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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **May 12, 1999**

MEMORANDUM

SUBJECT: ***Creosote*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Timothy F. McMahon, Ph.D. 5/18/99
Senior Toxicologist, RASSB
Antimicrobials Division (7510C)

THROUGH: Pauline Wagner, Co-Chair Pauline Wagner 5/14/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Jess Rowland, Co-Chair 5/12/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Adam Heyward
PM Team 34 / RMB II
Antimicrobials Division (7510C)

PC Code: 025004

On April 1, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Creosote** and selected the toxicological endpoints for short-term, intermediate-term; and long-term occupational/residential exposure risk assessments. An acute and chronic Reference Dose (RfD) was not selected, as there are no food uses for creosote or expected dietary exposure to creosote. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to creosote as required by the Food Quality Protection Act (FQPA) of 1996, as there are potential residential exposures to creosote. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Virginia Dobozy, Pamela Hurley, Mike Ioannou, Susan Makris, Nicole Paquette, Jess, Rowland, PV Shah, Pauline Wagner, and Brenda Tarplee (executive secretary). Data were presented by Tim McMahon of the Risk Assessment and Science Support Branch, Antimicrobials Division .

Data Presentation:
and
Report Presentation

Timothy F. McMahon, Ph.D.
Toxicologist

Report Concurrence:

Brenda Tarplee
Executive Secretary

I. INTRODUCTION

On April 1, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Creosote** and selected the toxicological endpoints for short-term, intermediate-term, and long-term occupational/residential exposure risk assessments. An acute and chronic Reference Dose (RfD) was not selected, as there are no food uses for creosote or expected dietary exposure to creosote. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to creosote as required by the Food Quality Protection Act (FQPA) of 1996, as there are potential residential exposures to creosote.

II. DIETARY

A. ACUTE DIETARY [Acute Reference Dose (RfD)]

Type of Study : none

MRID No.:

Executive Summary: none

Dose and Endpoint selected for risk assessment: not applicable

Uncertainty Factor(s) : none

Proposed ACUTE RfD: none

Comments about Study/Endpoint/Uncertainty Factor(s): An acute dietary risk assessment is not required for creosote, as there is no anticipated dietary exposure to creosote.

This Risk Assessment is not required.

B. CHRONIC DIETARY (Chronic RfD)

Type of Study: none

MRID No.: none

Executive Summary: none

Dose Selected for risk assessment: not applicable

Uncertainty Factor(s) : none

Proposed RfD: none

Comments about Study/Endpoint/Uncertainty Factor(s): A chronic dietary risk assessment is not required for creosote, as dietary exposure is not anticipated for this chemical.

This risk assessment is not required.

C. OCCUPATIONAL / RESIDENTIAL EXPOSURE—DERMAL

1. DERMAL ABSORPTION

Study Selected: No dermal absorption studies are available.

Percentage (%) Dermal Absorption Proposed for Consideration: 50%

Comments about Dermal Absorption: The value of 50% dermal absorption was estimated by comparison of the oral and dermal LOAELs from the developmental toxicity study in rats (MRID # 43584201) and the 90-day dermal toxicity study in rats (MRID # 43616101) using the P1/P13 blend. The oral LOAEL of 175 mg/kg/day observed in the developmental toxicity study, when compared to the dermal LOAEL of 400 mg/kg/day observed in the dermal toxicity study, yields an absorption factor of 44%, which was rounded up to 50% by the Committee. The rounding to 50% took into account the significant dermal irritation which occurs from dermal exposure to creosote.

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2. SHORT-TERM DERMAL (1 - 7 days)

Study Selected: Developmental Toxicity in Rats (P1/P13) **Guideline #:** 83-3

MRID No.: 43584201

Executive Summary: In a developmental toxicity study using P1/P13 creosote (MRID # 43584201), pregnant female Sprague-Dawley rats (30/dose) were administered P1/P13 creosote at dose levels of 0, 25, 50, and 175 mg/kg/day on gestation days 6 through 15 inclusive. Decreased body weight and food consumption were observed at the 175 mg/kg/day dose level in this study in maternal rats. Decreased uterine weight was observed in maternal rats at the high dose, which is reflected partly by the decreased live fetuses per litter at the high dose (although mean fetal weight was not affected). Cesarean section observations showed significantly increased resorptions and post-implantation loss as well as decreased number of live fetuses per litter at the 175 mg/kg/day dose. Based on the results of this study, the Maternal NOAEL is 50 mg/kg/day, and the Maternal LOAEL is 175 mg/kg/day, based on decreased body weight gain and food consumption during the study.

