg}$$

Although there are methods for estimating absorbed doses in workers based on the amount of chemical handled per day (Rubin et al. 1998), the methods are based on data involving various forms of broadcast or directed spraying. Consequently, the methods are not suitable for estimating exposure to "bubble cap" formulations because the MCH is contained in a plastic matrix.

Another approach could be based on the release rate of MCH from the "bubble cap" (4 mg/day or $\approx$0.166 mg/hour) after the cap is removed from the packing material. At a rate of 108 bubble caps/acre, the release rate of MCH would be about 18 mg/hour×acre or 144 mg/day×acre.

Taking the very conservative assumption that all of the MCH released in 1 day would remain in the 2 m of air directly above the ground, the concentration in the air would be about 18 μg/m^3,

$$144 \text{ mg/day} \times \text{acre} \div (4047 \text{ m}^2/\text{acre} \times 2 \text{ m}) = 0.01779 \text{ mg/m}^3.$$

Once reasonable assumptions concerning aerial dispersion are incorporated as part of the exposure assessment, the levels in air become negligible in terms of the human health effects that might be estimated.

The only exposure scenario that might actually be useful in assessing potential risks to workers involves accidental contamination of the skin. For example, a worker could accidentally rupture the bubble cap containing 0.39 g or 390 mg MCH and contaminate the surface of the hands with MCH.

For this risk assessment, a more conservative exposure scenario is used. It is assumed that the worker accidentally ruptures a bubble cap and contaminates the inside of protective gloves with MCH. This is scenario is extremely conservative and perhaps implausible. In general, protective gloves will prevent dermal absorption. Nonetheless, this scenario is based on the assumption that the inside of the protective gloves is contaminated and that the gloves serve as a poultice, preventing the evaporation of MCH and keeping the MCH in contact with the exposed skin.

Under these conditions, the absorbed dose may be calculated assuming zero-order absorption. Any duration of exposure could be used. For this risk assessment, two durations are calculated in an attempt to encompass arbitrary variability: 1 minute and 1 hour. An exposure duration of 1 minute is based on the reasonable that the worker promptly terminates exposure by removing the gloves and cleaning the hands. The 1-hour exposure duration is based on the assumption assumes that the worker does not behave prudently.

The calculations for these exposure scenarios are detailed in worksheet 11. For a 1-minute exposure period, the absorbed dose is 1.3 (0.84-2.1) mg/kg. If a bodyweight of 70 kg is assumed for the worker, as specified in worksheet 02, the total absorbed dose is 91 (58.8-147) mg [70 kg × 1.3 (0.84-2.1) mg/kg]. Since each bubble cap contains 390 mg of MCH, the value for dermal absorption is equivalent to approximately 23%(15-38%) of the available MCH [100 × 91(58.8-147) mg ÷ 390 mg].

As also detailed in worksheet 11, the dose absorbed over a 1-hour period would be 79 (51-130 mg/kg). This corresponds to a total absorbed dose of 5530 (3570-9100) mg [70 kg × 79 (51-130 mg/kg)]. Even the lower range of this estimate exceeds the amount of MCH available in a bubble cap by a factor of about 9 [3570 mg ÷ 390 mg = 9.1]. In other words, under the assumption of zero-order absorption with a duration period of 1 hour, the gloves would have to be contaminated with far more MCH than is contained in a single bubble cap. This event is not unimaginable, but it is certainly improbable enough to disregard. Thus, since only 390 mg of MCH is in a single bubble cap, the maximum absorbed dose is taken as 5.6 mg/kg (i.e., 390 mg/70 kg bw).

3.2.3. General Public. As is the case for workers, the general public should not be exposed to high levels of MCH. Nevertheless, there are several exposure scenarios that can be developed to reflect essentially arbitrary situational variability.

The most conservative, yet reasonable, assumption considered quantitatively in this risk assessment involves a small child coming into contact with a bubble cap, either by finding a bubble cap inadvertently dropped during application or removing a newly affixed bubble cap from a tree.

Variations of this scenario can be developed in which the child then effectively absorbs all of the MCH either by ingestion or dermal exposure. If a body weight of 13 kg is used for a 2- to 3-year-old child (worksheet 03), the total dose is approximately 30 mg/kg (i.e., 390 mg/13 kg bw). This dose would be an upper limit.

More plausible estimates of the amount that might effectively be absorbed or consumed cannot be determined analytically. For this exposure assessment, a range of 3 to 30 mg/kg bw, with a central estimate of 10 mg/kg, is used. The lower range is based on the arbitrary assumption that 10% of the available MCH is consumed or otherwise absorbed, and the central estimate is based on the approximate geometric mean of the range (i.e., $3\times30^{0.5} \approx 10$).

More conservative scenarios could be developed; however, in the more conservative scenarios, the child must either come into contact with numerous bubble caps that were discarded or otherwise misplaced or actively seek out and consume bubble caps. Although these events are not unimaginable, they are not plausible enough to be considered quantitatively.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview. Except for a few acute toxicity studies, there is no information on dose-response relationships for MCH in humans or experimental mammals. Although MCH is similar to other compounds for which better data are available, the usefulness of these data for assessing the likely effects of exposure to MCH is limited.

3.3.2. Existing Guidelines. Other than the classification of MCH as an approved food additive (see section 3.1.11), there is no evidence of existing guidelines or standards for MCH. As part of the documentation for the approval of MCH as a food additive, the FDA estimates that exposure to the compound is likely to be 0.0001 mg/kg bw/day. The basis of this estimate is not well-described in PAFA, except for a statement that the estimated exposure is based on an assumption that 10% of the population consumes 100% of the MCH that might be present in food (Clydesdale 1997).

As discussed by Kotsonis et al. (1996), the approval of a compound as a food additive amounts to a statement by the FDA that no plausible risk can be identified at the anticipated level of exposure. As illustrated in Table 30-15 of Kotsonis et al. (1996, p. 926), estimated safe levels of exposure to food additives are generally 20- to more than 3000-fold greater than the estimated levels of actual exposure.

The FDA has not published any specific information about the toxicology of MCH, which may have been used in the process of approving the compound as a food additive. Consequently, given the information available during the preparation of this risk assessment, an estimated safe level for human exposure cannot be inferred from the approval of MCH as a food additive, except to state that the FDA estimate of exposure implies that a dose of 0.0001 mg/kg/day will be below a safe level for human exposure. In other words, the FDA believes that MCH levels in food pose no unreasonable risk.

Neither the U.S. EPA nor the Agency for Toxic Substances and Disease Registry (ATSDR) derived an acceptable level of exposure for this compound. MCH is not listed on the INTERNET sites of any of the organizations responsible for setting occupational exposure recommendations, criteria or standards (i.e., OSHA, NIOSH, or ACGIH). Furthermore, publications from these agencies and organizations regarding occupational exposure to MCH were not encountered in the literature search, which included databases covering the Federal Register.

U.S. EPA (1997) derived an RfD for cyclohexanone. The RfD is set at 5 mg/kg/day. This value is based on a dietary study in rats, in which the NOAEL is 3300 ppm and there is a LOAEL of 6500 ppm for body weight depression. Converting the dietary levels to estimated intakes of cyclohexanone results in a NOEL of 462 mg/kg/day and a LOAEL of 910 mg/kg/day. An uncertainty factor of 100 was applied to the NOAEL, and the resulting value was rounded to 1 significant place to derive the RfD.

As indicated in section 3.1.2, there may be reason to believe that the acute toxicity of MCH is analogous to that of cyclohexanone and cyclohexane. Nonetheless, as emphasized in section 3.1.3, the uncertainty and reservations about using this approach to estimate chronic exposure limits is substantial. If metabolism plays a significant role in the toxicity of MCH, as speculated in section 3.1.9, analogies to compounds like cyclic hexanes rather than cyclic hexenes are tenuous at best.

3.3.3. Dose-Response and Dose-Severity Relationships. There are no subchronic or chronic studies from which to derive a provisional RfD for MCH. There is one acute toxicity study involving oral exposure (WARF Institute Inc. 1976); however, the study is severely limited in that it provides information only on mortality rates in the exposed animals, it involved relatively small numbers of dose groups and animals (three dose groups with 10 animals per dose group), and it apparently did not use a control (0 dose) group. Within these limitations, the study suggests that doses as low as 500 mg/kg, the lowest dose tested, may be lethal and that death is most likely to be delayed for 2-7 days after exposure.

As indicated in appendix 4, subchronic NOAELs are available on two other cyclohexenones: 5 mg/kg/day×90 days for 2-hydroxy-2-cyclohexen-1-one; 47.62 mg/kg/day×90 days for a mixture of isomers of tetramethyl ethylcyclohexenones (Clydsdale 1997). These values are both free standing NOAELs (i.e., only one dose group was used and no effects were seen). In addition, these studies did not meet the core standards used by FDA. Consequently, these studies are not used to assess the consequences of exposure to MCH.

3.4. RISK CHARACTERIZATION

3.4.1. Overview. This risk assessment is dominated by uncertainty because of the lack of adequate data on the toxicity of MCH. In the absence of adequate data, the characterization of risk must be conservative. The fact that MCH is an approved food additive and may be harmless at the levels found in food is of limited relevance in characterizing the potential risk of using MCH in bubble cap formulations.

MCH will be encased in a plastic matrix and released very slowly into the open air where concentrations should drop below any levels likely to cause adverse health effects. Thus, under foreseeable conditions of normal application and use, there is no reasonable basis for contending that the use of MCH proposed by the Forest Service poses a substantial risk to human health, either for workers or members of the general public.

