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REPORTABLE QUANTITY DOCUMENT FOR PROPHAM

NOTICE

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Office of Emergency and Remedial Response
U.S. Environmental Protection Agency
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CONTENTS

PREFACE

This report describes the relevant toxicity studies used to derive the RQ for propham based on chronic toxicity. Reportable Quantity Documents are intended to support the adjustment of release reporting triggers established under section 102 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Generally, EPA assigns one of five RQ values (1, 10, 100, 1000, or 5000 pounds) to a hazardous substance based on an evaluation of the intrinsic physical, chemical, and toxicological properties -- called "primary criteria" -- of the substance. Chronic toxicity is one of six primary criteria; RQs based on chronic toxicity are derived according to the procedures described in the draft *Methodology for Evaluating Chronic Toxicity in Support of Reportable Quantity Adjustment Pursuant to CERCLA Sections 101 and 102* (U.S. EPA, 1994).

The studies used in this report were identified through computerized literature searches. The automated data bases that were searched included CHEMLINE, TOXLINE, TOXLINE 65, TOXLIT, TOXLIT 65, CANCERLIT, RTECS, and IRIS. The on-line searches were extended as far back as the data bases would allow. A key word strategy was used to narrow the retrieval in cases where the electronic search produced in excess of 500 citations. The data bases were searched (most recently in November 1999) using the Chemical Abstract Service Registry Number (CASRN), the chemical name, and synonyms. Manual searches of *Current Contents, Health Effects Assessment Summary Tables*, bibliographies of relevant publications and secondary sources (International Agency for Research on Cancer [IARC] Monographs, National Institute for Occupational Safety and Health [NIOSH] documents, and U.S. EPA reports) were conducted to identify both recent literature and also key older studies (pre-1970). A request was submitted to the U.S. EPA's Office of Pesticide Programs (OPP) for any additional relevant unpublished information; the results presented herein, however, do not reflect any unpublished data from OPP. All chronic, subchronic, and subacute toxicological studies in mammals using oral and inhalation routes of exposure were reviewed for relevant information. Appropriate secondary sources were also reviewed. Every attempt was made to rely upon primary publications rather than summaries of data or abstracts contained in secondary sources.

EXECUTIVE SUMMARY

An RQ based on the evaluation of chronic toxicity data for a chemical reflects only possible or potential hazards from long-term exposure to that substance. Such an RQ, however, does not represent a determination that releases of an amount above the RQ necessarily are harmful to public health or the environment, or that releases below the RQ necessarily are not harmful. The actual hazard caused by the release of a hazardous substance will vary with the circumstances of each release.

As described in U.S. EPA (1994), the RQ is determined from a CS, which is based upon the potency of the chemical (RV_d) and the severity of the observed effects (RV_e). The RV_d and RV_e for a compound are derived from the human MED of a chemical and the critical adverse effect observed at the MED. Both the RV_d and RV_e are expressed on a scale of 1 to 10. The CS is the product of the RV_d and the RV_e and, therefore, ranges from 1 to 100. The higher the CS (i.e., the greater chronic toxicity of the chemical), the lower the RQ of the chemical.

An evaluation of chronic toxicity data on propham results in an RQ of 1000 pounds. The critical effect, increased spleen weight, was observed in male rats administered 2000 ppm of propham in feed at a dose of 126 mg/kg/day for 90 days (PPG Industries, 1979). Because of the subchronic duration (90 days), an uncertainty factor of 10 was used to estimate chronic exposure from subchronic exposure data. In accordance with the recommendations provided in U.S. EPA (1994), this study is given a high confidence rating. The study was well conducted and proper documentation has been provided concerning investigative procedures and results. The data base is given a low confidence rating because it is limited. Reproductive/developmental studies were not located in the available literature. A chronic toxicity study available for another mammalian species (hamster) provided a limited investigation of potential effects. Available human data are not applicable to deriving an RQ based on chronic toxicity. Because the principal study is rated high and the data base on propham is assigned a low confidence rating, the 1000-pound RQ for propham is given a medium confidence rating. A summary table appears on the following page.

PROPHAM

(CASRN 122-42-9)

MED and RQ

Route:	Oral (diet)
Species/sex:	Sprague-Dawley rat/male
Study dose:	2000 ppm in the diet (126 mg/kg/day)
MED*:	223 mg/day
Duration:	90 days
Effect:	Increased spleen weight
RV_d	1.98
RV_e	4
CS:	7.9
RQ:	1000 pounds
Reference:	PPG Industries, 1979

*Equivalent human dose; an uncertainty factor of 10 was used to estimate chronic exposure from subchronic exposure data.