No treatment-related malformations (external, visceral or skeletal) were observed in any of the fetuses at 25 mg/kg bw/day. At 50 mg/kg bw/day, the overall incidence of malformations on a fetal and litter basis were statistically elevated compared to controls. However, these individual malformations were not

seen at higher dose levels and/or fell within the range of historical control data. At 175 mg/kg bw/day there was (i) an overall significant increased incidence of developmental malformations, (ii) increased incidence of cardiovascular, vertebral and digital malformations, compared to lower dose levels, concurrent controls or historical controls (2429 and 2898 fetuses examined viscerally and skeletally respectively) and (iii) an increased incidence of malformations at this dose level in spite of increased fetal loss (resorptions) (Beck and Lloyd, 1963) thus resulting in fewer fetuses available for teratogenic examination. Although the incidence of fetal malformations observed at 175 mg/kg bw/day dose level in rats was low and could be related to maternal stress (decreased body weight gain and food consumption), the teratogenic potential of P1/P13 Creosote cannot be ruled out. Based on these data, the developmental toxicity NOAEL is 50 mg/kg/day, and the developmental toxicity LOAEL is 175 mg/kg/day, based on increased post-implantation loss, increased mean resorptions, decreased live fetuses per litter, and increased developmental malformations.

Dose and Endpoint selected for Risk Assessment: The Maternal NOAEL of 50 mg/kg/day was selected, based on decreased body weight gain during the study at 175 mg/kg/day.

Comments about Study/Endpoint: Although a 90-day dermal toxicity study was available, the developmental toxicity study was chosen for the following reasons: 1) concern for developmental toxicity seen in the rat study, which was not measured in the dermal toxicity studies (including the 2-week range-finding studies); 2) Developmental effects are presumed to occur following a single exposure. Therefore, this study is appropriate for this risk assessment.

An uncertainty factor (MOE) of 100 is applied to this risk assessment. The dermal absorption factor of 50% should be used when converting from an oral to dermal risk assessment.

This risk assessment is required.

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3. INTERMEDIATE-TERM DERMAL (1-Week to Several Months)

Study Selected: 90-Day Dermal Toxicity Study in Rats **Guideline #:** 82-3

MRID No.: 43616201

Executive Summary: In a 90-day dermal toxicity study (MRID # 43616201), Charles River rats (10/sex/dose) were given dermal applications of P2 creosote in corn oil at dosage levels of 0, 4, 40 or 400 mg/kg bw/day. There was no mortality observed in this study at any dose level. Body weight in high dose males was decreased 7-8% during weeks 9-12 of the study, and bodyweight gain decreased 15% in high dose males for the treatment period. Food consumption in high dose males was decreased during weeks 2-4 and week 6 by 4-10% vs control. Only slight dermal irritation was observed in high dose males. No effects were observed on hematology or clinical chemistry. Treated skin in the 400 mg/kg/day dose groups (male and female) was observed with increased incidence of dermal inflamation. Based on the results of this study, the systemic LOAEL is 400 mg/kg/day, based on decreased body weight gain in male rats. The systemic NOAEL is 40 mg/kg/day. For females, the NOAEL is set at 400 mg/kg bw/day since no systemic toxic effects were noted in any of the treated groups.

Dose and Endpoint Selected for risk assessment: A NOAEL of 40 mg/kg/day was selected, based on decreased body weight gain at 400 mg/kg/day.

Comments about Study/Endpoint: As a dermal endpoint was used for this risk assessment, the dermal absorption factor does not need to be employed .

This risk assessment is required.

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4. LONG-TERM DERMAL (Several Months to Lifetime)

Type of Study Selected: 2-Generation Reproduction **Guideline #:** 83-4

MRID No.: N/A (reviewed by CAL EPA)