The potential hazards associated with accidental exposure, misuse, or misapplication are much more difficult to assess because of the limited nature of the available toxicity data on MCH. Because of these uncertainties, a conservative interpretation of risk is prudent. For workers, there is no plausible basis for anticipating overt health effects. The possibility of covert health effects cannot be characterized. For members of the general public, conservative scenarios admittedly lead to exposure levels that raise concern about the possibility of overt adverse effects. In the absence of additional toxicity data, this component of the risk characterization cannot be further elaborated.

3.4.2. Workers. Under anticipated and normal conditions of application, workers should not be exposed to substantial levels of MCH. Given the presumption that MCH, at least at very low levels of exposure, poses no unreasonable risk, with proper handling (i.e., avoiding dermal contact and working outdoors), MCH poses no identifiable risks to workers. Like every other aspect of this risk characterization, the assessment of worker exposure is tempered by the paucity of toxicity data on MCH.

In cases of accidental dermal exposure limited by prudent corrective actions (the removal of contaminated gloves after 1 minute), absorbed doses in workers could reach 2.1 mg/kg. This estimated dose is about 240 times less than the lowest reported lethal level in rats [500 mg/kg ÷ 2.1 mg/kg = 238]. It is also a factor of 21,000 above the FDA estimate of daily exposure in food [2.1 mg/kg ÷ 0.0001 mg/g]. About all that can be said is that an accidental exposure involving the absorption of 2.1 mg/kg MCH is not likely be lethal.

In cases of imprudent application (wearing contaminated gloves for 1 hour), absorbed doses could be as high as 5.6 mg/kg/day. This again is well below the lowest reported lethal dose in rats (a factor of about 89) but far above the estimated level of exposure to MCH in foods (a factor of about 56,000).

None of these ratios of exposure to either the anticipated levels in food or lethal levels in rats support any serious numerical expression of risk. While the level of exposure to MCH that the

FDA anticipates in food (i.e., 0.0001 mg/kg/day) may be taken as a functional human NOAEL, it does not suggest that higher levels of exposure are in any way hazardous or harmless. The rat study, as discussed above, did not use a control group and did not use a large number of animals. The acute oral study in rats is an appropriate basis on which to design a range-finding study but is not appropriate for any quantitative expression of risk in humans.

As indicated in section 3.1.6, MCH may cause transient eye irritation. Again, the risk of observing this effect is reduced by the encasement of MCH in a bubble cap. The irritation could occur, however, if the product is misused, misapplied, or otherwise accidentally ruptured.

3.4.3. General Public. The risk characterization for the general public is similar to that for workers. Under normal conditions, members of the general public could be exposed to trace levels of MCH in the air. There is no plausible reason to suspect that these levels would be in any way harmful.

Conversely, accidental exposures, while perhaps extreme, are not implausible. The bubble caps will be attached to trees and may be accessible to young children. Even if the bubble caps were to be secured and generally out of reach, a bubble cap could be inadvertently dropped during application or dislodged by wildlife after application. In such an event, exposures of up to 30 mg/kg bw would be possible. This exposure scenario requires the child to consume virtually all of the MCH in a bubble cap. This event may not be plausible, and a lower dose, like 3 mg/kg bw may be more plausible (see section 3.2.3). The upper limit of 30 mg/kg bw is about 17-fold less than the minimum lethal dose for rats (i.e., 0.5 g/kg bw or 500 mg/kg bw), which was associated with death in 1 of 10 rats (see section 3.3.3).

The proximity of an estimated dose for human exposure to the presumed lethal dose in a rat study is of substantial concern. As discussed in section 3.3.3, however, the quality of the rat study is limited and it is not clear that the death of the one animal in the 0.5 g/kg dose group can be attributed to exposure. Nonetheless and notwithstanding the limitations in the available data, the potential for adverse human health effects after accidental exposure to MCH seems evident.

3.4.4. Sensitive Subgroups. There are no data that permit an identification of sensitive subgroups.

3.4.5. Connected Actions. Information regarding toxicological interactions between MCH and other compounds is not available. Speculations in section 3.1 suggest that MCH could display some form of joint action with low molecular weight alcohols, aldehydes, and ketones , which are metabolized by various oxidation and reduction enzymes. The direction of such a joint action (i.e., antagonistic or synergistic) cannot be assessed. Similarly, if MCH is conjugated with glutathione as further speculated in section 3.1.9, toxicological interactions may be plausible events. Based on the supposition that the acute toxicity of MCH may be due to a metabolite (see section 3.1.9.), compounds that inhibit the metabolism of MCH are likely to decrease its apparent toxic potency. Conversely, compounds that stimulate the metabolism of MCH are likely to

increase its apparent toxic potency. The tenuous nature of these speculations, however, prevents them from having a substantial impact on this risk assessment other than to increase the uncertainty.

3.4.6. Cumulative Effects. The limited nature of the proposed use of MCH does not suggest a substantial concern for cumulative effects. Nonetheless, the subchronic and chronic toxicity of this compound is not characterized. Thus, no quantitative or qualitative assessment can be made about potential cumulative effects.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview. Like the human health risk assessment, the ecological risk assessment is governed by the limitations of the toxicity data on MCH. The acute toxicity of MCH was determined in rats, certain species of birds, and some aquatic species. There are few additional data on MCH. As in the case of the human health risk assessment, the lack of information regarding the toxicity of MCH is mitigated somewhat by the limited use that the Forest Service proposes for the compound. In general, because the Forest Service proposes limited use of MCH, the paucity of information regarding numerous organisms usually considered in an ecological risk assessment is not a severe limitation.

One possible exception involves the potential for MCH to act as a pheromone, either attractant or disaggregant, in non-target species. This concern is based on information that compounds similar in structure to MCH act as repellents in bees and are endogenous in cockroaches. Like MCH, some of these structurally similar compounds act as repellents to the Douglas-fir beetle.

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals– As summarized in the human health risk assessment (see section 3.1), the mammalian toxicity of MCH is not well characterized. Like cyclohexanone and cyclohexane, which are structually similar to MCH (ATSDR 1997, U.S. EPA 1994, Snyder and Andrews 1996), MCH seems to cause neurological effects ranging from decreased activity to narcosis in mammals. At least in mammals, the limited acute toxicity data indicate a pattern of delayed mortality that is consistent with the speculation that the toxicity of MCH may be attributable to a metabolite.

4.1.2.2. Birds– As summarized in appendix 3, the toxicity of MCH to birds is addressed in four studies: three of which involve dietary exposure (Beavers et al. 1991a,b, WARF 1977a) and one that involves gavage administration (Campbell et al. 1991). In each study, decreased weight gain or body weight loss is observed at doses below those associated with frank signs of toxicity. Signs of neurotoxicity are reported in only one dietary study. In the high exposure group (5620 ppm in the diet), Beavers et al. (1991b) observed intermittent loss of coordination in bobwhite quail. In the gavage study (Campbell et al. 1991), signs of neurotoxicity in bobwhite quail were consistently noted at dose levels greater than or equal to 486 mg/kg/day. The neurological effects included weakness of the extremities, loss of coordination, and decreased responsiveness to external stimuli. As discussed in section 3.1.2, this observation is consistent with neurological effects observed in mammals exposed to chemicals like cyclohexanone and cyclohexane, which are structurally similar to MCH.

Unlike the apparent delayed toxicity of MCH in rats (see section 3.1.9.), there is no consistent evidence for delayed toxicity in birds. In the gavage study on bobwhite quail by Campbell et al. (1991), there is a suggestion of delayed toxicity at the 810 mg/kg bw dose group but not in the lower dose group (292 mg/kg bw) or any of the higher dose groups (810 mg/kg bw through 2250

mg/kg bw). Since only one rat study is available, the apparent difference in the response of bird species cannot be clearly interpreted. Nonetheless, this difference is consistent with the speculation that the mechanism of action or metabolism of MCH in birds and mammals may be different.

4.1.2.3. Terrestrial Invertebrates– The literature for MCH does not include information regarding toxicity to terrestrial invertebrates.

Compounds similar in structure to MCH, like various isomers of methylcyclohexanone, are endogenous to cockroaches and may serve as attractant pheromones (Brossut et al. 1975). In the honey bee, however, methylcyclohexanones appear to act as repellents (Gupta 1989a,b), which is similar to the effect of MCH on the Douglas-fir beetle.

The activities of methylcyclohexanes, either as attractants or repellents, to other species cannot be directly generalized to the potential effects of MCH on other species. Nonetheless, MCH, 3-methylcyclohexanone, and other structurally similar compounds all act as repellents to the Douglas-fir beetle (Rudinsky et al. 1975). Hence, it is plausible that MCH could act as a pheromone in other species, either as an attractant or antiaggregant.

4.1.2.4. Terrestrial Plants (Macrophytes)– The literature for MCH does not include information regarding toxicity to terrestrial plants.

4.1.2.5. Terrestrial Microorganisms– The literature for MCH does not include information regarding toxicity to terrestrial microorganisms. In general, microorganisms readily metabolize methylcyclohexanones and related compounds and generate such compounds in the metabolism of other simpler compounds such as benzoic acid (Doi et al. 1990, Gribic-Galic and Young 1985, Onishi et al. 1996). Although this information cannot be used to characterize the potential toxic potency of MCH to terrestrial microorganisms, it suggests that terrestrial microorganisms may be able to metabolize and hence remove MCH from soil.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish– The only information available on the toxicity of MCH to fish exists in standard acute toxicity bioassays (appendix 5). Typically these bioassays only report mortality and do not provide information on signs of toxicity, which is true for the bioassays on MCH.

