Poly(hexamethylenebiguanide) hydrochloride (PHMB)

Case 3122
PC Code: 111801

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

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1.0 HAZARD CHARACTERIZATION

Poly(hexamethylenebiguanide) hydrochloride (PHMB) is used as a swimming pool sanitizer and algicide. PHMB is the active ingredient in Vantocil Ib®.

The acute toxicity of PHMB is low for both oral and dermal toxicity (Toxicity Category III or IV); however, PHMB is a severe to moderate eye irritant (Toxicity Category I or II) and slight to moderate dermal irritant (Toxicity Category II or IV). In addition, PHMB causes moderate dermal sensitization in guinea pigs.

The 21-day dermal study showed no systemic toxicity, but it did show severe dermal irritation in the acute assay. The 21-day dermal study did not test to limit dose because a severe dermal irritation was found at a dose level of 300 mg/kg in a preliminary study.

Dermal studies demonstrate that the target organ is the liver. Reduced body weight is the primary effect of concern in all animal studies.

No quantitative or qualitative susceptibility was shown in the prenatal studies or the reproductive study. The rat prenatal study showed increased incidence of extra ribs in fetus, but with no increased susceptibility. The rabbit prenatal study showed possible toxicity in the form of reduced numbers of litters and skeletal abnormalities, but no increased susceptibility. The reproductive study showed no adverse effects on reproduction.

Chronic toxicity studies showed multiple effects on the liver in both sexes of rats as well as body weight decrement. The dog study showed testes and liver changes in male, and clinical signs of toxicity and clinical effects and alterations in clinical chemistry in 1 out of 4 females.

There were no neurotoxic effects seen in any subchronic or chronic toxicity studies. Due to the lack of neurotoxic affects no neurotoxicity tests were required.

The carcinogenicity studies showed an apparent increase in hemangiosarcomas in the liver of female rats, increased hemangiosarcomas in mice, and increased squamous cell carcinomas of the rectal-anal junction in mice. The potential cancer causing effects are referred to CARC.

There is no evidence of a mutagenic response in a battery of mutagenicity studies, including a lack of clastogenic responses in peripheral human lymphocytes.

Rat metabolism studies showed that PHMB is metabolized in a similar fashion by male and female rats. PHMB was excreted mainly through feces. Pooled urine showed the presence of more than one metabolite.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for non-food use for PHMB are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Toxicity Data Requirements for PHMB

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	no	-
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	yes	yes†
870.3465 90-Day Inhalation	no	-
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes*
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes*
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	no	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.7485 General Metabolism	yes	yes

† Satisfied by the 90-day oral study and the dermal absorption value, which will be used for dermal risk assessments

* Satisfied by Chronic/Oncogenicity test

3.0 DATA GAPS

None

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of database for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time.

The acute toxicity data on PHMB (20% a.i.; technical grade) is summarized below in Table 2.

Table 2. Acute Toxicity Data on PHMB (20% a.i.; technical grade)

Product **a.i. / EPA Reg.No.**	**Baquacil** **20% PHMB / 72674-19**	**Baquacil Ultra** **20% PHMB / 72674-22**	**A-Breeze** **96% PHMB / 72674-32**
870.1100 Acute oral toxicity MRID Tox Category	LD_{50} = 2747 mg/kg 00030330 III	LD_{50} = 1831mg/kg (M) LD_{50} = 1617mg/kg (F) 44940701 III	LD_{50} = 1049mg/kg (F) 45916505 III
870.1200 Acute dermal toxicity MRID Tox Category	LD_{50} > 2.0 ml/kg 00065124 III	LD_{50} > 2000mg/kg 44940702 III	LD_{50} > 5000mg/kg 45916506 IV
870.1300 Acute inhalation toxicity MRID Tox Category	waived	LC_{50} = 1.76mg/L 44970403 III	waived
870.2400 Acute eye irritation MRIDs Tox Category	moderate irritant 00046789; 00065120 II	moderate irritant 44963902 II	corrosive 45916508 I
870.2500 Acute dermal irritation MRIDs Tox Category	moderate irritant 00046789; 00065120 II	slight irritant 44949704 IV	slight irritant 45916509 IV
870.2600 Skin sensitization MRID	moderate sensitizer 42674201	Moderate Sensitization	mild sensitizer 44940705

4.2 Subchronic Toxicity

Adequacy of database for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

There were no systemic effects observed, however dermal irritation was caused by PHMB.

870.3100 90-Day Oral Toxicity - Rat

Executive Summary: In a 90-day subchronic toxicity study (MRID 00053460), young adult specific pathogen free (S.P.F.) rats (25 M + 25 F) received 0, 2500, and 5000 ppm of PHMB in the diet for 90 days. Food consumption, general clinical observations, body weight, and hematological parameters were examined. At the end of the 90-day test period all animals were sacrificed with chloroform and an immediate post mortem examination made. Organ weights were recorded and organ/body weight ratios calculated from a randomly selected five males and five females from each group. The following organs were included: liver, heart, lung, adrenals, kidneys, and spleen. Tissues from the remaining animals were fixed in Fenker's fluid, except brains and spinal cords, which were fixed in 10% formal saline and examined microscopically. The following were examined liver kidney, spleen, heart, lung, adrenals, gonads, thymus, thyroid, pancreas, stomach, duodenum, jejunum, ileum, cecum, colon, salivary gland, messenteric lymph nodes, spinal cord and brain (cerebrum, cerebellum, and pons).

