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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: April 18, 2001

MEMORANDUM

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

FROM: Jonathan Chen, Ph.D.
Risk Assessment and Science Support Branch
Antimicrobial Division (7510C)

Jonathan Chen 4/20/01

THROUGH: Jess Rowland, Co-Chair Jess Rowland 4/24/01
and
Elizabeth Doyle, Co-Chair E.A. Doyle 4/20/01
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Norm Cook, Chief
Risk Assessment and Science Support Branch
Antimicrobial Division (7510C)

PC Code: 111801

On 12/18/2000 and 01/25/2001, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Poly(hexamethylenebiguanide) (PHMB),** established the Reference Doses (RfDs) and selected the toxicological endpoints for dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to ethyl parathion as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

12/18/2000 Members present were:	W. Burnam, E. Doyle, P. Hurley, J. Rowland, A. Assaad J. Chen and Brenda Tarplee.
Also in attendance were:	Bill Dykstra of the Health Effects Division Tim McMahon of the Antimicrobial Division.
12/18/2000 Members present were:	W. Burnam, E. Doyle, P. Hurley, E. Mendez, D. Nixon, J. Rowland, Y.Yang, B. J. Chen Tarplee and A. Assaad.
Also in attendance were:	Bill Dykstra of the Health Effects Division Paula Deschamp of the Health Effects Division Tim McMahon of the Antimicrobial Division.

Data evaluation prepared by: Jonathan Chen of the Antimicrobial Division.

Data Evaluation / Report Presentation

Jonathan Chen
Toxicologist

1 INTRODUCTION

In the two meetings hold on December 18, 2000 and January 25, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for PHMB with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to PHMB was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

2 HAZARD IDENTIFICATION

2.1 Acute Dietary

2.1.1 Acute Reference Dose (RfD) Subpopulation Females 13+

Study Selected: Developmental Toxicology - Rabbit §83-3

MRID No.: 42865901

Executive Summary: Administration of PHMB technical to pregnant female New Zealand White rabbits resulted in maternal toxicity at 40 mg/kg/day in the form of increased mortality and clinical toxicity. There was evidence of possible developmental toxicity of PHMB at 40 mg/kg/day, in the form of reduced number of litters and skeletal abnormalities (non-ossified 5th sternebrae, fused 3rd, 4th, and 5th sternebrae). The **Maternal NOAEL**= 20 mg/kg/day and the **Maternal LOAEL**= 40 mg/kg/day (increased mortality; reduced food consumption; clinical toxicity). The **Developmental toxicity NOAEL** = 20 mg/kg/day and the **Developmental toxicity LOAEL** = 40 mg/kg/day (reduced number of litters and skeletal abnormalities).

Dose and Endpoint for Establishing RfD: The **Developmental toxicity NOAEL** = 20 mg/kg/day (based reduced number of litters, and skeletal abnormalities)

Uncertainty Factor (UF): 100X (10X for intraspecies extrapolation; and 10X for interspecies extrapolation)

$$\text{Acute RfD} = \frac{20\ \text{mg/kg/day (NOAEL)}}{100\ \text{(UF)}} = 0.2\ \text{mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The developmental endpoint is presumed to occur after a single exposure. Since the effect developed from in utero exposure, they are applicable for risk assessment for female 13-50 subpopulation group

only.

2.1.2 Acute Reference Dose (RfD) — General Population Including Infants and Children+

No appropriate endpoint attributable to a single dose was identified for general population subgroup. The maternal toxicity observed in maternal animals in the rabbit study is not appropriate since the effects are not attributable to a single exposure (dose). Other oral studies did not indicate endpoints that are appropriate for this exposure period.

2.2 Chronic Dietary

2.2.1 Chronic Reference Dose (RfD)

Study Selected: 26 Weeks Oral Toxicity Study - Dog

MRID No.: 00086362

Executive Summary: In the 26 weeks dog oral toxicity study (MRID 00086362), 4 healthy adult beagle dogs per sex per group were administered PHMB (20%) at dosages of 0, 500, 1500 and 4500 ppm (0, 13, 38 and 113 mg/kg/day) for 26 weeks. Body weight losses occurred in the high-dose animals ranging from a mean of 4.8% in the males to 15.9% in the females. Histopathological lesions in the mid and high-dose groups consisted primarily of bile stasis, focal hepatocellular degeneration and necrosis, and focal proximal nephrosis. The **NOAEL = 13 mg/kg/day and the LOAEL = 38 mg/kg/day** (Based on the histopathological changes).