The lowest reported LC_{50} is 0.91 mg/L, calculated from mortality data on bluegill sunfish after 96 hours of exposure (WARF 1977b). In all of the studies summarized in appendix 5, LC_{50} values decrease with increasing duration of exposure. In an early study on bluegill sunfish (WARF Institute Inc. 1977b), the difference between the 24- and 96-hour LC_{50} is substantial (i.e., approximately 8-fold). In a more recent bioassay on bluegills (Graves and Peters 1991b), the difference is negligible. It is also noteworthy that the toxic potency of MCH in the more recent bioassay is much less than that in the earlier bioassay. Reasons for these difference are not

apparent. Nonetheless, it is common for similar bioassays conducted in different laboratories or the same laboratory at different times to vary substantially.

It cannot be determined from the available data whether the pattern of decreasing LC_{50} values with increasing exposure duration is related to delayed toxicity. In studies on aquatic species, decreases in LC_{50} values over time may be related to bioconcentration of the chemical from the water into the organism. Although there is no measured bioconcentration factor (BCF) for MCH, a BCF of 12 can be estimated from a general relationship of K_{ow} to bioconcentration (worksheet 07).

4.1.3.2. Amphibians– The literature for MCH does not include information regarding toxicity to amphibians.

4.1.3.3. Aquatic Invertebrates– The literature for MCH includes one acute toxicity bioassay for an aquatic invertebrate (see appendix 5). The 48-hour LC_{50} for *Daphnia magna*, a common laboratory test species, is 51.4 mg/L. This value is similar to the 48-hour LC_{50} of 26.5 mg/L for bluegill sunfish reported by Graves and Peters (1991b). Given the scatter in the available data from fish bioassays, there is no reason to believe that sensitivity to MCH is remarkably different for daphnids and fish.

4.1.3.4. Aquatic Plants– The literature for MCH does not include information regarding toxicity to aquatic plant species.

4.1.3.5. Other Aquatic Microorganisms– The literature for MCH does not include information regarding toxicity to aquatic microorganisms.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview. As with the human health risk assessment, there is a set of relatively consistent exposure scenarios typically developed for terrestrial and aquatic animals and plants. These scenarios are typically developed for chemicals applied by aerial broadcast, ground broadcast/mechanical, or backpack spray. Because of the limited manner in which MCH will be used by the Forest Service, however, most of the typical exposure scenarios are not applicable to this risk assessment.

The only exposure scenarios developed for quantitative use in the risk characterization involve the consumption of MCH bubble caps by terrestrial animals. This scenario is plausible, given that the placement of bubble caps is likely to make them available to terrestrial species.

Quantitative exposure scenarios for aquatic species are not plausible. Nonetheless, the extremely low levels of MCH that might be found in water are taken into consideration.

By the very nature of the bubble cap dispenser, many organisms will be exposed to MCH in air. The levels of MCH in air, however, will be extremely low and not likely to be toxicologically

significant. Nonetheless, if MCH can act as a pheromone in non-target species, the occurrence of certain effects is possible. This issue is dicussed further in the risk characterization (section 4.4).

4.2.2. Consumption by Terrestrial Animals. Because MCH will be placed on trees, some terrestrial organisms could tamper with the bubble cap and consume its contents. Any number of similar scenarios can be developed; however, the usefulness of those assessments is limited by the available toxicity data (section 4.3).

The consumption of the MCH in a bubble cap formulation most closely parallels gavage administration. As discussed in section 4.3, there are adequate data regarding effects in rats and quail after exposure to MCH by gavage. Consequently, exposure scenarios involving the consumption of MCH in a bubble cap by rats and quail can be developed directly from the available data. Thus, it is not necessary to extrapolate for species differences in order to assess the consequences exposure for these two species. Furthermore, extrapolation to other species can be made by calculating dose rates based on known differences in body weight.

A summary of ingested doses for various species of birds and mammals is given in Table 4-1. All of these scenarios are based on the general assumption that the animal encounters a recently placed bubble cap containing 390 mg of MCH and that the animal consumes all of the MCH. Note that small rodents typically consume food amounts equivalent to about 15% of their body weight per day. For a 20 g animal, this is equivalent to about 3 g or 3000 mg. Similarly, a robin will consume about 1.5 g of food per g of body weight (U.S. EPA 1993, p. 197). For an 80 g robin, this is equivalent to 120 g or 120,000 mg. Thus, although it sounds extreme, it is fair to assume that these small animals could consume all of the available MCH in a bubble cap, since the quantity of MCH in the bubble cap, 390 mg, is within the normal range of food consumed by these animals. In Table 4-1, the selection of bird species is based on the availability of body weight and food consumption data from U.S. EPA (1993) and Campbell et al. (1991). Other bird species, like blue jays, crows, and chickadees would be likely to tamper with bubble caps.

More extreme exposure scenarios could be constructed involving an animal seeking and consuming multiple bubble caps, but the scenarios are likely to be implausible. Moreover, as discussed in the risk characterization (section 4.4), the single bubble cap scenario is extreme enough to suggest the likelihood of risk for some small species.

4.2.3. MCH in Air. Levels of MCH in air are likely to be extremely low. As discussed in section 3.2.2, an extremely simplistic approximation of 18 µg MCH/m^3 of air can be made based on the release rate from bubble caps and an approximate application rate of 42 g/acre or about 108 bubble caps/acre [108 bubble caps/acre × 0.39 g/bubble cap = 42.12 g/acre]. Because this estimate assumes that all of the released MCH is contained in the 2 m of air directly above the ground and is not dispersed, it is likely to overestimate the exposure by several orders of magnitude. Because there is no basis for assuming that concentrations on the order of 18 µg MCH/m^3 are likely to be associated with toxic effects, further modeling of air levels is unnecessary.

Table 4-1. Exposure for scenarios for the consumption of MCH by small mammals and birds.

Species	Body Weight (kg)	Reference for Body Weight	Estimated Dose[a] (mg/kg bw)
Mammals			
Short-tailed shrew	0.022	U.S. EPA 1993, p. 2-209	17727
Mouse, Deer	0.025	U.S. EPA 1993, p. 2-291, average of range	15600
Rat, young albino	0.150	WARF 1976[b]	2600
Racoon, small	3	U.S. EPA 1993, p. 2-233	130
Racoon, large	9	U.S. EPA 1993, p. 2-233	43
Birds			
Robin	0.08	U.S. EPA 1993, p. 2-194, average for both sexes	4875
Bobwhite quail	0.75	Campbell et al. 1991[b]	520
Mallard duck	1.8	U.S. EPA 1993, p. 2-43, maximum weight	217
Herring Gull	1	U.S. EPA 1993, p. 2-157	390
Bald eagle	5	U.S. EPA 1993, p. 2-95, typical weight	78

[a] Assuming that all of the 390 mg of MCH from the bubble cap is consumed.
[b] Study used for dose-response assessment in mammals.
[c] Study used for dose-response assessment in birds. Approximate average body weight of males and females

Although inhalation toxicity is not a substantial concern, the potential for MCH to act as a pheromone in other species is a concern (see section 4.1.2.3). Since MCH appears to be effective in controlling infestations of Douglas-fir beetles, it is reasonable to conclude that MCH will be present in air in sufficient amounts and for sufficient periods of time to function as an insect pheromone. This issue discussed further in the risk characterization (section 4.4).

4.2.4. Aquatic Organisms. Given the method of MCH application proposed by the Forest Service, there is no reason to assume that aquatic organisms will be exposed to significant levels of MCH. Although it is possible to construct numerous accidental exposure scenarios involving relatively small amounts of MCH (i.e., a bubble cap dropped into a pond), generating the scenarios would lead to trivial levels of exposure. For example, a one-quarter acre pond has a surface area of about 1000 m^2. If the pond has an average depth of 1 m, it will contain 1000 m^3.

This is equivalent to 1,000,000 L of water (i.e., 1 m^3= 100 cm ×100 cm × 100 cm = 1,000,000 cm^3 = 1,000,000 mL = 1,000 L). If a bubble cap containing 390 mg of MCH were ruptured and released into the water, the concentration with instantaneous dilution would be 0.00039 mg/L [390 mg/1,000,000L] or 0.39 µg/L. This amount is about 2300 times less than the lowest reported 96-hour LC_{50} (i.e., 0.91 mg/L) (WARF Institute Inc.1977b) (appendix 5).

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview. Dose-response relationships for acute toxic effects can be characterized for rats, two species of birds, and various aquatic organisms. No toxicity data are available on plants, microorganisms, or terrestrial invertebrates. As discussed in the human health risk assessment, the one rat study that is available reports mortality at doses as low as 500 mg/kg after gavage administration. Studies in birds clearly indicate gavage dosing—placing the chemical directly into the stomach of the animal by intubation—is more hazardous than dietary administration. With gavage administrations to birds, doses less than 500 mg/kg did not cause death. Gavage doses of approximately 800 mg/kg and higher, however, caused death in all treated birds. Based on the available data, rats appear to be somewhat less sensitive than birds to MCH; however, the data supporting this generalization are extremely limited (i.e., one gavage study in rats and one gavage study in quail). Regardless, the magnitude of the differences in sensitivity to MCH is not substantial.

The acute toxicity to aquatic species is relatively well characterized, with 96-hour LC_{50} values ranging from approximately 1 to approximately 50 mg/L. Given the proposed use of MCH and the unlikelihood that ambient water would become contaminated with MCH, these data have no substantial impact on this risk assessment.