All animals survived the 90-day test period, There were no specific adverse effects of the compound. Food consumption was comparable for the test groups and controls. Body weight was moderately reduced in males (13.2% less than controls, and females (16.6% less than controls) fed the compounds at the highest dietary level (5000 ppm). No abnormalities in hematological parameters were observed. No gross abnormalities were observed. No remarkable change in organ/body weight ratios was detected. Microscopic evaluation revealed that the liver of some females given the compound at a level of 5000 ppm showed an unusual degree of iron pigment both within the liver cells and kupffer cells. Although the report states that no iron pigments was seen in animals fed 2500 ppm test material in the diet, the study does not include detailed histopathological results of the 2500 ppm animals. **Therefore, the NOAEL cannot be determined in this study.**

870.3150 90-Day Oral Toxicity - Dog

Executive Summary: In a 90-day subchronic toxicity study in the dog (MRID 00053461), three groups of Beagle Dogs (4M + 4F per group), 12.4 - 14.6 kg initial BW, received dietary levels of 0, 5500, and 11000 ppm of PHMB ad-libitum for 90 days. General observation, food consumption, body weight and the following clinical chemistry measurements were performed: hemoglobin, packed cell volume (hematocrit), leucocyte count (total), leucocyte count (differential), blood urea, serum alkaline phosphatase, BSP (liver function test) and urine analyses (reaction (pH) specific gravity, glucose, protein, bilirubin, microscopy of centrifuge deposit). At the end of the test period the animals were sacrificed with an overdose of pentobarbitone

administered intravenously. A full post-mortem examination was performed at the time of necropsy: heart, liver, kidneys, adrenals, spleen, thyroid, epididymics, brain and pituitary. Representative pieces of tissues for microscopic examination were taken from the following: brain (cerebrum, cerebellum and pons, spinal cord, pituitary, submaxillory gland, thyroid, thymus, heart, lung, aorta, stomach, duodenum, jejunum, ileum, colon, liver, spleen, kidney, bladder, adrenal, ovary and uterus or testis and epididymes, sciatic nerves.

Both treated and control animals maintained an excellent condition throughout and no adverse effects were noted. No food consumption data was submitted. Mean body weights were comparable between control and treated animals except for the 11,000 ppm female dogs which gained significantly less total weight than the female dogs. Results of the hematological parameters were unremarkable. Clinical function test show no difference in retention of BSP attributable to test material. Urine analyses do not appear to be influenced by treatment. Organ/body weight ratios showed no significant variation from the normal as a result of treatment. No gross pathology attributable to test material was detected. Microscopic examination revealed slight hemosiderons in 2 out of 4 males at 11,000 ppm. No other microscopic abnormalities attributable to treatment were present at either dose level.

The NOAEL for this 90 day dog feeding study appears to be 5500 ppm (low dose). The high dose treatment caused a less total weight gain in female dogs and slight hemosiderons in 2 out of 4 male dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

Executive Summary: In a 21-Day Dermal Toxicity Study (MRID 430477-01), PHMB was applied at dose levels of 0, 20, 60, and 200 mg/kg to the shorn backs of 5 male and female Alpk:APfSD (Wistar-derived) rats over the course of 30 days for a total of 21 applications of 6 hours duration each.

There was no evidence of systemic toxicity at any dose level in this study. Dermal toxicity was evident at the 60 mg/kg and 200 mg/kg dose levels in the form of erythema, edema, scabbing, acanthosis, and inflammatory cell infiltration in both sexes. **Based on the data in this study, the Systemic Toxicity NOAEL is greater than or equal to 200 mg/kg/day for both sexes, and the Systemic Toxicity LOAEL is greater than 200 mg/kg/day for both sexes. The Dermal Toxicity NOAEL is 20 mg/kg/day for both sexes, and the Dermal Toxicity LOAEL is 60 mg/kg/day for both sexes, based on the increased incidence of erythema, edema, and scabbing observed at this dose**.

Although there was no evidence for systemic toxicity at any dose level tested in this study, higher dose levels were not tested due to the presence of severe dermal irritation at a dose level of 300 mg/kg in a preliminary study. Therefore, this study is classified as **core minimum** data and **satisfies the guideline requirement** (**870.3200 §82-2**) for a repeated dermal toxicity study in rats.

870.3250 90-Day Dermal

This requirement is satisfied by the 80-week dermal carcinogenicity study in mice, which will be used for dermal risk assessments.

870.3465 90-Day Inhalation – Rat

A 90-day inhalation toxicity study with PHMB was not available. Inhalation risk assessment was performed using the NOAEL value of 20 mg/kg/day from the developmental toxicity study in rabbits (MRID 42865901).

4.3 Prenatal Developmental Toxicity

Adequacy of database for prenatal developmental toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time.

There was no quantitative/qualitative evidence of increased susceptibility of developmental effects following *in utero* exposure in the rat or rabbit. Maternal toxicity was reported at lower dose levels than the developmental toxicity in rats. In rabbits, developmental effects were observed at the same dose level as the maternal effects.

870.3700a Prenatal Developmental Toxicity Study - Rat

Executive Summary: In the rat developmental toxicity study (Report # CTL/P/1262, 1976 cited in Report # 003810, 1978. Section C-11), groups of at least 20 pregnant Alderley Park female rats were fed diets containing 0, 200, 1000, or 2000 ppm (0, 10, 50, or 100 mg/kg/day) PHMB throughout gestation. On gestation day 20, animals were killed by cervical dislocation until at least 20 pregnancies in each group were established. Mean maternal body weight and food consumption were reduced significantly in animals receiving 50 or 100 mg/kg PHMB (20% a.i.). Maternal microscopic findings revealed an enlarged and hemorrhagic thymus in one female which had received 100 mg/kg/day 20% PHMB. **Based on the reduced body weight and reduced food consumption, the Maternal Toxicity LOAEL is 50 mg/kg/day. The Maternal Toxicity NOAEL is 10 mg/kg/day.**

There was no increase in late resorptions in any group. The fetal weight and litter weight were not reduced in the PHMB treated groups. No adverse effects in ossification were seen in the fetuses from the PHMB treated animals. The fetus from the 100 mg/kg/day group showed a significant increase in extra ribs. **Based on the increased incidence of ribs in fetus, the Developmental Toxicity LOAEL is 100 mg/kg/day. The Developmental Toxicity NOAEL is 50 mg/kg/day.**

Note: In the registrant's 'error only' response to the draft preliminary risk assessment, it was stated that the dose levels for this study should be reported as 17.2, 86.2, and 172.4 mg/kg/day rather than the stated values of 10, 50, and 100 mg/kg/day. Once verification is received on this

from the registrant, the appropriate change can be made to the executive summary.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Executive Summary: In the rabbit developmental study (MRID 42865901), administration of PHMB to 20 pregnant female New Zealand White rabbits per group at levels of 0, 10, 20, and 40 mg/kg/day on gestation days 8 through 20 resulted in maternal toxicity at 40 mg/kg/day in the form of increased mortality and clinical toxicity. Mortality occurred in 6 rabbits at this dose. One rabbit died probably as a result of mis-dosing; one rabbit was killed *in extremis* on day 22 due to inappetance and weight loss starting on day 11; and the remaining 4 rabbits were killed due to abortion of fetuses and thus a lack of data for analysis. There are 6 rabbits that died in the 40 mg/kg/day dose group; clinical signs included coldness (6/20 vs. 0/20 in control), few feces (16/20 vs. 7/20 in control), no feces (6/20 vs. 0/20 in control), thin appearance (6/20 vs. 0/20 in control) and subdued behavior (3/20 vs. 1/20 in control). **Based on the increased mortality; reduced food consumption; and clinical toxicity, the Maternal Toxicity LOAEL is 40 mg/kg/day. The Maternal Toxicity NOAEL is 20 mg/kg/day.**