LIST OF ABBREVIATIONS

CS	Composite Score
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
LOFEL	Lowest-observed-frank-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

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1. TOXICOLOGY

Propham (Chemical Abstract Service Registry Number [CASRN] 122-42-9), also known as isopropyl N-phenylcarbamate or IPC, is a widely used pre-planting, pre- and post-emergence herbicide that is used to control grassy and broadleaf weeds. The chemical formula of propham is $C_{10}H_{13}NO_2$ and the molecular weight is 179. The rat oral LD_{50} of propham is approximately 1-9 g/kg (IARC, 1976), indicating that propham has a relatively low order of acute toxicity.

The herbicidal action of propham has been attributed to its inhibitory effects on the formation of microtubules and microfilaments, which have essential roles in cell replication and general cell physiology. In *in vitro* experiments, propham has been shown to inhibit microtubule formation and/or structure in mammalian cells (Sentein and Ates, 1978; Bartels and Hilton, 1973; Oliver et al., 1978; Coss et al., 1975). This observation is supported by a study showing inhibited meiotic maturation in conjunction with decreased formation and orientation of microtubules occurring near the nucleus of mouse oocytes (Crozet and Szollosi, 1979). Michel et al. (1980) obtained similar findings with human lymphocytes. It is unknown if these effects occur in mammalian systems *in vivo*.

Biokinetic studies of propham in adult male and female Wistar rats yielded data on the oral absorption and excretion of propham. In these studies, male rats were administered 15 mg of radiolabelled propham via gavage and observed for four days following treatment (Bend et al., 1971). Groups of two to four female rats were administered doses of 0.94 mg to 50.94 mg radiolabelled propham via gavage and observed for three days following treatment (Fang et al., 1974). In each study, excretion of radiolabelled compound in urine, feces, and expired air was measured in 24-hour intervals. In male rats, 92% of the administered dose was recovered, 83% of which was recovered in non-fecal sources (urine and expired air). In female rats, 93% of the administered dose was recovered, 88% of which was recovered in non-fecal sources. Conservatively assuming that excretion of radiolabelled compound from non-fecal routes is representative of the quantity of orally administered propham that was absorbed from the gastrointestinal tract, oral absorption coefficients of 83% and 88% are obtained for male and female rats, respectively. Use of the lower oral absorption efficiency accommodates conservative assumptions. Therefore, an oral absorption efficiency of 83% has been derived for propham, based on the results obtained by Bend et al. (1971).

1.1. ANIMAL STUDIES

Studies in the available literature involving the exposure of experimental animals to propham via the oral route are summarized below.

1.1.1. Oral. van Esch and Kroes (1972) investigated the effects on Golden hamsters of long-term oral exposure to propham. Groups of six-week-old hamsters (22 males/27 females per dose group) were administered either 0 or 0.2% (2000 ppm) propham (purity unspecified) in the diet for 33 months. Body weights were recorded weekly for the first 15 weeks, and then monthly through the end of the study. At sacrifice at study termination, all animals were examined for gross lesions. Because this study focused on the potential carcinogenicity of propham, many parameters typically assessed in a well-designed chronic toxicity study were not examined. Only organs that exhibited gross abnormalities were evaluated for histopathological effects. No significant differences in growth or mortality were observed between the control and treated groups of either sex. The incidence of testicular atrophy was significantly greater in treated males (seven occurrences) than in control males (one occurrence). No other treatment-related effects were observed in male or female hamsters. Parameters such as testicular and reproductive function (e.g., sperm count, fertility) were not assessed; therefore, the potential effects of propham on the male reproductive system may not have been adequately assessed in this study.

The effects of subchronic oral exposure to propham were studied in rats (PPG Industries, 1979). Sprague-Dawley rats (30 animals per sex for each dose [30/sex/dose]) were administered doses of 0, 250, 1000, or 2000 ppm propham (98% purity) in the diet for 13 weeks, from 4 weeks of age through 16 weeks. Clinical signs, including behavioral changes and signs of overt toxicity, were monitored daily. Individual weight gain and food consumption were measured weekly, and periodic evaluations of urinalysis, hematology, blood chemistry, and plasma and red blood cell (RBC) cholinterase (ChE) activity were conducted on 10 animals randomly selected from each test group. At sacrifice at the end of the study, organ weights (heart, liver, spleen, brain, kidneys and gonads) were measured, and histopathological examinations were on all tissues and gross lesions in the high-dose and control groups. In low-dose animals, the liver, heart, kidney, and all gross lesions were examined histologically. Male rats receiving a dietary dose of 2000 ppm propham (126 mg/kg/day) had increased spleen weights at study termination. Female rats receiving a dietary dose of 2000 ppm propham (141 mg/kg/day) had decreased plasma ChE levels

after 45 days of treatment, but clinical effects that could result from decreased ChE levels in female rats were not observed. No effects were observed in treated rats receiving doses of 1000 ppm or lower. Based on these findings, a LOAEL of 2000 ppm (126 mg/kg/day) for increased spleen weight and a NOAEL of 1000 ppm (approximately 50 mg/kg/day) were determined.