4.3.2. Toxicity to Terrestrial Organisms.

4.3.2.1. Mammals– Although the mammalian toxicity of MCH is not well characterized, the available data regarding gavage administration of MCH (WARF Institute Inc. 1976) are highly relevant to an assessment of the consequences of ingesting liquid MCH from a bubble cap. As detailed in appendix 2 and discussed in section 3.3.3, gavage doses as low as 500 mg/kg, the lowest dose tested in the WARF Institute Inc. (1976) study, may be lethal to rats. A dose of 2000 mg/kg bw caused death in 8 of 10 treated rats. This range is very narrow (i.e., the slope of the dose-response curve is relatively steep). Consequently, at doses less 500 mg/kg, the probability of death occurring would decrease quickly. At doses greater than 2000 mg/kg, the probability of death occurring could be extremely high.

A comparison of the rat study by WARF Institute Inc. (1976) and the available oral toxicity data on birds is presented in Table 4-2 and illustrated in Figure 4-1. The purpose of this comparison is to determine whether the pattern of sensitivity for birds and rats is similar. Table 4-2 contains all of the acute oral toxicity data presented in appendices 2 and 3. The dietary levels (mg MCH/kg diet) in the dietary studies on birds were converted to doses in units of mg MCH/kg bw by examining the full text copies of the studies from U.S. EPA files and calculating the ratio of food consumed per unit body weight in each experimental group.

Table 4-2. Mortality data on MCH

Species/ Route/ Study	Exper-iment-al Dose	Dose Units	Ratio of food consumption per day to bw[a]	Dose for Anal-ysis	P Number responding	N Number tested	Proportion responding (P/N)
Rats/ Gavage/ WARF (1976) MRID 00010359	0.5	g/kg bw		500	1	10	0.1
	1.0			1000	2	10	0.2
	2.0			2000	8	10	0.8
Bobwhite quail/ Gavage/ Campbell et al. 1991 MRID 42745404	292	mg/kg bw		292	0	10	0
	486			486	0	10	0
	810			810	10	10	1
	1350			1350	10	10	1
	2250			2250	10	10	1
Bobwhite quail/ Dietary×5 days/ WARF 1977a MRID 00010359	0	ppm (mg/kg diet)	N/A	0	0	8	0
	2500		0.15	375	0	8	0
	5000		0.175	875	0	8	0
	10000		0.162	1620	0	8	0
	20000		0.157	3140	0	8	0
	40000		0.142	5680	1	8	0.125
	80000		0.09	7200	2	8	0.25
Bobwhite quail/ Dietary×5 days/ Beavers et al. 1991b MRID 42745403	0	ppm (mg/kg diet)	N/A	0	0	10	0
	562		0.25	141	0	10	0
	1000		0.32	320	0	10	0
	1780		0.47	837	0	10	0
	3160		0.47	1485	0	10	0
	5620		0.24	1349	1	10	0.1
Mallard Ducks/ Dietary×5 days/ Beavers et al. 1991a MRID 42745402	0	ppm (mg/kg diet)	N/A	0	0	10	0
	562		0.27	152	1	10	0.1
	1000		0.34	340	0	10	0
	1780		0.32	570	0	10	0
	3160		0.18	569	0	10	0
	5620		0.31	1742	0	10	0

As illustrated in Figure 4-1, several studies (Beavers et al. 1991a, WARF Institute Inc. 1976, 1977a) report no mortality to moderate mortality (10%-20%) at dose levels of approximately 150-1500 mg/kg bw. The studies on bobwhite quail (Beavers et al. 1991a, Campbell et al. 1991,

WARF Institute Inc. 1977a) are clearly inconsistent with one another. The most obvious difference among the studies is the route of exposure. The study by Campbell et al. (1991), which reports 100% mortality at dose levels below 1000 mg/kg, is a gavage study; the studies that report fewer incidences of mortality at dose levels greater than 1000 mg/kg (Beavers et al. 1991b, WARF Institute Inc. 1977a) involve dietary administration.

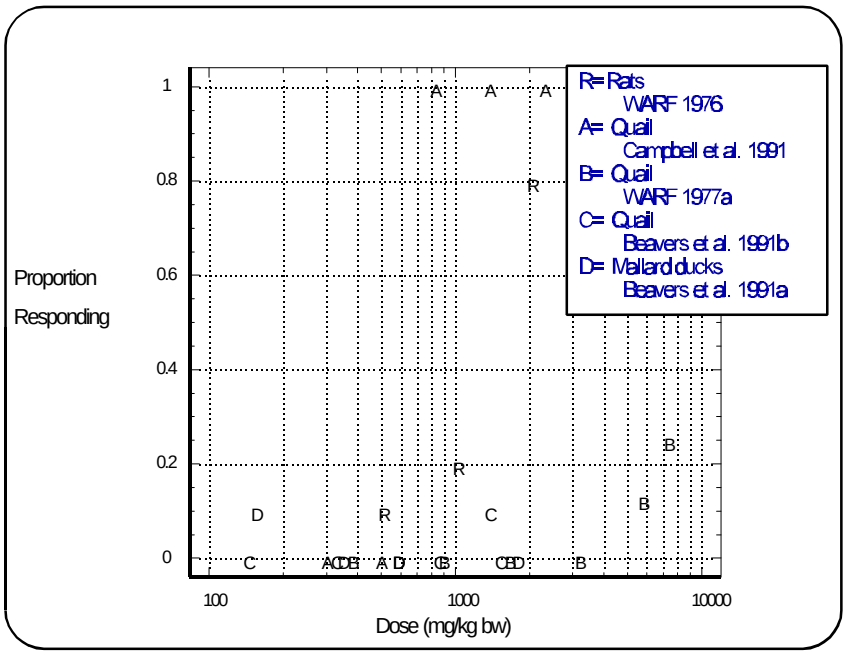


Figure 4-1: Summary of acute oral toxicity data on rats and birds.

The apparent difference in toxicity is consistent with the supposition that gavage administration, which involves placing the toxic agent in the stomach of the animal by intubation, presents a more severe toxic stress than the more gradual intake of a toxic agent by dietary administration.

Since the exposure scenarios considered in this risk assessment postulate a rapid ingestion of liquid MCH, rather than MCH contamination of the diet, the gavage studies, which are the most relevant, are illustrated in Figure 4-2, which is just a subset of the data illustrated in Figure 4-1.

The dose-response curve appears to be extremely steep (i.e., there is a rapid increase in mortality above a certain dose level) for birds, and to a lesser degree for rats. Numerous forms of statistical analyses could be

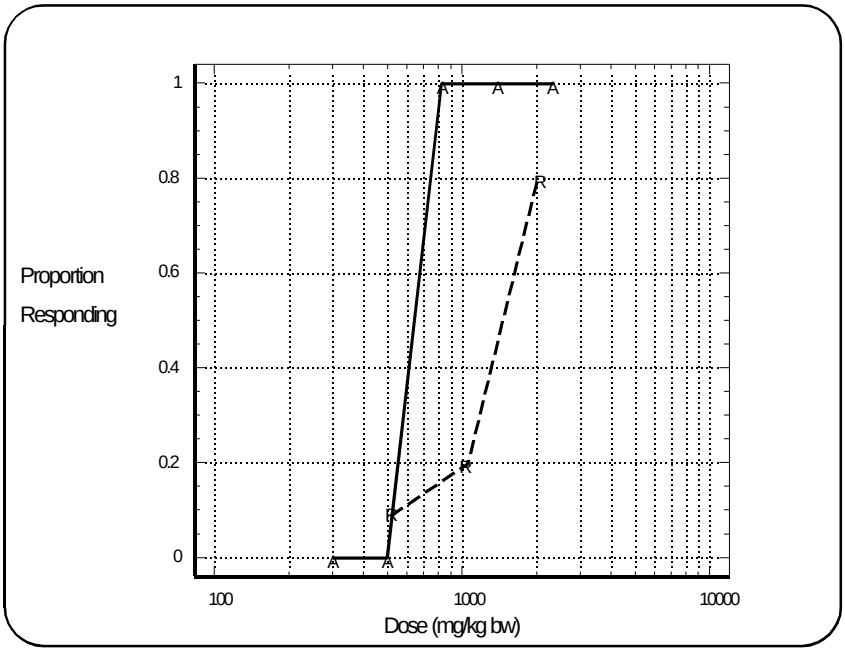


Figure 4-2: Summary of the gavage toxicity studies in rats (R) and birds (A). Based on gavage studies by Campbell et al. 1991 and Warf Institute Inc. 1976. [codes are identical to Figure 4-1].

conducted on these data. Given the limitations of the rat study by WARF Institute Inc. (1976) (see section 3.3.3.) and the lack of incremental mortality rates (i.e., only 0 or 100% responses) in the quail study by Campbell et al. (1991), additional analyses are not warranted. Furthermore, it is impossible to determine from the available data how useful these analyses might be in quantifying toxic responses in other species. Finally, the estimated levels of exposure (see Table 4-1) are sufficiently close to the experimental doses (see Table 4-2) to preclude the need for extrapolation models. Thus, in section 4.4, these data are used directly for the characterization of risk.

4.3.2.2. Birds– Data regarding the toxicity of MCH in Northern bobwhite quail after exposure to the compound by gavage are available in the study by Campbell et al. (1991). Moreover, the experimental doses from the study, 292-2250 mg/kg, are reasonably close to the exposure estimates summarized in Table 4-1, 78-4875 mg/kg. As is the case for mammalian exposure to MCH, little or no extrapolation of the dose-response relationship is required. Also, as with mammalian toxicity studies, the available data on birds are inadequate to support a quantitative species to species extrapolation. This uncertainty is discussed further in the risk characterization (section 4.4).