There was evidence of possible developmental toxicity of PHMB at 40 mg/kg/day, in the form of reduced numbers of litters and skeletal abnormalities (non-ossified 5th sternebrae, fused 3rd, 4th, and 5th sternebrae). The incidence of non-ossified 5th sternebrae was found in 12 (10.1%) of fetuses from the 40 mg/kg/day dose group vs. 6 (3.3%) in control, and a fused 4th and 5th sternebrae, found in 7 (5.9%) of fetuses and 6 (46.2%) of litters at the 40 mg/kg/day dose level, compared to 1 (0.6%) fetus and 1 (5.3%) liter in controls. The incidence of fetuses and litters with fused 3rd and 4th sterebrae at the 40 mg/kg/day dose is 5 (4.2%) of fetuses and 3 (23.1%) of litters vs. 1 fetus (0.6%) and 1 litter (5.3%) in controls. **The developmental toxicity NOAEL is 20 mg/kg/day, based on reduced number of litters and skeletal abnormalities; the developmental toxicity LOAEL is 40 mg/kg/day.** Developmental effects occurred at doses that also caused maternal toxicity. Therefore, the data indicate that developmental toxicity at the high dose was related to maternal toxicity (6 out of 20 animals died in the group, no quantitative / qualitative evidence of increased susceptibility of developmental effects in this study). (Note: Dosing started at gestation day (gd) 8 which is different from the guideline specifying that the study should start at gd 6)

4.4 Reproductive Toxicity

Adequacy of database for reproductive toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

There was no evidence of quantitative or qualitative susceptibility in the multi-generation reproduction study.

870.3800 Reproduction and Fertility Effects - Rat

Executive Summary: In a multi-generation reproduction study (MRID 43617401), male and female Alpk:APfSD rats (26 males/dose; 26 females/dose), obtained from the Barriered Animal

Breeding Unit at Zeneca Pharmaceuticals, Alderley Park, UK, received PHMB (20.2% a.i.) in the diet at nominal doses of 0, 200, 600, and 2000 ppm (23.0, 69.6, and 238.9 mg/kg/day for F0 males; 25.3, 77.0 and 258.2 mg/kg/day for F0 females; 23.9, 71.3, and 249.3 mg/kg/day for F1 males; and 26.1, 79.2, 270.5 mg/kg/day for F0 [note: we believe this to be a typo and should be the data for F1] females). The rats in each generation received test diets continuously until termination. Systemic toxicity was observed at the 2000 ppm dose level in the F0 generation as indicated by a decrease in group body weight (9-10%) and food efficiency (7%) for the 10 week pre-mating period. The weight of the epididymes and kidneys were also significantly decreased in F0 generation males. There were no corresponding effects in the F1 parental generation except for decreased food efficiency (15%) in females for weeks 5-7 pre-mating. There were no detrimental effects of treatment with PHMB on reproduction in this study, but it is noted that there was a dose-related *decrease* in number of pup deaths on days 1-5 post-partum for both generations.

The Parental Systemic Toxicity NOAEL is 600 ppm (69.6 mg/kg/day [F0 males]; 77.0 mg/kg/day [F0 females]; 71.3 mg/kg/day [F1 males]; 79.2 mg/kg/day [F1 females]); The Parental Systemic Toxicity LOAEL is 2000 ppm (238.9 mg/kg/day [F0 males]; 258.2 mg/kg/day [F0 females]; 249.3 mg/kg/day [F1 males]; 270.5 [F1 females]) based on decreased body weight and food efficiency in F0 males and females, and decreased epididymes and kidney weight in F0 males.

Reproductive/Systemic Toxicity NOAEL is 2000 ppm; Reproductive/Systemic Toxicity LOAEL is greater than 2000ppm.

This study is classified as **acceptable** and satisfies the guideline requirement (**OPPTS 870.3800; § 83-4**) for a 2-generation reproduction study in rats.

4.5 Chronic Toxicity

Adequacy of database for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time.

There were multiple effects on the liver of both sexes in the rat study. Body weight decrement was also noted in the rat study. The dog study showed a change in testes and liver of male dogs, and clinical signs of toxicity and clinical chemistry alterations in a female dog.

870.4100a (870.4300) Chronic Toxicity/Carcinogenicity Study – Rat

Executive Summary: In a rat chronic/oncogenicity study (MRID 44059301) male and female Alpk:APfSD Wistar rats (64/sex/dose) were fed diets containing PHMB at 0, 200, 600, or 2000 ppm (equivalent to 0, 12.1, 36.3, and 126.1 mg/kg/day in males and 14.9, 45.3, and 162.3 mg/kg/day in females) for 2 years. An interim sacrifice of 12 rats/sex/dose was conducted at 52 weeks.

At the high dose (2000 ppm), survival was decreased in females by 25% vs. controls.

Body weights were significantly ($p<0.01$ or 0.05) reduced by 5-8% in high-dose females throughout the study. In high-dose males, body weights were significantly ($p<0.01$ or 0.05) reduced vs. controls through week 79. Food utilization (g growth/100 g feed) for the first 12 weeks decreased significantly ($p<0.01$) vs. controls, ↓7-8% in both sexes at 2000 ppm.

The liver was the target organ in males and females. Plasma alkaline phosphatase activity was elevated significantly ($p<0.01$) over controls ↑43-74% in females from the main study dosed at 2000 ppm; in 2000 ppm males the enzyme was significantly increased by 36 and 27% at weeks 14 and 27. In females at 2000 ppm absolute liver weight was reduced significantly ($p<0.05$) by 11%. In 2000 ppm males, microscopic observations of liver hepatocyte fat and spongiosis were ↑44 and 22% over controls; corresponding increase in these lesions were not seen in females. There were no corroborating gross pathology findings of the liver abnormalities.