Dose and Endpoint for Establishing RfD: The **NOAEL** of 13 mg/kg/day (based on increased incidences of histopathological lesions)

Uncertainty Factor(s): 100X (10X for intraspecies extrapolation; and 10X for interspecies extrapolation)

$$\text{Chronic RfD} = \frac{13\ \text{mg/kg/day (NOAEL)}}{100\ \text{(UF)}} = 0.13\ \text{mg/kg/day}$$

Comments about Study/Endpoint/UF: Although a short-term study (6-months) was selected, the HIARC did not apply additional uncertainty factors because hepatotoxicity was seen following longer exposures in mice and rats.

3 Occupational/Residential Exposure

3.1 Incidental Oral Exposure

3.1.1 Short-Term Oral (1-7 days) Exposure

No appropriate endpoint was identified for short term incidental oral exposure scenarios.

3.1.2 Intermediate Term Oral (7 Days to Several Months) Exposure

Study Selected: 26 Weeks Oral Toxicity Study - Dog

MRID No.: 00086362

Executive Summary: In the 26 weeks dog oral toxicity study (MRID 00086362), 4 healthy adult beagle dogs per sex per group were administered PHMB (20%) at dosages of 0, 500, 1500 and 4500 ppm (0, 13, 38 and 113 mg/kg/day) for 26 weeks. Body weight losses occurred in the high-dose animals ranging from a mean of 4.8% in the males to 15.9% in the females. Histopathological lesions in the mid and high-dose groups consisted primarily of bile stasis, focal hepatocellular degeneration and necrosis, and focal proximal nephrosis. The **NOAEL = 13 mg/kg/day and the LOAEL = 38 mg/kg/day** (Based on the histopathological changes).

Dose and Endpoint for Establishing RfD: The **NOAEL** of 13 mg/kg/day (based on increased incidences of histopathological lesions)

3.2 Dermal Absorption

3.2.1 Dermal Absorption Factor:

The dermal absorption factor is not required since a dermal toxicity study was used for dermal exposure risk assessments.

3.2.2 Short-Term Dermal (1-7 days) Exposure

Study Selected: 80 Weeks Skin Painting Study §

MRID No.: 00066475 and 00104796

Executive Summary: Four groups of specific pathogen free (50M + 50F) alderley Park Mice received dermally 0.3ml at doses of 0 (solvent in ethanol), 0.6mg (0.2% PHMB in ethanol), 6.0mg (20% PHMB in ethanol) and 30.0mg (10.)% PHMB in ethanol) per day for five days a week for 80 weeks. The treatment dosages are equivalent to 0, 15, 150 and 750 mg/kg/day of 20% PHMB solutions. Mice received the highest dose level showed a poorer condition being very thin throughout the experiment. Death in the both

males and females in the highest dose group were 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 was 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, 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 received the highest dose level. There were no overall differences in food consumption between the control and treatment groups. There was a significant increase in the incidence of liver tumors in the highest treated group. Therefore for 20% PHMB solution, the **NOAEL = 150 mg/kg/day and the LOAEL = 750 mg/kg/day** (Based on increase mortality rate, decrease body weight and the liver effects).

Dose/Endpoint for Risk Assessment:
The **NOAEL** of 150 mg/kg/day of the 20% PHMB (Based on increase mortality, decrease body weight and liver effects).

Comments about Study/Endpoint:
The HIARC selected the NOAEL in the 80 Weeks Skin Painting Study for dermal toxicity is because it is a route specific study and because there is no significant dermal irritation happened at the dose selected. Although it is a long term study, the selected dose should be protective for both short- and intermediate-exposure. A margin of exposure (MOE) of 100 is required.

In addition HIARC also identified that dermal sensitization issue should be addressed on the label of the final product if the dermal contact is the primary exposure concern for this product. The reasons are:

(1) PHMB is a moderate skin sensitization agent in guinea pig study (MRID # 00160084) and
(2) PHMB is demonstrated to be a human skin sensitizer as demonstrated in the 1981 dermal sensitization study (MRID # 00127871).

3.2.3 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: 80 Weeks Skin Painting Study

MRID No.: 00066475 and 00104796

Executive Summary: See short term dermal above.

Dose/Endpoint for Risk Assessment:
The NOAELof 150 mg/kg/day of the 20% PHMB (Based on increase motality, decrease body weight and liver effects).