4.3.2.3. Terrestrial Invertebrates– There are no toxicity studies the exposure of terrestrial invertebrates to MCH. Although acute contact bioassays in bees are typically required by U.S. EPA for the registration of pesticides, this requirement appears to have been waived for MCH. While frank toxic effects associated with the consumption of MCH from bubble caps cannot be ruled out, there is no information on which to base a dose-response assessment. In addition, there is no information to quantify the potential activity of MCH as a pheromone in other insects.

4.3.2.4. Terrestrial Plants (Macrophytes) and Microorganisms– There are dose-response data regarding the toxicity of MCH to terrestrial plants or microorganisms. As discussed in section 4.1, there is no basis for suggesting that MCH would be toxic to either macrophytes or microorganisms under the conditions of use proposed by the Forest Service.

4.3.3. Aquatic Organisms.

4.3.3.1. Animals– As summarized in appendix 5, the toxicity of MCH to two species of fish, bluegills and trout, as well as one aquatic invertebrate, *Daphnia magna*, was assayed. As discussed in section 4.1.3.1, the two studies on bluegills (WARF Institute Inc.1977b, Graves and Peters 1991b) are inconsistent, with the earlier study reporting much lower LC_{50} values than the later study. Although the inconsistency would be of interest if significant levels of aquatic contamination were plausible, these differences in dose-response patterns are essentially irrelevant to this risk assessment.

4.3.3.2. Aquatic Plants and Microorganisms– There are no data regarding the toxicity of MCH to aquatic plants or microorganisms. Given the proposed use of MCH, this deficiency has no substantial impact on this risk assessment.

4.4. RISK CHARACTERIZATION

4.4.1. Overview. Given the limited use of MCH proposed by the Forest Service, two exposure scenarios are plausible: tampering with a bubble cap and exposure to very low levels of MCH in the air.

If an animal were to tamper with a bubble cap, the amount of MCH that might be consumed or otherwise absorbed could range from negligible to the total amount of MCH in a bubble cap, about 0.39 g or 390 mg. The consequences of such an event will vary depending on the size of the animal. If a small mammal, such as a mouse, shrew or rat, consumes 390 mg of MCH, it will probably die. Similarly, a small bird would probably die. Somewhat larger animals about the size of small racoons, crows, or gulls, would probably become ill, but are less likely to die. Still larger animals, such as large racoons or large birds, would probably not exhibit overt signs of toxicity.

The probability of any wildlife species consuming lethal amounts of MCH cannot be assessed, based on the available data. The MCH in bubble caps would clearly be available. Nonetheless, numerous field studies were conducted on the efficacy of MCH, including MCH in bubble cap formulations. If wildlife species commonly consumed MCH, the event would probably be reported in the field studies. Moreover, Forest Service workers conducting efficacy studies on MCH have found no indication that wildlife will consume or otherwise tamper with MCH in either bubble cap or granular formulations. Thus, despite the potential risk to an individual animal if such an event were to occur, it seems unlikely that the consumption of MCH by wildlife will have a detectable or substantial impact on the population of any species.

Several species are likely to be exposed to low levels of MCH in air because of the proposed way in which the compound will be used by the Forest Service. There is no evidence that exposure to low levels of airborne MCH will cause toxicological effects. In fact, the available toxicity data as well as the wide use of MCH in foods suggests that toxicological effects are unlikely to occur at very low levels of exposure. Nevertheless, the potential for MCH to act as a pheromone in other species is of some concern. The available data indicate that both MCH and other related compounds, like methylcyclohexanone, can act as an antiaggregant to the Douglas-fir beetle. Methylcyclohexanone also acts as a repellent to bees. This information suggests, albeit tenuously, that MCH could also act as a repellent to bees and perhaps other species as well.

4.4.2. Terrestrial Organisms.

4.4.2.1. Mammals– As discussed in section 4.2.2, the most plausible, however unlikely, exposure scenario for terrestrial mammals involves tampering with the bubble caps and consuming the enclosed liquid MCH. The amount of MCH that would be consumed could range from almost 0 to 390 mg (the amount encased in an individual bubble cap).

Under the assumption that all of the bubble cap encased MCH (390 mg) is consumed, some species clearly will be at risk if the sensitivity of those species to MCH is the same as the sensitivity in the population of rats used in the WARF Institute Inc.(1977) bioassay. If equal sensitivities among species is assumed, small mammals (i.e., shrews, mice, and rats) would

consume doses that substantially exceed the potentially lethal dose of 500 mg/kg reported in WARF Institute Inc. (1977). Mammals like racoons would be subject to lower doses in terms of mg/kg body weight, as a function of their higher body weights. It is possible that mammals as large as small racoons could be at some risk. Larger mammals, like deer and bear, would be exposed to doses far below the lethal levels reported in the rat study (WARF Institute Inc.1977).

This interpretation, however, is predicated on the assumption of equal sensitivity among species. Wildlife species are not commonly used as experimental animals; consequently, direct data on the toxicity to species of concern are seldom available. Nonetheless, for some well studied compounds, information may be available on a variety of different experimental mammals that allows for some assessment of differences in sensitivity among species. No such information is available for MCH.

Because of this lack of information, there is uncertainty in this characterization of risk. Notwithstanding this uncertainty, the limited nature of plausible exposures should be appreciated. Unless an animal actually eats the bubble cap, there is no evidence that adverse effects are plausible. The likelihood that numerous individuals of any species will consume the bubble cap cannot be determined. As detailed in the Forest Service submissions to the U.S. EPA, several efficacy studies were conducted on MCH, including MCH in bubble cap formulations and no incidents of wildlife tampering with the MCH formulations was noted. Furthermore, the apparent efficacy of this compound in these field studies suggests that consumption of the formulation by wildlife species is not a common event.

4.4.2.2. Birds– The risk characterization for birds is quite similar to that of mammals. As detailed in appendix 5, the minimum lethal dose for quail is 810 mg/kg. At this dose level, 10 of 10 birds died. As in the case of mammalian exposure to MCH, the dose-response curve appears to be relatively steep: no birds died at the next lowest dose level of 486 mg/kg.

Based on the exposure estimates summarized in Table 4-1, birds that are about the size of a robin, bluejay, or smaller could ingest sufficient quantities of MCH from a bubble cap to cause death. The likelihood of ingestion occurring, however, for any small bird cannot be determined. Larger birds, including gulls, would not be likely to die but they could exhibit signs of toxicity, primarily neurological effects. Much larger predatory birds would probably not display any effect even in the unlikely event that they were to consume the MCH or consume an organism that recently consumed MCH.

As in the case of mammalian exposure to MCH, this characterization is based on the assumption of equal sensitivity among different bird species.

4.4.2.3. Terrestrial Insects– As summarized in section 4.1.2.3, there is suggestive evidence that MCH could act as a pheromone in other species. This speculation is based on the pheromone activity of both MCH and 3-methylcyclohexanone in the Douglas-fir beetle as well as apparent pheromone activity of methylcyclohexanones in bees and possibly cockroaches. In the absence of more information specific to MCH, however, this concern is only speculative.

4.4.2.4. Other Terrestrial Species– No risk characterization for terrestrial plants or microorganisms is possible because of the lack of toxicity data. Unlike the case with terrestrial insects, however, there is no plausible basis for asserting that a hazard may exist.

4.4.2. Aquatic Organisms.

4.4.2.1. Fish and Aquatic Invertebrates– The acute toxicity of MCH to fish and aquatic invertebrates was not studied extensively; however, acute bioassays are available. Because the two bioassays on bluegills are not consistent with one another, there is some uncertainty in the dose-response assessment. Nonetheless, the major factor in the characterization of risk for aquatic species is that the plausibility of exposure seems to be extremely remote.

4.4.2.2. Aquatic Plants– There are no data available on the toxicity of MCH to aquatic plants. Nonetheless and as is the case with fish, the plausibility of exposure is remote. Thus, this particular data gap has no substantial impact on this risk assessment.

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6. GLOSSARY

Absorption -- The process by which the agent is able to pass through the body membranes and enter the bloodstream. The main routes by which toxic agents are absorbed are the gastrointestinal tract, lungs, and skin.

Acute exposure -- A single exposure or multiple exposure occurring within a short time (24 hours or less).

Adjuvant(s) -- Formulation factors used to enhance the pharmacological or toxic agent effect of the active ingredient.

Adverse-effect level (AEL) -- Signs of toxicity that must be detected by invasive methods, external monitoring devices, or prolonged systematic observations. Symptoms that are not accompanied by grossly observable signs of toxicity. In contrast to Frank-effect level.

Assay -- A kind of test (noun); to test (verb).

Bioconcentration factor -- The concentration of a compound in an aquatic orgainism divided by the concentration in the ambient water of the organism.

Chronic exposure -- Long-term exposure studies often used to determine the carcinogenic potential of chemicals. These studies are usually performed in rats, mice, or dogs and extend over the average lifetime of the species (for a rat, exposure is 2 years).

Connected actions -- Exposure to other chemical and biological agents in addition to exposure to the control agent during program activities to control vegetation.

Contaminants -- For chemicals, impurities present in a commercial grade chemical. For biological agents, other agents that may be present in a commercial product.

Controls -- In toxicology or epidemiology studies, a population that is not exposed to the potentially toxic agent under study.

Cumulative exposures -- Exposures that may last for several days to several months or exposures resulting from program activities that are repeated more than once during a year or for several consecutive years.

Dermal -- Pertaining to the skin.

Dose-response assessment -- A description of the relationship between the dose of a chemical and the incidence of occurrence or intensity of an effect. In general, this relationship is plotted by statistical methods. Separate plots are made for experimental data obtained on different species or strains within a species.