Executive Summary: In this study, Charles River Crl:CD rats, 26/sex/group, were dosed by gavage with P1/P13 creosote in corn oil at doses of 0, 25, 75, and 150 mg/kg/day. Pre-mating treatment phase lasted approximately 17 weeks, which may have contributed to the decreased fertility observed in this study. Systemic effects observed in this study for parental animals included decreased body weight during the pre-mating period at all dose levels, with a dose-response noted for this effect. Salivation was also observed at 75 mg/kg/day and above in the F1 generation. Effects in offspring included a dose-related decrease in growth of offspring of the F0 generation starting at 25 mg/kg/day (as shown by decreased pup weight). For the F0 pups, mean number of liver pups per litter was decreased at 75 and 150 mg/kg/day, and percent live pups at 175 mg/kg/day was also decreased. In the F1 pups, the percent live pups was decreased at 75 nad 150 mg/kg/day, but pup growth was affected only at 150 mg/kg/day as shown by decreased mean pup weight. Decreased fertility and pregnancy indices were observed in the F1 female parental rats at all dose levels, but this was not interpreted as a treatment-related effect, as it was more likely related to the fact that the critical weight for fertility was exceeded by the 17-week pre-mating interval. Based on the results of this study, the Parental Systemic NOAEL is < 25 mg/kg/day, and the Parental Systemic LOAEL is 25 mg/kg/day, based on decreasedpre-mating body weight. The developmental NOAEL in this study is < 25 mg/kg/day, and the developmental LOAEL is 25 mg/kg/day, based on a dose-related decrease in pup body weight for the F0 pups from days 14-21. The reproductive NOAEL is < 25 mg/kg/day, and the reproductive LOAEL is 25 mg/kg/day, based on reduced pregnancy and fertility indices in F1 female parental rats.

Dose and Endpoint Selected for risk assessment: The Parental LOAEL of 25 mg/kg/day was selected, based on decreased pre-mating body weight.

Comments about Study/Endpoint: An extra uncertainty factor of 3x was applied to the MOE of 100, based on the use of a LOAEL . The dermal absorption factor of 50% should be used when converting from oral to dermal risk assessment.

This risk asessment is required.

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5. INHALATION (ANY-TIME PERIOD)

Type of Study: 90-day inhalation toxicity in rats **Guideline #:** 82-4

MRID No.: 43600901

Executive Summary: In a 13-week inhalation toxicity study (MRID # 43600901), 20 Sprague-Dawley rats/sex/group were treated for 5 days/week, 6 hours/day with P2 Creosote CTM via whole body exposure at doses of 0, 4.7, 48 or 102 mg/m^3 (0, 0.005, 0.048 or 0.102 mg/L) in air measured gravimetrically. The aerosol size MMAD was between 2.4 and 2.9 microns with a geometric standard deviation between 1.85 and 1.91. Subsequent to the exposure period 10 rats/sex/group were allowed to recover from treatment for 6 weeks.

During the exposure period, two animals (low dose female; mid dose male) were sacrificed in extremis and the cause of morbidity was not related to treatment. Significant treatment-related findings in mid and high dose animals included decreased terminal body weight and body weight gain (m/f), altered hematological parameters (decreased hemoglobin content, hematocrit, erythrocyte and platelet counts; increased reticulocyte counts and mild poikilocytosis, m/f) and biochemical parameters (increased serum cholesterol levels, m/f). In both sexes macroscopic discolouration of the lungs persisted through the recovery period and correlated with the presence of black pigment granules within alveolar macrophages. Both sexes showed increased absolute and relative liver and thyroid weights and increased lung/trachea/body weight ratios. Absolute and relative thyroid weights of high dose animals actually increased after the recovery period. An increased incidence of lesions of the nasal cavity epithelium (chronic inflammation) was noted following treatment (all treatment groups, m/f) but appeared to lessen in incidence and severity during the recovery period (mainly the high dose group, m/f). During exposure an increased incidence of thyroid follicular epithelial cell hypertrophy occurred in all male groups including control and in the high dose female group. At recovery the male incidence remained similar to that observed at exposure while the incidence in females of the high dose group had declined. The incidence of thyroid follicular cell hypertrophy was slightly increased in low and mid dose females after the recovery period. Slightly increased incidence of mild poikilocytosis was observed in all treatment groups (m/f) including the low dose group and control, which persisted through the recovery period. Low dose animals exhibited lesions of the nasal cavity epithelium which had resolved after the recovery period. Based on the results of this study, the systemic LOAEL is 48 mg/m^3 , based on decreased body weight and weight gain, altered hematology ad clinical chemistry, increased absolute and relative weight of the liver ad thyroid, and increased incidence of lesions of the nasal cavity. The systemic NOAEL is set at 4.7 mg/m^3 (0.0047 mg/L) for P2 Creosote CTM in rats.

Dose and Endpoint Selected for risk assessment: NOAEL of 0.0047 mg/L, based on decreased body weight gain, altered hematology and clinical chemistry, and increased absolute and relative weight of the liver and thyroid observed at 0.048 mg/L.