Comments about Study/Endpoint:
The HIARC selected the NOAEL in the 80 Weeks Skin Painting Study for dermal toxicity is because it is a route specific study and because there is no significant dermal irritation happened at the dose selected. Although it is a long term study, the selected dose should be protective for both short- and intermediate-exposure. A margin of exposure (MOE) of 100 is required.

3.2.4 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: 80 Weeks Skin Painting Study

MRID No.: 00066475 and 00104796

Executive Summary: See short tern dermal above.

Dose/Endpoint for Risk Assessment:
The NOAELof 150 mg/kg/day of the 20% PHMB (Based on increase motality, decrease body weight and liver effects).

Comments about Study/Endpoint:
The HIARC selected the NOAEL in the 80 Weeks Skin Painting Study for dermal toxicity is because it is a route specific study and because there is no significant dermal irritation happened at the dose selected. A margin of exposure (MOE) of 100 is required

3.2.5 Inhalation Exposure (All Durations)

Due to the low vapor pressure, inhalation exposure risk assessment is not required

3.2.6 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is selected for intermediate incidental oral and short, intermediate, and long-term dermal risk assessments.

3.3 Recommendation for Aggregate Exposure Risk Assessments

The risk assessment associated with both oral and dermal exposure routes should be aggregated in both intermediate and long term exposure situations.

4 CLASSIFICATION OF CARCINOGENIC POTENTIAL

4.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 44059301 and 44042801

Discussion of Tumor Data
In a rat chronic/oncogenicity study (MRID 44059301) male and female Alpk:APfSD Wistar rats (64/sex/dose) were fed diets containing polyhexamethylene biguanide (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. 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 determined that there were 3/64 incidences of hemangiosarcoma of the liver in 2000 females; the benign hemangioma was not observed. The increased incidence of the hemangiosarcoma in females gave positive results in trend analyses ($p<0.05$). A single observation of benign hemangioma was made in each the control and high dose males; 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 determined that there were 2/64 incidences of the hemangioma and 1/64 of the hemangiosarcoma 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 (§83-5)** and satisfies the guideline requirements for a chronic/oncogenicity study in rats.

Aequacy of the Dose Levels Tested: Yes

4.2 Carcinogenicity Study in Mice

MRID No. 44074201

Discussion of Tumor Data
In a mouse oncogenicity study (MRID 44074201), plyhexamethylene biguanide (PHMB, 20.2% a.i.) 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, or 715 mg/kg/day for males and 69, 217, or 856 mg/kg/day for females) for 2 years. Carcinogenic potential was evidenced by statistically significant ($p<0.01$) increased incidence of hemangiosarcomas in both sexes of

mice in the 4,000 ppm treatment group. In males at this treatment level 20/55 animals (36%) exhibited hemangiosarcomas and 17/55 (31%) females exhibited hemangiosarcomas at all sites vs 6/55 (11%) and 7/55 (13%) at all sites for respective controls. 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 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 or 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 polyhexamethylene biguanide (equivalent to 715 mg/kg/day in males and 856 mg/kg/day in females).**

Adequacy of the Dose Levels Tested Yes

4.3 Dermal Carcinogenicity Study in Mice

MRID No. 00066475 and 00104796

Discussion of Tumor Data
In a 80 week mouse skin painting study, four groups of Aderley Park Mice received dermal 0.3ml of the test material at doses of 0 (solvent in ethanol), 0.6 mg (0.2% PHMB in ethanol), 6.0mg (20% PHMB in ethanol) and 30.0 mg (10.0% PHMB in ethanol) for five days a week for 80 weeks. Mice receiveing the highest dose level (30 mg/day) showed poorer condition being very thin throughout the reminder of the study. High incidence of liver angiosarcoma were notice in the highest dose. The incidece is higher than the historical control.

4.4 Classification of Carcinogenic Potential

The issues of potential cancer causing effects will be referred to CARC.

5 MUTAGENICITY

In two independently performed microbial gene mutation assays (MRID No. 41687004), 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 an 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 test system in dimethyl sulfoxide. All strains responded in the expected manner to the nonactivated and S9-activated positive controls. There was, however, no evidence that Ventocil IB induced a mutagenic response in any strain at any nonactivated or S9-activated dose.

In a mouse micronucleus assay (MRID No. 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 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. The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a micronucleus assay.

In two independently performed in vivo/in vitro unscheduled DNA synthesis (UDS) assays (MRID No. 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 posttreatment 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. This study is classified as Acceptable and satisfies the guideline requirement for a UDS assay (84-4).