For chronic toxicity, the LOAEL for PHMB is 2000 ppm (126.1 and 162.3 mg/kg/day for males and females respectively) and the NOAEL is 600 ppm (36.3 and 45.3 mg/kg/day).

Under the conditions of this study, PHMB appears to have the potential to induce vascular neoplasms in female rats of this strain. The study pathologist and study peer reviewer observed hemangiosarcomas of the liver in 3/64 2000 ppm females; benign hemangioma was not observed. The increased incidence of hemangiosarcoma in females gave positive results in trend analyses ($p<0.05$). A single observation of benign hemangioma was made in each of the control and high dose male groups; no hemangiosarcoma was observed in males. A Pathology Working Group (PWG) was convened to confirm the diagnoses of the vascular neoplasms (MRID 44042801). The PWG observed hemangioma (2/64) and hemangiosarcoma (1/64) in 2000 ppm females and 2/64 hemangiomas in 2000 ppm males. The PWG concluded that the findings of vascular neoplasms in high dose females were incidental. However, the report of the PWG consensus indicated that no hemangiosarcoma or hemangioma had been observed in female controls in 18 studies with the same strain of rat. Furthermore, there was a significant increase ($p<0.01$ or 0.05) in hemangiosarcomas in both sexes in a mouse oncogenicity study with PHMB. **Therefore it is concluded that PHMB appears to induce hemangiosarcomas of the liver in female Alpk:APfSD rats. Liver hemangiosarcomas are rare in this strain of rat.**

This study is classified as **acceptable (guideline 870.4300 §83-5)** and satisfies the guideline requirements for a chronic/oncogenicity study in rats.

870.4100b Chronic Toxicity - Dog

Executive Summary: In a chronic toxicity study (MRID 43620501), PHMB was administered to groups of 4 male and female Beagle dogs in the diet initially at dose levels of 0, 300, 1500, and 4500 ppm (0, 7.5, 37.5, and 112.5 mg/kg/day nominal dose) for one year. Following an unexpectedly severe reaction in 3 of 4 males at 4500 ppm (scrotal skin lesions), the high dose was discontinued on week 9 or 10, reduced to 3000 ppm (75 mg/kg/day), and then recommenced on week 11 or 12. Up to and including the 3000 ppm dose, there were no consistent effects of PHMB on body weight, weight gain, food consumption, or hematological parameters. Plasma alanine aminotransferase (ALT) activity was significantly increased in male and female dogs at the 3000 ppm dose level beginning at week 8, but there was variability in the response, and only one

male dog was available for measurement after week 10. Testes weight was decreased 29% and 32% for the left and right testis of high dose male dogs, and testicular tubular degeneration was observed in the surviving male dog as well as in one dog sacrificed intercurrently. Liver weight in high dose male dog was decreased 14% at the high dose, and microscopic changes of the liver were also observed in male dogs at the high dose. In one female dog at the high dose, significant clinical signs (decreased activity, stiff/splayed gait, slight tremors) were observed which were not reversible. In addition, plasma alanine aminotransferase was increased almost 10-fold over the pre-treatment level by week 35 of treatment. Plasma aspartate aminotransferase in this dog was almost doubled by week 35 of treatment. Marked dermatitis of the limbs was also observed in this dog. **The Systemic Toxicity LOAEL is 3000 ppm (75 mg/kg/day) for male and female dogs, based on changes in testis and liver weight and microscopic observations in male dogs, and based on clinical signs of toxicity and clinical chemistry alterations in the female dog. The Systemic Toxicity NOAEL is 1500 ppm (37.5 mg/kg/day) for male and female dogs.**

This study is **acceptable** and satisfies the guideline requirement [OPPTS 870.4100; OPP § 83-1] for chronic oral toxicity in dogs.

Note: In the registrant's 'error only' response to the draft preliminary risk assessment, it was stated that the dose levels for this study should be reported as 9, 46, and 91 mg/kg/day for males and 9, 45, and 91 mg/kg/day for females rather than the stated values of 7.5, 37.5, and 75 mg/kg/day. Once verification is received on this from the registrant, the appropriate change can be made to the executive summary.

4.6 Carcinogenicity

Adequacy of database for carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time.

The combined chronic/carcinogenicity study in rats showed an apparent increase in hemangiosarcomas in the liver of female rats. The mouse study showed increased hemangiosarcomas and squamous cell carcinomas of the rectal-anal junction in both sexes.

870.4200a Carcinogenicity Study - Rat

See above Chronic toxicity/Oncogenicity study rat (MRID 44059301)

870.4200b Carcinogenicity (feeding) - Mouse

Executive Summary: In a mouse oncogenicity study (MRID 44074201), PHMB was administered to C57B1/10J$_f$CD-1/Alpk mice (55/sex/group) at 0, 400, 1,200, or 4,000 ppm (equivalent to 55, 167, or715 mg/kg/day for males and 69, 217, or 856 mg/kg/day for females) for 2 years.

At the 1,200 ppm level, mice were observed with decreased overall body weight gains (males, ↓7%; females ↓2%); increases in hematology parameters ($p<0.05$) including hemoglobin

in females (↑6%), hematocrit in females (↑6%), and RBCs in females (↑5%); decreased absolute weight of the liver in males (↓15%) and in females (↓21%); increased incidences of gross pathological changes including distended caeca in females (4% treated vs. 0% in controls); traumatized pinnae of ears in males (36% treated vs. 4% controls) and females (44% treated vs. 4% controls); increased incidences of non-neoplastic lesions including luminal dilatation of the gall bladder in females (9% treated vs. 2% controls), hepatocyte hypertrophy of the liver in males (13% treated vs. 0% controls) and females (35% treated vs. 0% controls), increased ploidy of the liver in males (13% treated vs. 0% controls) and females (36% treated vs. 0% controls), pigmentation of the liver in females (11% treated vs. 0% controls), and inflammation of the rectal-anal junction in males (44% treated vs. 2% controls) and females (47% treated vs. 21% controls).