Comments about Study/Endpoint: A Margin of Exposure of 100 is considered adequate for this risk assessment.

This risk assessment is required.

D. Margins of Exposure for Occupational / Residential Risk Assessments

A Margin of Exposure of 100 is adequate for short-term and intermediate-term dermal and inhalation occupational risk assessments. A Margin of Exposure of 300 is adequate for long-term occupational dermal risk assessments. For long-term occupational inhalation risk assessment, a Margin of Exposure of 100 is adequate. Margins of Exposure for residential risk assessments will be determined by the FQPA

Safety Factor Committee.

E. Recommendation for Aggregate Risk Assessments

Separate Margins of Exposure should be calculated for dermal and inhalation routes since oral and dermal NOAELs were selected for dermal risk assessmentand an inhalation NOAEL was selected for this route of exposure. Residential exposure to creosote may occur through farm use by certified applicators. If residential exposures need to be included in an aggregate risk assessment, aggregation of risk should be performed. For long-term aggregate risk assessment, the aggregate risk index approach should be used, based on the differences in acceptable MOE's for long-term exposure (100 for inhalation, 300 for dermal).

III. CLASSIFICATRION OF CARCINOGENIC POTENTIAL

The Agency has classified creosote as a B1 (probable) human carcinogen on IRIS, on the basis of limited evidence of occupational exposure to creosote and development of tumors, and on the basis of sufficient evidence for tumor development following dermal exposure in experimental animals. The International Agency for Research on Cancer has classified creosote as Group 2A (probable human carcinogen) for essentially the same reasons. The HIARC expressed concern that a quantitative assessment of the carcinogenicity of creosote be performed if such data are available to allow quantitation of the unit risk. Currently, the B1 classification has not been subject to review by the Office of Pesticide Programs for quantitative evaluation of carcinogenicity. It is known that creosote and various fractions contained within creosote act as "complete" carcinogens (i.e. the capability of initiation and promotion of intitiated cells). However, it is of interest to point out that very low doses of complete carcinogens can act to initiate the carcinogenic process, but cannot sustain the process of promotion. It is the Agency's intention to use one of four approaches for quantitation of carcinogenic risk of creosote: 1) from available carcinogenicity data, calculate a "worst case" estimation of carcinogenic risk (i.e. q*); 2) base the carcinogenicity of creosote upon the q* calculated for ethylene dibromide (EDB; this approach was used in the 1987 DCI for antimicrobial pesticides); 3) use the most conservative q* value from examination of carcinogenic risk data from each component of creosote; and 4) to the extent possible, obtain dose-response data on components of creosote as tested by NCI or other research agencies.

IV. MUTAGENICITY

In consideration of the available evidence that creosote is a positive mutagen, the Agency waived the requirement for the standard mutagenicity battery, and instead required dominant lethal testing of both the P1/P13 and P2 blends. The executive summaries of these studies are shown below.

In a rat dominant lethal assay (MRID not available), male HSD:Sprague-Dawley CD rats were treated orally once per day for five consecutive days with Cresosote P1/P13 at target doses of 725, 362.5 or 181.25 mg/kg body weight/day in a volume of 2.5 mL/kg. Actual doses determined by chemical analysis were 857.5, 330.5 and 230.8 mg/kg/day. Twenty-one rats were dosed at the two lower doses and 26 rats at the highest dose. The vehicle was corn oil. Seven days after the initial dosing, each male was mated

with two untreated females per week for 10 weeks. Females were sacrificed 13 days after the midweek of the presumptive mating day and the following data collected: total implantations per female, corpora lutea per female, preimplantation losses per female, live implantations per female, dead implantations per female, proportion of females with one or more dead implantations, proportion of females with two or more dead implantations and dead implantations/total implantations (expressed as a percentage). The fertility index, computed as the number of fertile females (with corpora lutea present) per number of mated females, was also determined.