In an in vitro mammalian cell cytogenetic assays (MRID No. 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, 100 or 187.5 μ g/mL + S9 (male donor) or at 250 μ g/mL + S9 (female donor)sitive 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. This study is classified as Acceptable and satisfies the guideline requirement for an in vitro cytogenetic assay.

6 FQPA CONSIDERATIONS

6.1 Adequacy of the Data Base

6.2 Neurotoxicity

In the chronic dog 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. In one female dog at the high dose,show signs of neurotoxic effects include decreased activity, stiff/splayed gait and slight tremors. However, body weight loss, peeling of the skin on the pads of the paws, staining of paws and hocks, forelimb, hindlimb and forepaw abrasions, scarbs, and sores, and elevated plasma alanine transminase and aspartate transferase activities were also evident in this dog. Therefore, the effects may be due to the general health condition, in stead of neurotoxic effects.

6.3 Developmental Toxicity

There are three developmental studies.

MRID #: 42865901

In the rabbit developmental study (MRID #: 42865901), administration of PHMB technical (20.2% a.i.) 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. There are 6 rabbits died in the 40 mg/kg/day group. The incidence of several clinical signs appeared in increased in the 40mg/kg/day dose group, and included coldness (6/20 vs. 0/20 in control), few feces (16/20 vs. 7/20 in controls), no feces (6/20 vs. 0/20 in controls), thin appearance (6/20 vs. 0/20 in controls) and subdued behavior (3/20 vs. 1/20 in control). **Based on the increased mortality; reduced food consumption; clinical toxicity, the Maternal LOAEL= 40 mg/kg/day. The maternal toxicity NOAEL = 20 mg/kg/day.**

There was evidence of possible developmental toxicity of PHMB at 40 mg/kg/day, in the form of reduced number of litters and skeletal abnormalities (non-ossified 5th sternebrae, fused 3rd, 4th, and 5th sternebrae). The incidence of non-osified 5^{th} 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 4^{th} and 5^{th} sternebrae, found in 7 (5.9%) of fetuses and 6 (46.2%) of liters at the 40mg/kg/day dose level, compared to 1 (0.6%) fetus and 1 (5.3%) liter in controls. The incidence of fetuses and litter with fused 3^{rd} and 4^{th} sternebrae at the 40mg/kg/day dose is 5 (4.2%) of fetuses and 3 (23.1%) of liters vs. 1 fetus (0.6%) and 1 liter (5.3%) in controls. **The**

developmental toxicity NOAEL = 20 mg/kg/day, based on reduced number of litters, and skeletal abnormalities, the Developmental toxicity LOAEL = 40 mg/kg/day. However, because the developmental effects is happened at noticed at the dose cause severe maternal toxic effects, 6 out of 20 animal died in the group no quantitative / qualitative evidence of increased susceptibility of developmental effects in this study. (Note: This study stat the dosing at GD 8 which is different from the guideline specified stdy should star at GD 6).

Report No. CTL/P/335, 1977 (cited in Report No. 003810, 1978. Section C-9)

In the mice developmental study, groups of at least 21 pregnant Alderley strain pregnant mice were doses orally by gabage with 0, 10, 20 or 40 mg/kg of 20% PHMB at gestation days (GD) 6 through 15. On GD 18, the animals were killed by cervical dislocation. The mean maternal body weight was similar in the control, 10 mg/kg and 20 mg/kg groups. Slight but not significant reduced body weight gain was noticed in the 40 mg/kg groups. Food consumption was similar for all groups. Marginal reduction of ossification appears to occur at each of the treatment level (10,20 and 40 mg/kg). There is no clear teratogenic effects in the treatment groups.

Report No. CTL/P/1262, 1976 (cited in Report No. 003810, 1978. Section C-11)

In the rat developmental toxicity study, groups of at least 20 pregnant Aderley Park female rats were fed diets containing 0, 200, 1000 or 2000 ppm (0, 10, 50 or 100 mg/kg/day) of 20% aqueous solution of 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 LOAEL= 50 mg/kg/day. The maternal toxicity NOAEL = 10 mg/kg/day.**

There was no increase in late resorptions in any group. The fetal weight and litter weight was 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 increased incidence of extra ribs in fetus, the developmental toxicity LOAEL = 100 mg/kg/day. The developmental toxicity NOAEL = 50 mg/kg/day.**