At the 4,000 ppm dose level, decreased overall body weight gain was observed in males (↓50%) and females (↓32%); increased food consumption ($p<0.05$ or 0.01) from approximately week 12 through termination in males (↑7-29%) and females (↑7-26%); decreased food utilization ($p<0.01$) during weeks 1-12 in males (↓40%) and females (↓20%); increased hemoglobin in males (↑7%) and females (↑17%), hematocrit in males (↑5%) and females (↑16%), and RBCs in males (↑10%) and females (↑17%); decreased weight of the liver in males (20%) and females (30%); decreased weight of the testes of males (↓15%) and in adrenals of females (↓22%); increased incidences of gross pathological changes including swollen anuses in males (18% treated vs. 0% controls) and females (7% treated vs. 0% controls), distended caeca in males (9% treated vs. 0% controls) and females (13% treated vs. 0% controls), pinnae of ears traumatized in males (27% treated vs. 4% controls) and females (22% treated vs. 4% controls), distention of the gall bladder in males (49% treated vs. 11% controls) and females (47% treated vs. 9% controls); liver mass 1 in males (48% treated vs. 20% controls) and females (39% treated vs. 2% controls), epithelial hyperplasia of the gall bladder in males (25% treated vs. 0% controls) and females (13% treated vs. 0% controls), hepatocyte hypertrophy of the liver in males (53% treated vs. 0% controls) and females (49% treated vs. 0% controls), increased ploidy of the liver in males (53% treated vs. 0% controls) and females (38% treated vs. 0% controls), pigmentation of the liver in males (36% treated vs. 0% controls) and females (42% treated vs. 0% controls), and inflammation of the rectal-anal junction in males (82% treated vs. 2% controls) and females (74% treated vs. 21% controls).

Toxicity observed common to both sexes of the 1,200 and 4,000 ppm treatment groups included decreased overall weight gains, pinnae of ears traumatized, hepatocyte hypertrophy of the liver, increased ploidy of the liver, and inflammation of the rectal-anal junction. There was also epithelial hyperplasia of the gall bladder common to females of both treatment groups, but occurring in males only at 4,000 ppm.

No treatment related effects were seen in mice in the 400 ppm dose group.
Based on decreased body weight gains and non-neoplastic histopathological changes in the gall bladder, liver, and rectal-anal junction of mice in the 1,200 ppm and 4,000 ppm treatment groups, the Systemic Toxicity LOAEL in male and female mice is 1,200 ppm (equivalent to 55 mg/kg/day in males and 69 mg/kg/day in females). The Systemic Toxicity NOAEL is 400 ppm.

Carcinogenic potential was evidenced by increased incidence of hemangiosarcomas and hemangiomas in both sexes of mice in the 4,000 ppm treatment group. In males at this treatment level a statistically significant ($p < 0.01$) increase was observed in combined incidence of hemangiosarcoma and hemangioma combined (20/53 animals [38%]) vs. 6/55 in control (11%). In females, a significant increase ($p < 0.05$) in combined incidence of hemangioma and hemangiosarcoma was also observed at this dose (15/49 vs. 8/54 in control). Historical control incidence of angiosarcoma in all tissues within this strain of mouse ranged from 2-15% in males and 0-9% in females. Concurrent control incidences of hemangiosarcomas were within the historical control range. The earliest hemangiosarcomas occurred at 39 and 42 weeks in males and females, respectively. Hemangiosarcoma of the liver was a statistically significant factor contributing to the death of male and female mice at 4,000 ppm PHMB. Treatment-related squamous cell carcinomas of the rectal-anal junction were found in 5/49 (10%) males and 8/39 (21%) females of the 4,000 ppm treatment group. Two males in the 4,000 treatment group had papillomas in the gall bladder with none in controls or at other treatment levels. No treatment-related carcinogenic effects were observed at 400 of 1,200 ppm. **Based on the study results, carcinogenic effects (vascular system and anus) were observed for male and female mice at dietary levels of 4,000 ppm PHMB (equivalent to 715 mg/kg/day in males and 856 mg/kg/day in females).**

Dosing was considered to be excessive at the high dose of 4000 ppm based on decreased overall body weight gains of 50% in males and 32% in females at termination. In addition, decreased body weight gains of 33% in males and 19% in females at 13 weeks. The study indicated that the animals at the 4000 ppm dose group had increased food consumption ($p<0.05$ or 0.01) from approximately week 12 through termination in males (↑7-29%) and females (↑7-26%).

Dosing was considered to be adequate, but not excessive, in both males and females at the mid-dose of 1200 ppm based on decreased overall body weight gains (males, 7%; females, 2%), and increases in hematology parameters, and non-neoplastic histopathological changes in the gall bladder, liver, and rectal-anal junction.

This study is classified as **Acceptable (Guideline)** and satisfies the guideline requirements for a carcinogenicity study [OPPTS 870.4200 (§83-2b)] in the mouse.

870.4200b Carcinogenicity (dermal) - Mouse

Executive Summary: In a 80-week skin painting study (00066475, 00104796), four groups of specific pathogen free (50/dose/sex) Alderley Park mice received dermal applications of 0.3 mL of the test material at doses of 0 (solvent in ethanol), 0.6 mg (0.2% PHMB in ethanol), 6.0 mg (2% PHMB in ethanol) and 30.0 mg (10% PHMB in ethanol) per day, five days a week for a period of 80 weeks. The treatment dosages are equivalent to 0, 15, 150, and 750 mg/kg-day of 20% PHMB solutions.

Mice that received the highest dose level of PHMB (750 mg/kg-day) showed a poorer health status, appearing very thin throughout the experiment. Mortality in both male and female mice in the highest dose group was slightly higher than in other groups during the first year. This

pattern continued throughout the remainder of the study resulting in a high mortality rate (75% in males and females) in the highest dose animals at termination, compared with approximately 30% in the other groups. The highest dose level of PHMB resulted in noticeable irritation to the skin of both males and females immediately after application. Erythema and some clumping of the growing fur were noticed during the first few weeks and after the 4th week, hyperkeratosis became evident especially in males. No differences were apparent between the controls and those mice receiving 0.6 or 6.0 mg PHMB per mouse per application. A significant reduction in mean body weight was observed for both male and female animals that received the highest dose level. There were no overall differences in food consumption between the control and treatment groups.