Creosote P1/P13 was tested to toxic doses. In the dominant lethal study, all rats in the top two treatment groups but none in the low dose group showed decreased activity following dosing and all rats in the high dose group had dyspnea. Two animals in the low dose group and two in the high dose group had material around the nose and mouth. Other pharmacotoxic signs were limited to a few animals in the high dose group and included lacrimation, deposition of the test material around the eyes, increased salivation and anogenital staining. One high dose rat died following the fourth dose. A dose-related decrease in body weight in the low-, mid-, and high-dose animals, compared to the solvent controls, was seen during the dosing period, and this initial weight loss was not recovered in mid- and high-dose rats during the ten week mating period. Statistically significant differences from control values were seen in a number of endpoints throughout the study; however, with the exception of results from mating group nine, none were endpoints indicative of a dominant lethal effect. In mating group nine, statistically significant increases were seen in dead implantations per female, the percentage of females with ≥ one dead implantation, the percentage of females with ≥ two dead implantations and the percent dead implantations per total implantations. These increases were seen at the low and mid doses but not at the high dose. Also, the vehicle control values in mating group nine were unusually low compared to those in the other weekly mating groups (there were fewer preimplantation losses (0.85 per female) and fewer dead implantations (0.41 per female) than seen for the vehicle controls in the other mating groups (1.53 ± 0.37 and 0.85 ± 0.20 per female, respectively) and values for percentage of females with ≥ one and two dead implantations and the percent dead implantations per total implantations were depressed). The results, although statistically significant, are thus not considered biologically significant. Positive and solvent control values were appropriate except where noted for the vehicle controls in mating group nine. **Based on the results of this study, there was no evidence that Creosote P1/P13 induced dominant lethals in any germ cell stage in male rats as tested in this study.**

In a rat dominant lethal assay (MRID not available), male HSD:Sprague-Dawley CD rats were treated orally once per day for five consecutive days with Creosote P2 at target doses of 775, 387.5 or 193.75 mg/kg body weight/day in a volume of 2.5 mL/kg. Actual doses by chemical analysis were 866.3, 431, or 199.3 mg/kg body weight/day. Twenty-one rats were dosed at the two lower doses and 26 rats at the highest dose. The vehicle was corn oil. Seven days after the initial dosing, each male was mated with two untreated females per week for 10 weeks. Females were sacrificed 13 days after the midweek of the presumptive mating day and the following data collected: total implantations per female, corpora lutea per female, preimplantation losses per female, live implantations per female, dead implantations per female, proportion of females with one or more dead implantations, proportion of females with two or more dead implantations and dead implantations/total implantations (expressed as a percentage). The fertility index, computed as the number of fertile females (with corpora lutea present) per number of mated females, was also determined.

Creosote P2 was tested to an adequate dose. All rats in all treatment groups showed decreased activity following dosing. Other clinical signs, limited to a few animals in which there was a back-up of test material during dosing, were lacrimation, deposition of the test material around the eyes and increased salivation in one high-dose male, labored breathing in one low-dose male and two high-dose males, and material around nose and mouth in two low-dose, one medium-dose and four high-dose males. Reduced food consumption was seen in all high-dose rats. No dosing- or test material-related deaths occurred during the study. A dose-related decrease in body weight in the low-, mid-, and high-dose animals, compared to the solvent controls, was seen during the dosing period, and this initial weight loss was not recovered in mid- and high-dose rats during the ten week mating period. Statistically significant differences from solvent control values ($p \leq 0.05$) were seen for a number of endpoints during the first nine weekly mating intervals but, with one exception, not in endpoints considered indicative of dominant lethality. The one exception was a significant increase in the number of dead implants over the solvent control value in the sixth mating group at the lowest Creosote P2 dose. This increase was not considered biologically relevant because no significant increases were seen at higher doses or in other endpoints concerning dead implants. In the tenth mating group (exposure to the test material at the spermatogonial stem cell stage), an apparently dose-related increase was seen in the number of dead implantations per female, the percentage of females with ≥ 1 dead implant, the percentage of females with ≥ 2 dead implants and the percentage of dead implantations per total implantations. The increases reached statistical significance at the highest dose for the first two endpoints. Positive and solvent control values were appropriate. The data in this study, while indicating a positive effect at week 10 of treatment, are not considered to be treatment-related, based on the conclusion that while dead implantations per female was significantly increased at the highest dose tested at mating week 10, the number of live implants/female was not significantly reduced (<5% lower than control). In addition, no dominant lethal effects were seen at weeks 8 or 9, which would also sample spermatogonial cells. **Therefore, creosote P2 is considered to be negative for dominant lethal effects in rats.**

V. FQPA CONSIDERATIONS

1. Neurotoxicity Data

There are no current Agency guideline neurotoxicity studies available for creosote. Of the existing studies available, there is no evidence of neurotoxicity for either the P1/P13 or P2 blends of creosote, although there is valid concern for some of the components of creosote, which are known to be neurotoxic (i.e. naphthalene). Data from the ATSDR Toxicological profile for Creosote showed increased brain-to-body weight ratios after exposure of male and female rats to beechwood creosote (used therapeutically in the past as a disinfectant and expectorant, and composed mainly of phenol, cresols, guaicol, xylenol, and creosol) to 257 mg/kg/day in the diet for 3 months in male rats, or exposure of female rats for 52 weeks to 297 mg/kg/day in the diet, or exposure of male and female rats for 96 weeks in the diet to 143 and 394 mg/kg/day, respectively. Acute exposure of male and female rats to 600 and 313 mg/kg beechwood creosote resulted in convulsions. Although signs of neurologic involvement were evident, no treatment-related pathological findings of the central nervous system were noted at necropsy in these studies.

Based on the above data, and realizing that creosote is currently registered only for non -food use and is a restricted use pesticide, no additional neurotoxicity testing will be required at this time.

2. Developmental & Reproductive Toxicity

(i) Developmental Toxicity:

In a developmental toxicity study using P1/P13 creosote (MRID # 43584201), pregnant female Sprague-Dawley rats (30/dose) were administered P1/P13 creosote at dose levels of 0, 25, 50, and 175 mg/kg/day on gestation days 6 through 15 inclusive. Decreased body weight and food consumption were observed in dams at the 175 mg/kg/day dose level. Decreased uterine weight was observed in dams at the high dose, which is reflected partly by the decreased live fetuses per litter at the high dose (although mean fetal weight was not affected). Cesarean section observations showed significantly increased resorptions and post-implantation loss as well as decreased number of live fetuses per litter at the 175 mg/kg/day dose. Based on the results of this study, the maternal NOAEL is 50 mg/kg/day, and the maternal LOAEL is 175 mg/kg/day, based on decreased body weight gain and food consumption during the study.

No treatment-related malformations (external, visceral or skeletal) were observed in any of the fetuses at 25 mg/kg bw/day. At 50 mg/kg bw/day, the overall incidence of malformations on a fetal and litter basis were statistically elevated compared to controls. However, these individual malformations were not seen at higher dose levels and/or fell within the range of historical control data. At 175 mg/kg/day there was (i) an overall significant increased incidence of developmental malformations, (ii) increased incidence of cardiovascular, vertebral and digital malformations, compared to lower dose levels, concurrent controls or historical controls (2429 and 2898 fetuses examined viscerally and skeletally respectively) and (iii) an increased incidence of malformations at this dose level in spite of increased fetal loss (resorptions Although the incidence of fetal malformations observed at 175 mg/kg/day dose level in rats was low and could be related to maternal stress (decreased body weight gain and food consumption), the teratogenic potential of P1/P13 Creosote cannot be ruled out. Based on these data, the developmental toxicity NOAEL is 50 mg/kg/day, and the developmental toxicity LOAEL is 175 mg/kg/day, based on increased post-implantation loss, increased mean resorptions, decreased live fetuses per litter, and increased developmental malformations.

In a developmental toxicity study (MRID # 43584202), pregnant female Sprague-Dawley rats (30/dose) were administered P2 creosote by gavage on gestation days 6 through 15 inclusive at dose levels of 0, 25, 75, and 225 mg/kg/day. Decreased body weight gain and food consumption were observed at all dose levels and are considered treatment-related. Cesarean section data observed at 225 mg/kg/day showed decreased live fetuses per litter, decreased fetal body weight, and increased post-implantation loss. Based on the data in this study, the maternal NOAEL is determined to be < 25 mg/kg/day, and the maternal LOAEL is determined to be 25 mg/kg/day, based on decreased body weight gain and food consumption. The developmental NOAEL is determined to be 75 mg/kg/day,

and the developmental LOAEL is determined to be 225 mg/kg/day.

(ii) Reproductive Toxicity:

Charles River Crl:CD rats, 26/sex/group, were dosed by gavage with P1/P13 creosote in corn oil at doses of 0, 25, 75, and 150 mg/kg/day. Pre-mating treatment phase lasted approximately 17 weeks, which may have contributed to the decreased fertility observed in this study. Systemic effects observed in this study for parental animals included a dose-related decrease in body weight during the pre-mating period at all dose levels. Salivation was observed at 75 mg/kg/day and above in the F1 generation. Effects in offspring included a dose-related decrease in growth of the F0 generation starting at 25 mg/kg/day (as shown by decreased pup weight). For the F0 pups, mean number of live pups per litter was decreased at 75 and 150 mg/kg/day, and percent live pups at 175 mg/kg/day was also decreased. In the F1 pups, the percent live pups was decreased at 75 and 150 mg/kg/day, but pup growth was affected only at 150 mg/kg/day as shown by decreased mean pup weight. Decreased fertility and pregnancy indices were observed in the F1 female parental rats at all dose levels, but this was not interpreted as a treatment-related effect, as it was more likely related to the fact that the critical weight for fertility was exceeded by the 17-week pre-mating interval. Based on the results of this study, the Parental Systemic NOAEL is < 25 mg/kg/day, and the parental systemic LOAEL is 25 mg/kg/day, based on decreased pre-mating body weight. The developmental NOAEL in this study is < 25 mg/kg/day, and the developmental LOAEL is 25 mg/kg/day, based on a dose-related decrease in pup body weight for the F0 pups from days 14-21. The reproductive NOAEL is < 25 mg/kg/day, and the reproductive LOAEL is 25 mg/kg/day, based on reduced pregnancy and fertility indices in F1 female parental rats.

3. Determination of Susceptibility

Increased susceptibility was demonstrated in the prenatal developmental toxicity study in rats with testing of the P1/P13 blend of creosote at the 175 mg/kg/day dose level. A data gap was identified for a developmental toxicity study in rabbits.

4. Determination of the Need for Developmental Neurotoxicity Study

There is no requirement for a developmental neurotoxicity study for creosote at this time.

5. Recommendation for the FQPA Safety Factor

Based on hazard alone for creosote, the HIARC recommended that the FQPA safety factor **be retained** for creosote. This decision is based on the increased susceptibility observed in the developmental toxicity study in rats, the lack of a developmental toxicity study in rabbits, and deficiencies observed in a 2-generation reproduction study.

VI. HAZARD CHARACTERIZATION

Acute Toxicity of P1/P13 Creosote

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	43032101	LD_{50} = 2451 mg/kg (M); 1893 mg/kg (F)	III
81-2	Acute Dermal	43032102	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	43032103	LC_{50} > 5 mg/L	IV
81-4	Primary Eye Irritation	43032104	irritation clearing in 8-21 days	II
81-5	Primary Skin Irritation	43032105	erythema to day 14	III
81-6	Dermal Sensitization	43032106	study unacceptable	
81-8	Acute Neurotoxicity		no study available	

Acute Toxicity of P2 Creosote

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	43032301	LD_{50} = 2524 mg/kg (M); 1993 mg/kg (F)	III
81-2	Acute Dermal	43032302	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	43032303	LC_{50} > 5.3 mg/L	IV
81-4	Primary Eye Irritation	43032304	irritation clearing within 7 days	III
81-5	Primary Dermal Irritation	43032305	no irritation after 72 hours, but study must be upgraded	
81-6	Dermal Sensitization	43032306	study is unacceptable	
81-7	Acute Neurotoxicity	no study available		

Subchronic dermal testing with both the P1/P13 and P2 blends of creosote showa minimum of toxic effects in experimental animals (rats). Using the P2 blend, one mortality of questionable significance was observed at a dose of 400 mg/kg/day, while testing of the P1/P13 blend produced decreases in body weight gain. Effects on the skin in both studies were minimal to moderate.

Subchronic inhalation testing with creosote produced a wider spectrum of effects. At a dose of 0.049 mg/L, exposure to the P1/P13 blend produced myocardial pathology (degeneration, hemorrhage, cardiomyopathy) in males and females. Altered hematological parameters (decreased hemoglobin, hematocrit, erythrocytes; increased reticulocytes, polychromasia, poikilocytosis, anisocytosis) were also observed in males and females. Testing of the P2 blend by the inhalation route also produced altered hematological parameters, and resulted in increased absolute and relative liver and thyroid weights. Follicular cell hypertrophy was observed. Lesions of the nasal cavity were also observed with the P2 blend.

Developmental and reproductive testing of creosote showed potential sensitivity of offspring to the P1/P13 blend. Decreased body weight gain and decreased food consumption were observed in maternal animals at a dose of 175 mg/kg/day, and at this same dose, increased post-implantation loss, increased mean resorptions, and decreased live fetuses per litter were also observed. An overall significant increase in incidence of developmental malformations was also observed at the 175 mg/kg/day dose. Testing of the P2 blend did not show any apparent susceptibility of developing offspring to creosote, and reproductive testing of P1/P13 creosote did not show any apparent susceptibility, but the reproductive toxicity study contained several deficiencies that compromised interpretation of the data, such as a low fertility and pregnancy index for F1 female parental rats. Thus, there is some uncertainty associated with concluding that creosote is devoid of any reproductive effects. In this light, the additional 10-fold safety factor mandated by FQPA was employed to account for this uncertainty as well as for the effects observed from developmental toxicity testing of P1/P13 creosote.

The mutagenicity database for creosote shows positive effects from in vitro studies, although dominant lethal testing of both the P1/P13 and P2 blends failed to show a positive effect.

There are no reliable metabolism data on creosote, as the chemical is a complex mixture of several classes of polycyclic aromatic chemicals. Assays are in development to identify marker compounds to determine exposure to creosote.

The carcinogenicity data base for creosote as required by the Agency in the 1988 DCI consist of a six-month dermal oncogenicity study of creosote conducted in mice. Creosote in this study was tested both as an initiator (5 dermal applications per week for 2 weeks at doses of 500 μg/mouse, 25 mg/mouse, or 56 mg/mouse followed by TPA for 26 weeks) and as a promotor (DMBA as a positive initiator at 50 μg/mouse followed by twice weekly applications of creosote at the same doses as used for the initiation protocol). As an initiator, creosote did not produce any increase in incidence of benign tumors, but at the 25 and 50 mg doses, squamous cell carcinomas were observed in 2/30 mice at each dose. As a promotor in DMBA-initiated mice, creosote produced dose-related increases in skin papillomas, keratoacanthoma, squamous cell carcinoma, and basal cell carcinoma at the 25 and 50 mg doses. Increases in these tumor types were also observed when creosote was used as both initiator and promotor. This study shows that creosote acts most effectively as a promotor but also functions as a "complete" carcinogen.

A large body of experimental evidence exists which shows a positive relationship between dermal exposure to creosote and development of tumors in experimental animals. In addition to its tumor-promoting potential, the ability of creosote to induce lung tumors after dermal application was examined. Dermally applied creosote (0.25ml undiluted, twice weekly for 8 months) induced 5.8 lung adenomas per mouse in mice housed in stainless steel cages, while ntreated controls showed 0.5 lung adenomas/mouse (Roe et al, Cancer Res. 18: 1176-1178, 1958). Carcinogenicity of two high-temperature derived creosote oils was studied by Poel and Kammer (JNCI 18: 41-55, 1957). The light creosote fraction is composed mainly of benzene, toluene, xylene, and solvent naphtha, while the blended oil is composed of creosote oil, anthracene oil, and oil drained from recovery of naphthalene. Oils were applied by drops to the skin of mice at concentrations of 20%, 50%, or 80% three times a week for life. By weeks 21-26, both oils had induced skin tumors. Several mice exhibited metastases to the lungs or regional lymph nodes.

In humans, evidence for carcinogenicity of creosote varies. Several studies have associated occupational exposure to creosote with development of skin cancer, with a latency period of 20-25 years. These studies are very old (1920's to 1940's), when occupational safety practices were much more lax than today. More recent reports (1980) show no increase in risk of skin, bladder, or lung cancer in wood treatment plant workers, or after treatment for 4 years with coal-tar medicinal therapy for treatment of dermatitis. These reports, however, were limited in scope. Those reports associated with therapeutic use of coal tar did not mention the fact that the composition of the coal tar used therapeutically is of a different composition than that used for wood treatment. In the report on wood treatment workers, the population studied was small, and the follow-up period was too short to allow a long enough latency for tumor development.

From the above data, it is reasonable to assume that exposure to creosote may result in increased risk for cancer of the skin and possibly other sites such as the lung and bladder.

VI. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (General Population including Infants & Children)		**An acute dietary risk assessment is not required for creosote.**	
Chronic Dietary		**A chronic dietary risk assessment is not required for creosote.**	
Short-Term (Dermal) [a]	Oral NOAEL=50 UF = 100	decreased body weight gain at 175 mg/kg/day	Developmental -Rat
Intermediate-Term Dermal	Dermal NOAEL = 40 UF = 100	decreased body weight gain at 400 mg/kg/day	90-Day Dermal- Rat
Long-Term (Dermal) [a]	Oral LOAEL = 25 UF = 300	decreased pre-mating body weight	2-Gen. Repro. - Rat
Inhalation (Any Time Period)	Inhalation NOAEL= 0.0047 mg/L UF = 100	decreased body weight, body weightgain, altered hematology	90-day Inhalation-Rat

[a]a dermal absorption factor of 50% should be used for route-to-route extrapolation.