6.4 Reproductive Toxicity

In a rat multigeneration 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 technical (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 F_0 males; 25.3, 77.0, and 258.2 mg/kg/day for F_0 females; 23.9, 71.3, and 249.3 mg/kg/day for F_1 males; and 26.1, 79.2, 270.5 mg/kg/day for F_0 females). The rats in each generation received test diets continuously until termination. Systemic toxicity was observed at the 2000 ppm dose level in the F_0 generation as indicated by a decrease in group mean body weight (9-10%) and food efficiency (7%) for the 10 week pre-mating period. The weight of the epididymides and kidneys were also significantly decreased in F_0 generation males. There were no corresponding effects in the F_{-1} 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 days 1-5 post-partum for both generations. **The Parental Systemic Toxicity NOAEL = 600 ppm (69.6 mg/kg/day [F_0 males]; 77.0 mg/kg/day [F_0 females]; 71.3 mg/kg/day [F_1 males]; 79.2 mg/kg/day [F_1 females]); The Parental Systemic Toxicity LOAEL = 2000 ppm (238.9 mg/kg/day [F_0 males]; 258.2 mg/kg/day [F_0 females]; 249.3 mg/kg/day [F_1 males]; 270.5 mg/kg/day [F_1 females]) based on decreased body weight and food efficiency in F_0 males and females, and decreased epididymis and kidney weight in F_0 males. The reproductive toxicity NOAEL = 2000 ppm; and the reproductive Toxicity LOAEL > 2000 ppm.**

6.5 Determination of Susceptibility

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

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

6.6 Recommendation for a Developmental Neurotoxicity Study

Because there is no evidence PHMB will induce neurotoxic effects. In addtion, 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. Therefore, PHMB will not cause FQPA concern.

7 HAZARD CHARACTERIZATION

PHMB technical (20% aqueous solution) is Toxicity Category III for acute oral and acute dermal studies. There is no acute inhalation study. PHMB technical is a primary skin and eye irritant (Toxicity Category I). PHMB is a dermal sensitizer. Ph.B. technical is negative for mutagenic potential in a battery of required mutagenicity studies. The chronic rat and dog oral and chronic mouse. Dermal studies demonstrate that the target organ is the liver. Reduced body weight is the primary effects of concern in all the animal studies. The developmental studies in rats and rabbits did not demonstrate any prenatal extra-sensitivity. There were no developmental effects below the level of maternal toxicity. Signs of cancer causing effects were noticed in dog and rat oral studies. The determination of the potential of carcinogenic effects of PHMB technical is referred to Cancer review Committee. (CARC).

8 DATA GAPS

There is no data gap in the toxicology database for the PHMB technical (20% a.i.)

9 ACUTE TOXICITY

Acute Toxicity of 20% PHMB

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00030330	LD_{50} = 2747mg/kg	III
81-2	Acute Dermal	00065124	LD_{50} > 5.0 mg/kg	III
81-3	Acute Inhalation	None	LC_{50} = m/L	
81-4	Primary Eye Irritation	00046789 00065120	Severe Eye Irritant	I
81-5	Primary Skin Irritation	00046789 00065120	Severe dermal irritant	I
81-6	Dermal Sensitization	00150084	Moderate Sensitization	

10 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios for 20% PHMB

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Generla Population)	No Appropriate single dose effects can be selected for general population		
Acute Dietary (Female 13- 50)	NOAEL= 20 UF = 100	Based on reduced number of litters, and skeletal abnormalities	Rabbit Developmental Stud (MRID42865901)
	Acute RfD = 0.2 mg/kg/day (for Females age 13 - 50)		
Chronic Dietary	NOAEL = 13 UF = 100	Based on increased incidence incidence of histomorphological lesions in liver and kidney.	26 Week Dog Study (MRID 0007925 and 00086362)
	Chronic RfD = 0.13 mg/kg/day		
Short-Term Incidental Oral Exposure	No Appropriate single dose effects can be selected for short-term(1-7 days) incidental Oral Exposure		
Intermediate-Term Incidental Oral Exposure	NOAEL= 13 MOE = 100	Based on increased incidence incidence of histomorphological lesions in liver and kidney.	26 Week Dog Study (MRID 0007925 and 00086362)
Short-Term, Intermediate-Term, and Long Term Dermal Exposure	NOAEL= 150 MOE = 100	Decrease Body Weight and Liver Effects	80 Week Dermal Painting Study (MRID 00066475 and 00104796)