Therefore, the systemic toxicity NOAEL was 150 mg/kg-day and the LOAEL was 750 mg/kg-day based on increased mortality and decreased body weight in male and female mice receiving PHMB (20% a.i.).

There were no compound-related tumors observed in male mice. Female mice had significant increasing trends in liver angiosarcomas ($p<0.01$) and vascular tumors from all sites combined ($p<0.05$). There was a significant difference in the pair-wise comparison of the 30 mg dose group with the controls for liver angiosarcomas at $p<0.05$. The statistical analyses of the female mice were based on Peto's prevalence test.

The HED Cancer Assessment Review Committee considered the tumor increase at the high dose to be equivocal since tumors were observed at an excessive dose. Vascular tumors were not seen at lower doses. Dosing was considered to be excessive at the high dose (750 mg/kg/day of 20% PHMB equivalent) in both sexes due to increased mortality (78%, high dose, versus 33% and 28% in the male and female controls, respectively) and decreased body weight gain. Overall body weight gain decreases of 45% and 17% were seen in males and females, respectively. No treatment-related effects were noted at the mid-dose level of 150 mg/kg/day of 20% PHMB equivalent.

This carcinogenicity study is classified **Acceptable-Nonguideline**. Although this non-guideline (dermal painting) study does not fulfill any toxicity guideline requirement, it does provide useful information for assessing the carcinogenic potential of PHMB and should be evaluated in conjunction with the 1996 and 2002 guideline PHMB carcinogenicity studies (MRID 44059301, 44042801, 44074201, and 45710802).

4.7 Mutagenicity

Adequacy of database for mutagenicity: The following assays used PHMB at 19.6% (a.i.). The database for mutagenicity is considered adequate based on 1991 mutagenicity guidelines (note: assays were conducted before 1991, but appear to meet 1991 guidelines).

There is no evidence that Vantocil IB induced any genotoxicity.

Gene Mutation

Guideline OPPTS 870.5265 [§84-2], Microbial gene mutation assy MRID 41687004 This study is classified as **acceptable** and satisfies the guideline requirement for a microbial gene mutation assay (§84-2).	In two independently preformed assays Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 were exposed to 0.32-500 μg/plate Vantocil IB (19.6% a.i.) in the absence or presence of S9 activation. Additional testing was carried out using comparable doses with and without S9 in TA1537 and TA98. The S9 fraction was derived from Aroclor 1254-induced rat livers and the test material was delivered to the nonactivated and S9-activated positive controls. **There was, however, no evidence that Vantocil IB induced a mutagenic response in any strain at any nonactivated or S9-activated dose**.
Cytogenetics	
Guideline OPPTS 870.5393 [§84-2], Mouse micronucleus assay MRID # 41096901/41404503 Study is classified as **acceptable** and satisfies the requirements for FIFRA Test Guideline 84-2 for a micronucleus assay.	In a mouse micronucleus assay (MRID # 41096901/41404503), groups of five male and five female C57BL/6JfCD-1/Alpk mice received single oral gavage administrations of 250 or 400 mg/kg Vantocil IB (19.6% a.i.) prepared in deionized water. Mice in the high-dose group were sacrificed at 24, 48, and 72 hours post-administration and harvested bone marrow cells were examined for the incidence of micronucleated polychromatic erythrocytes (MPEs). Low-dose animals were sacrificed at 24 hours. Two animals receiving 400 mg/kg died prior to the scheduled sacrifice. There was also clear evidence of target cell cytotoxicity in the high-dose males and females at all sacrifice intervals. The positive control induced the expected high yield of MPEs in males and females. **Vantocil IB did not, however, induce a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.**
Guideline OPPTS 870.5375 [§84-2], *In vitro* cytogenetic assay with human lymphocytes MRID # 41404501/42149905 This study is classified as **acceptable** and satisfies the guideline requirement for an *in vitro* cytogenetic study.	In an *in vitro* mammalian cell cytogenetic assay (MRID # 41404501/42149905), human lymphocytes derived from male and female donors were exposed to Vantocil IB (19.6% a.i. in water) doses of 5, 25, or 50 μg/mL without S9 activation (both donors) and levels of 25, 100, or 187.5 μg/mL (male donor) or 25, 100, 250 μg/mL (female donor) with S9 activation for approximately 2.5-3.5 hours. The S9 liver homogenate was derived from Aroclor 1254 induced Sprague-Dawley rat livers and the test material was delivered to the test system in physiological saline. A 50% reduction in the mitotic index occurred at 50 μg/mL -S9 (both donors) and at 100 μg/mL +S9 (male donors) or at 250 μg/mL (female donors). The positive controls induced the expected high yield of chromosome aberrations in the lymphocytes derived from the male and female donors. **There was, however, no evidence that Vantocil IB induced a clastogenic effect.**
Other Mechanisms of Genotoxicity	
Guideline OPPTS 870.5550 [§84-2], *In vivo/In vitro* unscheduled DNA synthesis assay in primary rat hepatocytes MRID # 41404502/42149903 This study is classified as **acceptable** and satisfies the guideline requirement for a UDS assay (§84-4).	In two independently performed *In vivo/In vitro* unscheduled DNA synthesis (UDS) assays (MRID # 41404502/42149903), groups of two to three male rats were administered single oral gavage doses of 750 or 1500 mg/kg Vantocil IB (19.6%) prepared in deionized water. Animals were sacrificed at 4 and 12 hours post-treatment and recovered hepatocytes were scored for UDS. Clinical toxicity (i.e., excessive salivation and subdued nature) was observed at 1500 mg/kg; higher levels were lethal. No cytotoxicity for the target organ was seen at either level. The positive control induced the expected high yield of hepatocytes with net nuclear grains. **There was, however, no evidence that the Vantocil IB induced a genotoxic response at either dose or sacrifice time.**

4.8 Neurotoxicity

Adequacy of database for neurotoxicity: No indication of neurotoxicity, neuropathology, or histopathology of the nervous system has been reported in the available studies. No neurotoxicity data are required.

870.6100 Delayed Neurotoxicity Study - Hen

Not required since PHMB is not an organophosphate.

870.6300 Developmental Neurotoxicity Study

This study is not required because there is no evidence PHMB will induce neurotoxic effects. In addition, there is no quantitative or qualitative evidence of increased susceptibility of the fetus following *in utero* exposure in the prenatal developmental toxicity studies or in the offspring when exposed to adults in the two generation-reproduction study. Therefore, PHMB will not cause a FQPA concern.