Exposure assessment -- The process of estimating the extent to which a population will come into contact with a chemical or biological agent.

Extrapolation -- The use of a model to make estimates outside of the observable range.

Formulation -- A commercial preparation of a chemical including any inerts or contaminants.

Frank effects -- Obvious signs of toxicity.

Frank-effect level (FEL) -- The dose or concentration of a chemical or biological agent that causes gross and immediately observable signs of toxicity.

Gavage -- The placement of a toxic agent directly into the stomach of an animal, using a gastric tube.

Geometric Mean -- The measure of an average value often applied to numbers for which a log normal distribution is assumed.

Half-time or half-life -- For compounds that are eliminated by first-order kinetics, the time required for the concentration of the chemical to decrease by one-half.

Hazard identification -- The process of identifying the array of potential effects that an agent may induce in an exposed human population.

Herbicide -- A chemical used to control, suppress, or kill plants, or to severely interrupt their normal growth processes.

In vivo -- Occurring in the living organism.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

Inerts -- Adjuvants or additives in commercial formulations of glyphosate that are not readily active with the other components of the mixture.

Invertebrate -- An animal that does not have a spine (backbone).

Irritant effect -- A reversible effect, compared with a corrosive effect.

Lethal concentration$_{50}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal dose$_{50}$ (LD_{50}) -- The dose of a chemical calculated to cause death in 50% of a defined experimental animal population over a specified observation period. The observation period is typically 14 days.

Lowest-observed-adverse-effect level (LOAEL) -- The lowest dose of a chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Metabolite -- A compound formed as a result of the metabolism or biochemical change of another compound.

Microorganisms -- A generic term for all organisms consisting only of a single cell, such as bacteria, viruses, and fungi.

Microsomal -- Pertaining to portions of cell preparations commonly associated with the oxidative metabolism of chemicals.

Non-target -- Any plant or animal that a treatment inadvertently or unavoidably harms.

No-observed-adverse-effect level (NOAEL) -- The dose of a chemical at which no statistically or biologically significant increases in frequency or severity of adverse effects were observed between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-observed-effect level (NOEL) -- The dose of a chemical at no treatment-related effects were observed.

Octanol-water partition coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Ocular -- Pertaining to the eye.

Partition -- In chemistry, the process by which a compound or mixture moves between two or more media.

Pathway -- In metabolism, a sequence of metabolic reactions.

pH -- The negative log of the hydrogen ion concentration. A high pH (>7) is alkaline or basic and a low pH (<7) is acidic.

Pheromone – A naturally occurring chemical involved in the transmission of messages (i.e., chemical communication) within a species. Some pheromones act as attractants, while other pheromones have the opposite effect, causing organisms to be repelled or dispersed.

RfD -- A daily dose which is not anticipated to cause any adverse effects in a human population over a lifetime of exposure. These values are derived by the U.S. EPA.

Route of exposure -- The way in which a chemical or biological agent enters the body. Most typical routes include oral (eating or drinking), dermal (contact of the agent with the skin), and inhalation.

Scientific notation -- The method of expressing quantities as the product of number between 1 and 10 multiplied by 10 raised to some power. For example, in scientific notation, 1 kg = 1,000 g would be expressed as 1 kg = 1 x 10^3 g and 1 mg = 0.001 would be expressed as 1 mg = 1 x 10^{-3}.

Sensitive subgroup -- Subpopulations that are much more sensitive than the general public to certain agents in the environment.

Species-to-species extrapolation -- A method involving the use of exposure data on one species (usually an experimental mammal) to estimate the effects of exposure in another species (usually humans).

Subchronic exposure -- An exposure duration that can last for different periods of time, but 90 days is the most common test duration. The subchronic study is usually performed in two species (rat and dog) by the route of intended use or exposure.

Substrate -- With reference to enzymes, the chemical that the enzyme acts upon.

Synergistic effect -- A situation is which the combined effects of two chemicals is much greater than the sum of the effect of each agent given alone.

Systemic toxicity -- Effects that require absorption and distribution of a toxic agent to a site distant from its entry point at which point effects are produced. Systemic effects are the obverse of local effects.

Teratogenic -- Causing structural defects that affect the development of an organism; causing birth defects.

Teratology -- The study of malformations induced during development from conception to birth.

Threshold -- The maximum dose or concentration level of a chemical or biological agent that will not cause an effect in the organism.

Toxicity -- The inherent ability of an agent to affect living organisms adversely.

Uncertainty factor (UF) -- A factor used in operationally deriving the RfD and similar values from experimental data. UFs are intended to account or (1) the variation in sensitivity among members of the human population; (2) the uncertainty in extrapolating animal data to the case of humans; (3) the uncertainty in extrapolating from data obtained in a study that is less than lifetime exposure; and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10. See table 2-4 for additional details.

Vertebrate -- An animal that has a spinal column (backbone).

7. SUBJECT INDEX

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APPENDICES

Appendix 1: Selected efficacy studies with MCH.
Appendix 2: Toxicity to mammals.
Appendix 3: Toxicity to birds.
Appendix 4: Cyclohexenones approved as food additives.
Appendix 5: Toxicity to fish and aquatic invertebrates.

Appendix 1: Selected efficacy studies with MCH

Plant	Exposure	Response	Reference
FIELD STUDIES			
Felled Douglas-fir trees in four localities in Idaho, Oregon, and Washington	optimal concentration: approximately 1 g MCH eluted/acre/day (achieved by diffusion of liquid MCH from open 0.5 dram vials on 5-foot posts, spaced 10-feet apart)	significantly reduced brood production of Douglas-fir beetles in susceptible trees; although higher concentrations resulted in less mature broods, they were less effective than the optimal concentration in lowering brood density	Furniss et al. 1974 MRID 00010363
Felled Douglas-fir trees	hand application of five controlled release granular formulations of MCH at a release rate of $\geq$1 μg/hr for $\geq$30 days to field plots containing felled trees	Douglas-fir beetle attacks significantly fewer in trees treated with four/five different formulations	Furniss et al. 1977 MRID 00010364
Felled Douglas-fir trees	hand broadcast of formulation #10 on plots containing trees felled by saw, or uprooted	attacks on trees by Douglas-fir beetle were significantly less dense	Furniss et al. 1977 MRID 00010364

Appendix 2: MCH Toxicity to experimental mammals.

Animal	Dose	Response	Reference
ORAL			
Rats, Spraque Dawley, approximately 7 weeks old, body weight 125-168 g, 10 rats per dose group. Gavage	0.50, 1.00, or 2.00 g/kg	LD_{50} mortality incidence: 0.50 g/kg - 1/10 (day 2) 1.00 g/kg - 2/10 (days 2,3) 2.00 g/kg - 8/10 (days 2,4,7) Investigators concluded that LD_{50} = between 1 and 2 g/kg No information is reported on signs of toxicity. No information is given on a control group.	WARF Institute, Inc. 1976 MRID 00010358 Identical data in MRID 0046585; 00066789 Briefly summarized in MRID 00010357; 00046584; 00066788
EYES			
Rabbits, New Zealand white, approximately 14 weeks old, body weight = 2.5-3.5 kg, 6 rabbits per dose group	0.1 mL in one eye; untreated eye served as control. The eyes were not washed after exposure.	No effects on the cornea or iris at any time. Redness, swelling, and discharge in treated conjunctivas of all treated rabbits at 24 and 48 hours after treatment. Less pronounced redness and swelling but no discharge at 72 hours after treatment. No observed effects at 7 days after treatment.	WARF Institute, Inc. 1976 MRID 00010358 Identical data in MRID 0046585 00066789 Briefly summarized in MRID 00010357; 00046584; 00066788

Appendix 2: MCH Toxicity to experimental mammals.

Animal	Dose	Response	Reference
INHALATION			
Rats, Sprague Dawley, albino, approximately 7 weeks old, 10 treated rats, 10 controls	19.7 mg/L, 1-hour continuous exposure	observable physical effects during exposure, including rubbing noses immediately, struggling to escape at 5 minutes, laying down with eyes shut, no mortality.	WARF Institute, Inc. 1976 MRID 00010358 Identical data in MRID 0046585 0066789
		Gross tissue examination revealed alterations regarded as minimal in occurrence and severity; moreover, the incidence was similar in both treated and control groups	Briefly summarized in MRID 00010357; 00046584; 0066788

Appendix 3: Toxicity of MCH to birds.

Animal	Dose	Response	Reference
Quail, bobwhite, 10-days old, 8 chicks per dose group	0, 2500, 5000, 10,000, 20,000, 40,000, or 80,000 ppm in diet for 5 days	Dose-related body weight loss and decreased food consumption observed during treatment period, especially at high dose; both parameters recovered during 3-day post-treatment observation period. Mortality occurred only in the 40,000 (1/8) and 80,000 (2/8) dose groups, except for one quail in a control group.	WARF Institute, Inc. 1977a MRID 00010359 Data duplicated in MRID 00046586; 0066790
Mallard ducks (*Anas platyrhyn-chos*), 10-days old, 10 per treatment group	562, 1000, 1780, 3160 or 5620 ppm in diet for 5 days	LC_{50} >5620 ppm one mortality at 562 ppm, incidental to treatment; no mortalities at any other concentration; all birds normal in appearance and behavior throughout treatment; slight reduction in body weight gain at 5620 ppm during 5-day exposure period, compared with controls; no treatment-related effect on food consumption.	Beavers et al. 1991a MRID 42745402
Northern Bobwhite (*Colinus virginianus*), 10-days old, 10 per dose group	562, 1000, 1780, 3160 or 5620 ppm in diet for 5 days	LC_{50} >5620 ppm NOEL = 3160 ppm at 562, 1000, 1780, and 3160 ppm, no mortality or overt signs of toxicity; birds were normal in appearance and behavior at 5620 ppm, one mortality was observed on day 3 in the absence of any previous signs of toxicity; on days 4-6 one bird was observed intermittently laying on its side, stumbling, and walking in a crouched position, these effects appeared to be treatment related; beginning on the morning of day 7, all birds in this high dose group seemed to be normal in appearance and behavior; compared with controls, birds in the high dose group had a slight reduction in body weight gain, but there was no effect on food consumption.	Beavers et al. 1991b MRID 42745403

Appendix 3: Toxicity of MCH to birds.