1.1.2. Inhalation. No pertinent data regarding the chronic, subchronic, reproductive, or developmental toxicity of inhalation exposure to propham were located in the available literature.

1.2. HUMAN STUDIES

Workers in a chemical plant that produced carbamate pesticides, including propham, were evaluated for ChE activity levels in whole blood, plasma, and RBCs (Bellin and Chow, 1974). ChE levels did not significantly differ between employees directly exposed to the chemicals and those employees merely working in the plant (e.g., office workers). However, a significant difference in ChE levels between plant workers and the control population was evident. Additionally, plant personnel complained of numerous symptoms that could be associated with carbamate toxicity. Although the severity and profile of clinical symptoms in plant workers were not indicative of overt carbamate toxicity, control subjects did not report any clinical symptoms. Whether the clinical symptoms were attributable to test bias, or exposure to other chemicals within the plant such as methylene chloride, remains uncertain.

1.3. DERIVATION OF RQ

As summarized in Table 1-1 and indicated in Table 1-2, chronic toxicity composite scores for propham from the available studies range from 1.98 to 7.9. The most appropriate CS is 7.9, based on the dose-response data reported for male rats in the PPG Industries (1979) subchronic study of propham.

In the PPG Industries (1979) study, male rats administered doses of 2000 ppm propham in the diet (126 mg/kg/day) had increased spleen weights following exposure for 90 days. The RV_e for increased organ weight in the absence of altered organ function is 4. Based on an average male rat body weight of 0.287 kg (calculated from data presented in the study), an absorption efficiency of 83% (Bend et al., 1971), and an uncertainty factor of 10 to account for the subchronic duration of the study, the RV_d is 1.98. Together, the RV_d and RV_e result in a CS of 7.9.

Other effects reported in subchronic or chronic toxicity studies with propham included decreased plasma ChE levels in female rats (PPG Industries, 1979), and testicular atrophy in male hamsters (van Esch and Kroes, 1972). The effects observed in male hamsters receive an RV_e of 3 for organ atrophy in the absence of reported effects on organ weight/function. Applying the oral absorption efficiency of 83%, and standard assumptions for the food factor, 0.097 kg food/kg body weight/day, and average male rat body weight, 0.134 kg (U.S. EPA, 1988), the RV_d is 1. The resulting CS is 3.

Similarly, the change in enzyme activity of female rats (PPG Industries, 1979) in the absence of any reported pathological effects results in an RV_e of 1. The RV_d for the propham dose corresponding to these effects is 1.98, applying the same modifying factors as were applied to the RV_d calculation for the male rat and a female body weight of 0.181 kg, calculated from data presented in the study. The resulting CS is 1.98.

The effects reported in the study on chemical plant workers (Bell and Chow, 1974) could not be positively associated with exposure to propham alone, nor were exposure doses quantified. Therefore, a CS was not developed for this study. Based on available information on chronic toxicity, the CS of 7.9, calculated for the effects on the male rat (PPG Industries, 1979), is the most appropriate for propham. The CS of 7.9 corresponds to a chronic toxicity RQ of 1000 pounds for propham.

Table 1-1. Oral Chronic/Subchronic Toxicity for Propham

Species/ Strain	Sex/ Number	Average Weight (kg)	Exposure	Transformed Animal Dose [a] (mg/kg/day)	Equivalent Human MED (mg/kg/day)	Effect	Reference
Hamster/Golden	M/23	0.134[b]	2000 ppm (194 mg/kg/day) in the diet for 33 months	161[b]	33.7	Testicular atrophy	van Esch and Kroes, 1972
Rat/Sprague-Dawley	M/30	0.287[c]	2000 ppm (152 mg/kg/day) in the diet for 90 days	126[d]	3.2[e]	Increased spleen weight	PPG Industries, 1979
Rat/Sprague-Dawley	F/30	0.181[c]	2000 ppm (170 mg/kg/day) in the diet for 90 days	141[d]	3.2[e]	Decreased plasma cholinesterase levels	PPG Industries, 1979

[a]Based on an oral absorption efficiency of 83% (Bend et al., 1971).
[b]Chronic male golden Syrian hamster default body weight and food consumption values from U.S. EPA (1988).
[c]Determined by average body weights for 13 weeks as reported in Table 4 (PPG Industries, 1979).
[d]Determined by average of 13 weeks of food consumption data as reported in Table 5 (PPG Industries, 1979).
[e]An uncertainty factor of 10 was used to estimate chronic exposure from subchronic exposure data.