4.9 Metabolism

Adequacy of database for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time.

870.7485 Metabolism - Rat

Executive Summary: Bioavailability of PHMB was investigated in male and female Sprague-Dawley rats fed diets of 200 ppm or 2000 ppm (10 and 100 mg/kg nominal dose) for fourteen days followed by a single radiolabelled dose of either 0.08 mg/kg (MRID 43567001 and 43599901), or after a single 100 mg/kg dose (MRID 00077926 and 00086363). In both studies, feces represented the major route of excretion at all dose levels, comprising greater than 90% of the administered dose. A similar excretion in feces was observed in bile-cannulated rats after a single radiolabelled dose of 20 mg/kg (MRID 43567001). Thus, fecal excretion of PHMB-derived radioactivity represents unabsorbed test material. The excretion pattern of low, mid, and high molecular weight fractions of PHMB was similar. Bioavailability was 4.7% and 3.9% for males and females, respectively, at the 10 mg/kg dose, and 3.9% and 2.6% for males and females, respectively, at the 100 mg/kg dose. Tissue distribution in rats given 10 mg/kg PHMB showed concentrations in the liver and kidney of male rats to be 0.568 μg/g and 0.499 μg/g, respectively. As a percentage of the dose, liver of male and female rats contained 0.18% and 0.19% of the dose respectively, while kidneys contained 0.03% and 0.04% of the dose respectively. Metabolite analysis of pooled urine from rats administered a low molecular weight fraction of PHMB at 20 mg/kg (the fraction showing the greatest absorption) revealed the presence of more than one metabolite but identification was not performed due to the small amount sample available for analysis.

The studies when taken together are **acceptable**, and satisfy the §85-1 guideline [OPPTS 870.7485] requirement.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 8.2 for Endpoint Selection Table.

5.2 Dermal Absorption

A value for dermal absorption was not needed for PHMB based on the selection of dermal endpoints from a route-specific (dermal) toxzicity study.

5.3 Classification of Carcinogenic Potential

5.3.1 In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July 1999), the CARC classified PHMB into the category **"**Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential**"** by the oral and dermal routes. The weight-of-the-evidence considerations for this classification are as follows:

(i) A treatment-related statistically significant increase (trend and pair-wise) in vascular tumors (mainly benign) was seen in female rats at an oral dose that was considered to be adequate, but not excessive. This was considered as the strongest evidence in the CARC's evaluation of PHMB.

(ii) Oral exposure to male and female mice also resulted in treatment-related vascular tumors seen at an excessive dose. However, at the next highest dose level, which was considered adequate but not excessive, there was a slight, but not statistically significant, increase in this same tumor, which added to the CARC's concern for this tumor type.

(iii) It is noted that dermal exposure to female mice resulted in an equivocal increase in vascular tumors seen at only an excessive dose.

(iv) No treatment-related increase in any tumors was seen in male rats via the oral route or in male mice via the dermal route of exposure.

Based on the above, the Agency has determined that the quantification of human cancer risk is not required.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

There is no qualitative or quantitative evidence of increased susceptibility of rabbit, mice or rat fetuses *in utero* exposure in developmental studies.

There is no qualitative or quantitative evidence of increased susceptibility in multi-generation reproduction study in rats.

6.2 Recommendation for a Developmental Neurotoxicity Study

PHMB will not cause a FQPA concern, because there is no evidence PHMB will induce neurotoxic effects. There is no quantitative or qualitative evidence of increased susceptibility to

fetus following *in utero* exposure in the prenatal developmental toxicity studies or in the offspring when exposed to adults in the two-generation reproductive study.

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8.0 APPENDICES
Tables for Use in Risk Assessment

8.1 Toxicity Profile Summary Tables

8.1.1 Acute Toxicity Table - See Section 4.1

8.1.2 Subchronic, Chronic, and Other Toxicity Tables

Guideline No./ Study Type	MRID No. (year)/ Classification/ Doses	Results
870.3100 90-Day oral toxicity rodents	00053460 (1966) Supplementary 0, 2500, 5000 ppm	NOAEL and LOAEL were not established due to inadequate data.
870.3150 90-Day oral toxicity in nonrodents	00053461 (1966) Minimum 0, 5500, 11000 ppm	NOAL = 5500 ppm LOAEL = 11,000 ppm based on slight hemosiderosis in males, decrease total body weight gain in females.
870.3200 21/28-Day dermal toxicity	430477-01 (1993) Core minimum/guideline 0, 20, 60, and 200 mg/kg/d	NOAL = 20 mg/kg/day LOAEL = 60 mg/kg/day based on the increased incidence erythema, edema, and scabbing.
870.3250 90-Day dermal toxicity	This study is satisfied by the 80-week dermal carcinogenicity study in mice, which will be used for dermal non-cancer risk assessment	
870.3465 90-Day inhalation toxicity	No appropriate route-specific study was available. An older study conducted with Vantocil B contained many deficiencies.	
870.3700a Prenatal developmental in rodents	00065131 (1979) minimum/guideline 0, 200. 1000, 2000 ppm 0, 10, 50, 100 mg/kg/d	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on reduced body weight and reduced food consumption. **Developmental** NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on increased incidence of extra ribs in the fetuses.
870.3700b Prenatal developmental in nonrodents	42865901 (1993) minimum 0, 10, 20, 40 mg/kg/day	**Materna**l NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on increased mortality, reduced food consumption, and clinical toxicity. **Developmenta**l NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on reduced number of litters and skeletal abnormalities.