Animal	Dose	Response	Reference
Northern Bobwhite (*Colinus virginianus*), 17-weeks old, five males and five females per dose group	0, 292, 486, 810, 1350, or 2250 mg/kg single dose MCH in corn oil, administered by gavage	**Control Group:** no mortality or signs of toxicity. **292 mg/kg dose group**: reduced weight gain was observed in the absence of other signs of toxicity. **486 mg/kg dose group**: reduced body weight gain and signs characteristic of MCH toxicity (i.e., lower limb weakness, loss of coordination, ruffled appearance, decreased reaction to external stimuli (sound and movement), wing droop, lethargy, and depression) were observed approximately 1 hour and 10 minutes after dosing and persisted through the morning of day 2; by the afternoon of day 2, the appearance and behavior of the birds returned to normal and remained so until termination of the study. **810 mg/kg dose group**: signs of MCH toxicity were observed approximately 15 minutes after dosing; one bird died 4 and 1/2 hours after dosing and the remaining nine birds were found dead on the morning of day 2; effects on body weight gain and food consumption could not be determined. **1350 mg/kg dose group**: signs of toxicity were noted approximately 10 minutes after dosing; one bird died approximately 1 hour after dosing; all birds were dead by the end of day 0; effects on body weight gain and food consumption could not be determined. **2250 mg/kg dose group**: signs of toxicity were observed immediately after dosing, four birds died approximately 20 minutes after dosing; all birds were dead within 4 and 1/2 hours after dosing; effects on body weight gain and food consumption could not be determined.	Campbell et al. 1991 MRID 42745404

ADDENDIX 4:
Cyclohexenones Approved as Food Additives

NOTE: *This appendix is printed directly from the FDA/PAFA CD-ROM (Clydsdale 1997). Thus, these pages do no appear in the disk copy of or PDF file for this risk assessment and are not paginated.*

Appendix 5: MCH Toxicity to fish and aquatic invertebrates. [a.i. technical unless otherwise specified]

Animal	Exposure	Response	Reference
FRESHWATER			
Bluegill sunfish, 20 per dose group	0.25, 0.50, 1.00, 2.00, or 4.00 mg/L for 24, 48, or 96 hours	24-hr LC_{50} = 7.6 mg/L (3.62-15.96 mg/L) 48-hr LC_{50} = 5.75 mg/L (2.88-11.50 mg/L) 96-hr LC_{50} = 0.91 mg/L (0.63-1.32 mg/L)	WARF Institute, Inc. 1977b MRID 00010360; 00066791
Rainbow trout, 20 per dose group	40, 80, 160, or 320 mg/L for 24, 48, or 96 hours	24-hr LC_{50} = between 160 and 320 mg/L 48-hr LC_{50} = between 80 and 160 mg/L 96-hr LC_{50} = 72.0 mg/L (56.25-92.16 mg/L)	WARF Institute, Inc. 1977b MRID 00010360; 00066791
Daphnia magna	13, 22, 36, 60, or 100 mg MCH/L	48-hr EC_{50} = 51.4 (43.6-61.6 mg/L) NOEL = 22 mg/L	Holmes and Smith 1991 MRID 42745401
Rainbow trout (*Oncorhynchus mykiss*), juveniles (approximately 90-days old), 10 per dose group	0, 13.0, 21.6, 36.0, 60.0, or 100 mg MCH/L	LC_{50} values: 24 hr = >100 mg MCH/L 48 hr = 77.4 mg MCH/L (60-100 mg/L) 72 hr = 60 mg MCH/L (36-100 mg/L) 96 hr = 44.9 mg MCH/L (36-60 mg/L) NOEL = 22 mg/L mortality began occurring at highest concentration tested (100 mg MCH/L) within 24 hours; at 96-hours, total mortality was observed in the 60 and 100 mg MCH/L groups, only 5% mortality was observed in the 36 mg MCH/L group; no mortality or treatment-related effects were observed at concentrations ≤21.6 mg MCH/L.	Graves and Peters 1991a MRID 42745405

Appendix 5: MCH Toxicity to fish and aquatic invertebrates. [a.i. technical unless otherwise specified]

Animal	Exposure	Response	Reference
Bluegill sunfish (*Lepomis macrochirus*), juveniles (approximately 78-days old), 10 per dose group	0, 4.7, 7.8, 13.0, 21.6, or 36.0 mg MCH/L	LC_{50} values: 24 hr = 30.7 mg MCH/L (21.6-36.0 mg/L) 48 hr = 26.4 mg MCH/L (21.6-36.0 mg/L) 72 hr = 25.8 mg MCH/L (21.6-36.0 mg/L) 96 hr = 25.3 mg MCH/L (21.6-36.0 mg/L) 96-hr no mortality concentration = 13.0 mg MCH/L 75% mortality occurred at highest concentration tested (36.0 mg MCH/L) within 24 hours; at 96-hours, total mortality was observed in the 36.0 mg MCH/L groups, and 20% mortality occurred at 21.6 mg MCH/L; no mortality or treatment-related effects were observed at concentrations $\leq$13.0 mg MCH/L.	Graves and Peters 1991b MRID 42745406

WORKSHEETS FOR MCH

NOTE: Given the nature of the anticipated exposures to MCH, many of the standard worksheets used in Forest Service risk assessments are not used and have been omitted. In addition, many of the worksheets that are included have been substantially simplified.

Worksheet Table of Contents

Section/Title Page No.

GENERAL ASSUMPTIONS, VALUES, and MODELS

Worksheet 01: Constants and conversion factors used in calculations		
mg/lb	mg_lb	453,600
mL/gallon	ml_gal	3,785
lb/gallon to mg/mL	lbg_mgml	119.8
lb/acre to µg/cm^2	lbac_ugcm	11.21
lb/acre to mg/cm^2	lbac_mgcm	0.01121
gallons to liters	gal_lit	3.785

Worksheet 02: General Assumptions Used in Worker Exposure Assessments				
Parameter	Code	Value	Units	Reference
Body Weight (General)	BW	70	kg	ICRP (1975), p. 13
Surface area of hands	Hands	840	cm^2	U.S. EPA 1992

Worksheet 03: General Assumptions Used in Exposure Assessments for the General Public				
Description	ID	Value	Units	Reference
Body Weights				
Male, Adult	BWM	70	kg	ICRP (1975), p. 13.
Female, 45-55 years old, 50th percentile	BWF	64	kg	U.S. EPA, 1985, page 5, Table 2-2, rounded to nearest kilogram.
Child, male, 2-3 years old	BWC	13	kg	U.S. EPA, 1985, page 6, Table 2-3, rounded to nearest kilogram.

Worksheet 04: Estimate of first-order absorption rate (k_a in hours^{-1}) and 95% confidence intervals (from Durkin et al. 1998).			
Model parameters	ID	Value	
Coefficient for $k_{o/w}$	C_KOW	0.233255	
Coefficient for MW	C_MW	0.005657	
Model Constant	CONST	1.49615	
Number of data points	DP	29	
Degrees of Freedom (d.f.)	DF	26	
Critical value of $t_{0.025}$ with 26 d.f.[1]	CRIT	2.056	
Standard error of the estimate	SEE	16.1125	
Mean square error or model variance	MDLV	0.619712	
Standard deviation of model (s)	MSD	0.787218	MDLV$^{0.5}$
X′X, cross products matrix	0.307537	-0.00103089	0.00822769
	-0.00103089	0.000004377	-0.0000944359
	0.0082	-0.0000944359	0.0085286
[1] Mendenhall and Scheaffer, 1973, Appendix 3, 4, p. A31.			

Central (maximum likelihood) estimate:

$$\log_{10} k_a = 0.233255 \log_{10}(\boldsymbol{k_{o/w}}) - 0.005657\ \boldsymbol{MW} - 1.49615$$

95% Confidence intervals for $\log_{10} k_a$

$$\log_{10} k_a \pm \boldsymbol{t}_{0.025} \times \boldsymbol{s} \times (\boldsymbol{a}'\boldsymbol{X}'\boldsymbol{X}\,\boldsymbol{a})^{0.5}$$

where $\boldsymbol{a}$ is a column vector of {1, MW, $\log_{10}(\boldsymbol{k_{o/w}})$}.

NB: Although the equation for the central estimate is presented with $k_{o/w}$ appearing before MW to be consistent with the way a similar equation is presented by EPA, MW must appear first in column vector $\boldsymbol{a}$ because of the way the statistical analysis was conducted to derive X′X .

See following page for details of calculating $\boldsymbol{a}'\boldsymbol{X}'\boldsymbol{X}\,\boldsymbol{a}$ without using matrix arithmetic.

Details of calculating $a'X'X\,a$

The term $\mathbf{a}'\cdot(\mathbf{X}'\mathbf{X})^{-1}\cdot\mathbf{a}$ requires matrix multiplication. While this is most easily accomplished using a program that does matrix arithmetic, the calculation can be done with a standard calculator.

Letting

$$\mathbf{a} = \{a\_1, a\_2, a\_3\}$$

and

$$(\mathbf{X}'\mathbf{X})^{-1} = \{ \{b\_1, b\_2, b\_3\}, \{c\_1, c\_2, c\_3\}, \{d\_1, d\_2, d\_3\} \},$$

$\mathbf{a}'\cdot(\mathbf{X}'\mathbf{X})^{-1}\cdot\mathbf{a}$ is equal to

Term 1: {a_1 ×([a_1×b_1] + [a_2×c_1] + [a_3×d_1])} +
Term 2: {a_2 ×([a_1×b_2] + [a_2×c_2] + [a_3×d_2])} +
Term 3: {a_3 ×([a_1×b_3] + [a_2×c_3] + [a_3×d_3])}.

Worksheet 05: Estimate of dermal permeability (K_p in cm/hr) and 95% confidence intervals (data from U.S. EPA 1992).			
Model parameters	ID	Value	
Coefficient for $k_{o/w}$	C_KOW	0.706648	
Coefficient for MW	C_MW	0.006151	
Model Constant	CONST	2.72576	
Number of data points	DP	90	
Degrees of Freedom (d.f.)	DF	87	
Critical value of $t_{0.025}$ with 87 d.f.[1]	CRIT	1.96	
Standard error of the estimate	SEE	45.9983	
Mean square error or model variance	MDLV	0.528716	
Standard deviation of model (s)	MSD	0.727129	$MDLV^{0.5}$
X′X, cross products matrix	0.0550931	-0.0000941546	-0.0103443
	-0.0000941546	0.0000005978	-0.0000222508
	-0.0103443	-0.0000222508	0.00740677
[1] Mendenhall and Scheaffer, 1973, Appendix 3, Table 4, p. A31.			

NOTE: The data for this analysis is taken from U.S. EPA (1992), Dermal Exposure Assessment: Principles and Applications, EPA/600/8-91/011B, Table 5-4, pp. 5-15 through 5-19. The EPA report, however, does not provide sufficient information for the calculation of confidence intervals. The synopsis of the above analysis was conducted in STATGRAPHICS Plus for Windows, Version 3.1 (Manugistics, 1995) as well as Mathematica, Version 3.0.1.1 (Wolfram Research, 1997). Although not explicitly stated in the EPA report, 3 of the 93 data points are censored from the analysis because they are statistical outliers: [Hydrocortisone-21-yl]-hemipimelate, n-nonanol, and n-propanol. The model parameters reported above are consistent with those reported by U.S. EPA but are carried out to greater number of decimal places to reduce rounding errors when calculating the confidence intervals. See notes to Worksheet 04 for details of calculating maximum likelihood estimates and confidence intervals.

CHEMICAL SPECIFIC VALUES

Worksheet 06: Anticipated Application and Dilution Rates for MCH				
Item	Code	Value	Units	Reference/Source
Typical application rate	Typ	0.042	kg a.i./acre	108 bubble caps/acre with 0.39 g MCH/bubble cap. See Section 2.3 for details.
Lowest application rate	Low	No range of application rates are currently proposed.		
Highest application rate	Hi			

Worksheet 07: Chemical specific values used for MCH in exposure assessment worksheets.				
Parameter	ID	Value	Units	Source/Reference
Molecular weight	MW	110.16	grams/mole	Clydsdale 1997
$K_{o/w}$	Kow	56.2	unitless	Meylan and Howard 1995
Estimate BCF	BCFC	12	kg fish/L	Calabrese and Baldwin, 1993 [a]

[a] Recommended equation for concentration in fish muscle (edible portion) is:

$$\log(BCF) = 0.54 \log (K_{o/w}) + 0.124$$

Worksheet 08: Calculation of first-order dermal absorption rate (k_a) for MCH.							
Parameters	Value	Units			Reference		
Molecular weight	110.16	g/mole					
$K_{o/w}$ at pH 7	56.2	unitless					
$\log_{10} K_{o/w}$	1.75						
Column vector ***a*** for calculating confidence intervals (see Worksheet 04 for definitions.)							
a_1	1						
a_2	110.16						
a_3	1.75						
Calculation of $\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$ - see Worksheet 04 for details of calculation.							
Term 1	0.2083241576						
Term 2	-0.0786523128						
Term 3	0.0223119422						
$\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$	0.152	calculation verified in Mathematica 3.0.1.1					
$\log_{10} k_a = 0.233255 \log_{10}(\boldsymbol{k_{o/w}}) - 0.005657\ \boldsymbol{MW} - 1.49615$					see Worksheet 04		
$\log_{10}$ of first order absorption rate (k_a)							
Central estimate	-1.71119037571	±	$\boldsymbol{t}_{0.025}$	×	$\boldsymbol{s}$	×	$(\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a})^{0.5}$
Lower limit	-2.34220572012	-	2.0560	×	0.787218	×	0.38987177379
Upper limit	-1.0801750313	+	2.0560	×	0.787218	×	0.38987177379
First order absorption rates (antilog or 10^x of above values)							
Central estimate	0.0194450751	hours^{-1}					
Lower limit	0.004547726	hours^{-1}					
Upper limit	0.0831428618	hours^{-1}					

Worksheet 09: Calculation of dermal permeability rate (K_p) in cm/hour for MCH.							
Parameters	Value	Units	Reference				
Molecular weight	110.16	g/mole					
$K_{o/w}$ at pH 7	56.2	unitless					
$\log_{10} K_{o/w}$	1.75						
Column vector ***a*** for calculating confidence intervals (see Worksheet 05 for definitions.)							
a_1	1						
a_2	110.16						
a_3	1.75						
Calculation of $\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$ - see Worksheet 05 for details of calculation.							
Term 1	0.0266185043						
Term 2	-0.007407142						
Term 3	0.0002912						
$\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$	0.0195	calculation verified in Mathematica 3.0.1.1					
$\log_{10}$ of First order absorption rate							
Central estimate	-2.16690649208	±	$t_{0.025}$	×	s	×	$\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}^{0.5}$
Lower limit	-2.36592104849	-	1.9600	×	0.727129	×	0.13964240044
Upper limit	-1.96789193566	+	1.9600	×	0.727129	×	0.13964240044
First order absorption rates							
Central estimate	0.0068092	cm/hour					
Lower limit	0.0043060	cm/hour					
Upper limit	0.0107673	cm/hour					

Worksheet 10: Summary of chemical specific dermal absorption values used for MCH dermal absorption.				
Description	Code	Value	Units	Reference/Source
Zero-order absorption (K_p)				
Central estimate	KpC	0.0068	cm/hour	Worksheet 09, values rounded to two significant figures
Lower limit	KpL	0.0043	cm/hour	
Upper limit	KpU	0.011	cm/hour	
First-order absorption rates (k_a)				
Central estimate	AbsC	0.019	$hour^{-1}$	Worksheet 08, values rounded to two significant figures
Lower limit	AbsL	0.0045	$hour^{-1}$	
Upper limit	AbsU	0.083	$hour^{-1}$	

Worksheet 11: Workers: Dermal Exposure Assessments Using Zero-Order Absorption. See section 3.2.1 for verbal description.			
Parameter	Value	Units	Source
Density of MCH	971	mg/cm^2	Table 2-1
Body weight (*W*)	70	kg	Worksheet 02.BW
Surface Area of hands (*S*)	840	cm^2	Worksheet 02.Hands
Dermal permeability (K_p, cm/hour) [see Worksheet 09]			
Typical	0.0068	cm/hour	Worksheet 09.KpC
Lower	0.0043	cm/hour	Worksheet 09.KpL
Upper	0.011	cm/hour	Worksheet 09.KpU

Note that 1 mL is equal to 1 cm^3 and thus mg/mL = mg/cm^3.

Equation (U.S. EPA 1992)

$$K_p \cdot C \cdot Time(hr) \cdot S \cdot \div W = Dose(mg/kg)$$

where:

C = concentration in mg/cm^3 or mg/mL.
S = Surface area of skin in cm^2
W = Body weight in kg.

Wearing Contaminated Gloves for One-Minute

Typical Value: Use typical concentration and central estimate of K_p.
0.0068 cm/hr × 971 mg/cm³ × 1/60 hr × 840 cm² ÷ 70 kg = 1.3e+00 mg/kg [WZHT1M]

Lower Estimate: Use lower limit of K_p.
0.0043 cm/hr × 971 mg/cm³ × 1/60 hr × 840 cm² ÷ 70 kg = 8.4e-01 mg/kg [WZHL1M]

Upper Estimate: Use upper range of estimated concentration and upper limit of K_p.
0.011 cm/hr × 971 mg/cm³ × 1/60 hr × 840 cm² ÷ 70 kg = 2.1e+00 mg/kg [WZHU1M]

Wearing Contaminated Gloves for One-Hour

Typical Value: Use typical concentration and central estimate of K_p.
0.0068 cm/hr × 971 mg/cm³ × 1 hr × 840 cm² ÷ 70 kg = 7.9e+01 mg/kg [WZHT1H]

Lower Estimate: Use lower range of estimated concentration and lower limit of K_p.
0.0043 cm/hr × 971 mg/cm³ × 1 hr × 840 cm² ÷ 70 kg = 5.0e+01 mg/kg [WZHL1H]

Upper Estimate: Use upper range of estimated concentration and upper limit of K_p.
0.011 cm/hr × 971 mg/cm³ × 1 hr × 840 cm² ÷ 70 kg = 1.3e+02 mg/kg [WZHU1H]