Table 1-2. Oral Composite Scores for Propham

Species/ Strain	Animal Dose [a,b] (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ (pounds)	Reference
Hamster/Golden	161	2,357	1	Testicular atrophy	3	3	5000	van Esch and Kroes, 1972
Rat/Sprague-Dawley	126	223[c]	1.98	Increased spleen weight	4	7.9	1000	PPG Industries, 1979
Rat/Sprague-Dawley	141	223[c]	1.98	Decreased plasma cholinesterase levels	1	1.98	5000	PPG Industries, 1979

[a]Based on an oral absorption coefficient of 83% (Bend et al., 1971).
[b]Equivalent to Transformed Animal Dose in Table 1-1 of this report.
[c]An uncertainty factor of 10 was used to estimate chronic exposure from subchronic exposure data.

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APPENDIX - WORKSHEETS FOR CALCULATING COMPOSITE SCORES

WORKSHEET FOR CALCULATING COMPOSITE SCORES

Chemical: Propham
CAS#: 122-42-9
MW: 179
Study Citation: van Esch and Kroes, 1972

EXPOSURE ROUTE: Inhalation, (Oral)

STUDY DATA

TEST ANIMAL Species and Strain: Hamster Golden Sex: M Body Weight (kg): 0.134 (EPA '88)	EXPOSURE REGIMEN Study type (chronic or subchronic): Chronic Duration: 33 months feeding
CRITICAL ENDPOINT Effect(s): Testicular Atrophy	NOAEL Value: LOAEL Value: 2000 ppm (194 mg/kg/day) FEL Value:

1. Intermittent Exposure Adjustments (if necessary):

   Adj. LOAEL (mg/m^3) (..... ppm x .....(MW)/24.45 = ... mg/m^3)

   = chronic LOAEL (mg/m^3) x exposure/dosing regimen

   = ... mg/m^3 x ..... hrs/24 hours x ..... days/7 days

   = ... mg/m^3

2. Transformed Animal Dose (mg/kg/day)

   Air = Adj. LOAEL (mg/m^3) x [inhalation $rate_A$ (m^3/day) / body wt_A (kg)]

   = ... mg/m^3 x [..... m^3/day / ..... kg] x ..... (absorption coeff.)
   (1 if respiratory effect; 0.5 if extrarespiratory effect)

   OR

   Food = 2000 ppm or mg/kg diet x 0.097 (food factor) (EPA '88) x ~~1.0~~ 0.83 (Bond et al. 1971) (absorption coeff.)

   = 161 mg/kg/day

   OR

   Water = ... ppm or mg/L x ..... L/day x [1 /..... kg] x 1.0 (absorption coeff.)

   = ... mg/kg-day

3. Human MED (mg/day)

   = animal MED (mg/kg-day) x [body wt_A (kg) / body wt_H (kg)] $^{1/4}$ x body wt_H (kg)

   = 161 mg/kg-day x [0.134 kg/ 70 kg] $^{1/4}$ x 70 kg

   = 2357 mg/day

4. *For Subchronic Study only* (divide MED by 10 to obtain chronic MED): (..... mg/day) / 10 = ... mg/day

5. Assign RVd using Exhibit 1 and RVe using Exhibit 2:

   Human MED = 2357 mg/day
   Log Human MED = 3.37 mg/day
   RVd = 1
   RVe = 3

6. Calculate Composite Score (CS): = 1 (RVd) x 3 (RVe) = 3

[RQ = 5000]

2

WORKSHEET FOR CALCULATING COMPOSITE SCORES

Chemical: Propham
CAS#: 122-42-9
MW: 179
Study Citation: PPG Industries, 1979

EXPOSURE ROUTE: Inhalation, (Oral)

STUDY DATA

TEST ANIMAL Species and Strain: Rat Sprague-Dawley Sex: M Body Weight (kg): 0.287 (ave over 13 wks)	EXPOSURE REGIMEN Study type (chronic or subchronic): Subchronic Duration: 90 days in feed
CRITICAL ENDPOINT Effect(s): Increased spleen weight	NOAEL Value: 1000 ppm LOAEL Value: 2000 ppm (152 mg/kg/day) FEL Value:

1. Intermittent Exposure Adjustments (if necessary):

   Adj. LOAEL (mg/m^3) (..... ppm x .....(MW)/24.45 = ... mg/m^3)

   = chronic LOAEL (mg/m^3) x exposure/dosing regimen

   = ... mg/m^3 x ..... hrs/24 hours x ..... days/7 days

   = ... mg/m^3

2. Transformed Animal Dose (mg/kg/day)

   Air = Adj. LOAEL (mg/m^3) x [inhalation $rate_A$ (m^3/day) / body wt_A (kg)]

   = ... mg/m^3 x [..... m^3/day / ..... kg] x ..... (absorption coeff.)
   (1 if respiratory effect; 0.5 if extrarespiratory effect)

   OR

   Food = 2000 ppm or mg/kg diet x 0.076 (food factor) x ~~1.0~~ 0.83 (absorption coeff.) ← intake = 0.0217 — Bond et al 1971

   = 126 mg/kg/day

   OR

   Water = ... ppm or mg/L x ..... L/day x [1 /..... kg] x 1.0 (absorption coeff.)

   = ... mg/kg-day

3. Human MED (mg/day)

   = animal MED (mg/kg-day) x [body wt_A (kg) / body wt_H (kg)] $^{1/4}$ x body wt_H (kg)

   = 126 mg/kg-day x [0.287 kg/ 70 kg] $^{1/4}$ x 70 kg

   = 2234 mg/day

4. *For Subchronic Study only* (divide MED by 10 to obtain chronic MED): (2234 mg/day) / 10 = 223 mg/day

5. Assign RVd using Exhibit 1 and RVe using Exhibit 2:

   Human MED = 223 mg/day
   Log Human MED = 2.35 mg/day
   RVd = 1.98
   RVe = 4

6. Calculate Composite Score (CS): = 1.98 (RVd) x 4 (RVe) = 7.9

[RQ = 1000]

3

WORKSHEET FOR CALCULATING COMPOSITE SCORES

Chemical: Propham
CAS#: 122-42-9
MW: 179
Study Citation: PPG Industries, 1979

EXPOSURE ROUTE: Inhalation, Oral

STUDY DATA

TEST ANIMAL Species and Strain: Rat Sprague-Dawley Sex: F Body Weight (kg): 0.181 (ave over 13 wks)	EXPOSURE REGIMEN Study type (chronic or subchronic): Subchronic Duration: 90 days in feed
CRITICAL ENDPOINT Effect(s): Decreased plasma cholinesterase	NOAEL Value: 1000 ppm LOAEL Value: 2000 ppm (170 mg/kg/day) FEL Value:

1. Intermittent Exposure Adjustments (if necessary):

   Adj. LOAEL (mg/m^3) (..... ppm x .....(MW)/24.45 = ... mg/m^3)

   = chronic LOAEL (mg/m^3) x exposure/dosing regimen

   = ... mg/m^3 x ..... hrs/24 hours x ..... days/7 days

   = ... mg/m^3

2. Transformed Animal Dose (mg/kg/day)

   Air = Adj. LOAEL (mg/m^3) x [inhalation $rate_A$ (m^3/day) / body wt_A (kg)]

   = ... mg/m^3 x [..... m^3/day / ..... kg] x ..... (absorption coeff.)
   (1 if respiratory effect; 0.5 if extrarespiratory effect)

   OR

   Food = 2000 ppm or mg/kg diet x 0.085 (food factor) x ~~1.0~~ 0.83 (Bond et al 1971) (absorption coeff.)
   ← intake = 0.0154

   OR = 141 mg/kg/day

   Water = ... ppm or mg/L x ..... L/day x [1 /..... kg] x 1.0 (absorption coeff.)

   = ... mg/kg-day

3. Human MED (mg/day)

   = animal MED (mg/kg-day) x [body wt_A (kg) / body wt_H (kg)] $^{1/4}$ x body wt_H (kg)

   = 141 mg/kg-day x [0.181 kg/ 70 kg] $^{1/4}$ x 70 kg

   = 2225.7 mg/day

4. *For Subchronic Study only* (divide MED by 10 to obtain chronic MED): (2226 mg/day) / 10 = 223 mg/day

5. Assign RVd using Exhibit 1 and RVe using Exhibit 2:

   Human MED = 223 mg/day
   Log Human MED = 2.35 mg/day
   RVd = 1.98
   RVe = 1

6. Calculate Composite Score (CS): = 1.98 (RVd) x 1 (RVe) = 1.98

[RQ = 5000]