Guideline No./ Study Type	MRID No. (year)/ Classification/ Doses	Results
870.3800 Reproduction and fertility effects	43617401(1995) acceptable/guideline 1, 200, 600, 2000 ppm F0 males 23.0, 69.6, 238.9 mg/kg/d F0 females 25.3, 77.0, 258.2 mg/kg/d F1 male 23.9, 71.3, 249.3 mg/kg/d F1 female 26.1, 79.2, 270.5 mg/kg/day	**Parental/Systemic** NOAEL = 600 ppm LOAEL = 2000 ppm based on decreased body weight and food efficiency in F0 males and females; and decreased epididymis and kidney weight in F0 males. **Reproductive** NOAEL = 2000 ppm LOAEL not observed. **Offspring NOAEL = 2000 mg/kg/day**
870.4100a Chronic toxicity rodents	44059301/44042801 (1996) acceptable/guideline 0, 200, 600, 2000 ppm male 0, 12.1, 36.3, 126.1 mg/kg/day female 14.9, 45.3, 162.3 mg/kg/day	NOAEL = 600 ppm LOAEL = 2000 ppm based on decreased survival, reduced body weight, and decreased food utilization in females; decreased body weight, and decreased food utilization in males.
870.4100b Chronic toxicity dogs	43620501 (1995) acceptable/guideline 0, 300, 1500, 4500 ppm 0, 7.5, 37.5, 112.5 mg/kg/day 4500 ppm reduced to 3000 ppm (75 mg/kg/day)	NOAEL = 37.5 mg/kg/day LOAEL = 75 mg/kg/day based on changes in testis, liver weight, and microscopic observations in males; clinical signs of toxicity and clinical chemistry alterations in females.
870.4200 Carcinogenicity rats	44059301/44042801 (1996) acceptable/guideline 0, 200, 600, 2000 ppm male 0, 12.1, 36.3, 126.1 mg/kg/day female 14.9, 45.3, 162.3 mg/kg/day	NOAEL = 600 ppm LOAEL = 2000 ppm based on decreased survival, reduced body weight, and decreased food utilization in females; decreased body weight, and decreased food utilization in males. **Vascular tumors at 126/162 mg/kg/day**
870.4300 Carcinogenicity mice (oral)	44074201(1996) acceptable/guideline 0, 400, 1,200, 4000 ppm male 55, 167, 715 mg/kg/d female 69, 217, 856 mg/kg/d	NOAEL = 400 ppm LOAEL = 1,200 ppm based on decreased body weight, non-neoplastic histopathological changes in gall bladder, liver, and rectal-anal junction. **Vascular tumors and rectal-anal tumors at 715/856 mg/kg/day**

Guideline No./ Study Type	MRID No. (year)/ Classification/ Doses	Results
870.4300 Carcinogenicity mice (dermal)	93191028, 00066475, 00104796 (1990) acceptable/non-guideline 0, 15, 150, and 750 mg/kg/day PHMB	NOAEL = 150 mg/kg/day LOAEL = 750 mg/kg/day based on increased mortality and decreased body weight in male and female mice receiving PHMB.**Vascular tumors at 750 mg/kg/day**
Gene Mutation 870.5265 Microbial gene mutation assay	41687004 (1996) **acceptable** 3.3, 10, 33.3, 100, 333.3 μg/plate	No evidence of mutagenic response
Cytogenetics 870.5395 Micronucleus Assay	41096901/41404503 (1989) acceptable/guideline 250, 400 mg/kg	No evidence of clastogenic or aneugenic effects
870.5375 Cytogenetic assay with human lymphocytes	41404501/42149905 (1989) acceptable/guideline 5, 25, 50 μg/mL -S9 male 25, 100, 187.5 μg/mL +S9 female 25, 100, 250 μg/mL +S9	No evidence of clastogenic effects
Other Effects 870.5550 Unscheduled DNA synthesis assay in rat hepatocytes	41404502/42149903 (1989) acceptable/guideline 750, 1500 mg/kg	No evidence of a genotoxic response
870.6300 Developmental neurotoxicity	Not required; no evidence of neurotoxicity, no evidence of selective developmental or reproductive toxicity to offspring	
870.7485 Metabolism and pharmaco-kinetics	435999-01, 435670-01, 00077926, and 00086363 (1975&1995) together they are acceptable/guideline 200, 2000 ppm 10, 100 mg/kg	Metabolite analysis of pooled urine from rats administered a low molecular weight fraction of PHMB at 20 mg/kg (the fraction showing the greatest absorption) revealed the presence of more than one metabolite but identification was not performed due to the small amount of sample available for analysis.

8.2 Summary of Toxicological Dose and Endpoints for PHMB for Use in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = 20 mg/kg/day UF = 100 Acute RfD = 0.2 mg/kg/day	FQPA SF = 1 aPAD = acute RfD / FQPA SF = 0.2 mg/kg/day	Rabbit Developmental Study (MRID42865901) LOAEL = 40 mg/kg/day based on reduced number of litters, and skeletal abnormalities
Acute Dietary (General population including infants and children)	No Appropriate single dose effects were identified for general population		
Chronic Dietary (All populations)	NOAEL=20 mg/kg/day UF =100 Chronic RfD = 0.2 mg/kg/day	FQPA SF =1 cPAD = chronic RfD / FQPA SF =0.2 mg/kg/day	Rabbit developmental study (MRID #: 42865901) LOAEL = 40 mg/kg/day Based on the increased mortality, reduced food consumption, and clinical toxicity; Mouse developmental study (Report No. CTL/P/335, 1977 (cited in Report No. 003810, 1978. Section C-9)) LOAEL = 40 mg/kg/day; Based on reduced body weight gain; and Rat Developmental Study (Report No. CTL/P/1262, 1976 (cited in Report No. 003810, 1978. Section C-11)) LOAEL = 50 mg/kg/day Based on reduced food consumption.
Short-Term Incidental Oral (1-30 days)	NOAEL=20 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	See Chronic RfD
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL=20 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	See Chronic RfD

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term, Intermediate-Term, and Long Term Dermal Exposure	Dermal (or oral) study NOAEL= 150 mg/kg/day (Relative dermal absorption rate =100%)	Residential LOC for MOE =100 Occupational LOC for MOE =100	80 Week Dermal Painting Study (MRIDs 00066475 and 00104796) LOAEL = 750 mg/kg/day based on decrease body weight and liver tumors
Short-Term and Intermediate-Term Inhalation Exposure	No appropriate route-specific study was available. The oral endpoint of 20 mg/kg with a Margin of Exposure of 1000 (10x interspecies, 10x intraspecies, 10x for extrapolation from an oral endpoint) will be used for inhalation risk assessment.		
Cancer (oral, dermal)	The HED Cancer Assessment Review Committee. (CARC) classified PHMB as "Suggestive Evidence of Carcinogenicity, but not sufficient to Assess Human Carcinogenic Potential" by the oral and dermal routes. Quantification of human cancer risk is not required		

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure