UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 3-(Trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride (Bioshield AM 500): Non-dietary risk assessment.

EPA Identification Numbers:

DP Barcode: D260609	MRID: N/A
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Action Requested: Non-dietary risk assessment for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride as an active ingredient in BioShield® AM500.

1.0 Background

The registrant (BioShield Technologies, Inc.) has applied for amended registration of the Bioshield AM500 product containing the active ingredient 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride [also known as Dow Corning 5772 antimicrobial agent] as a materials preservative for application by homeowners. Similar uses are already registered but not for application by homeowners. Therefore, the non-dietary risk assessment must address risks from the residential exposures as a result of application of the product by homeowners, including exposures and risks to infants and children as mandated by the Food Quality Protection Act.

Previously, Toxicology data requirements for this active ingredient have been communicated to the registrant by the Agency. In a memorandum from Henry Spencer, Ph.D. to John Lee, dated July 28, 1988, several data gaps were listed for supporting the registration of this active ingredient. These data gaps were stated as: primary dermal irritation; acute inhalation toxicity; 90-day dermal, inhalation, and oral toxicity studies; a developmental toxicity study in a second species; and a mutagenicity battery.
In addition, in a memorandum dated December 4, 1997 (D239858, from Timothy F. McMahon to Velma Noble), the available Toxicology data for the active ingredient, 3-(Trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride, was listed in response to a request for waivers of acute toxicity studies with a related product, BST Mold and Mildew Remover. Of these data, it was noted that acute toxicity data existed for the product in question, but that several data gaps appeared to exist for a non-food use of the active ingredient. These were listed as: an acceptable dermal sensitization test; an acceptable subchronic toxicity test; an acceptable developmental toxicity test; and an acceptable mutagenicity battery (excepting the mouse micronucleus study, of which the Agency has an acceptable study).

Although the registrant's response to these memoranda is not known, a search of the available data within the Agency produced the following table of available Toxicology reviews of studies for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride:

2.0 TOXICOLOGY DATA MATRIX FOR: 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride

Guideline Number	Data Requirement	MRID Number (Accession No.)	Core Grade (Tox. Category)
870.1100	Acute Oral Toxicity (50% formulation)	40385201	acceptable (IV)
870.1200	Acute Dermal Toxicity (50% formulation)	40385201	acceptable (III)
870.1300	Acute Inhalation Toxicity (50% formulation)	not available	acceptable (IV)
870.2400	Primary Eye Irritation (50% formulation)	40385201	acceptable (I)
870.2500	Primary Dermal Irritation (50% formulation)	not available	acceptable (I)
870.2600	Dermal Sensitization	42197401	non-sensitizer
870.3100	Subchronic Dermal Toxicity	41339403	acceptable
870.3700	Developmental Toxicity in Rats	41438003	acceptable
870.5265	Salmonella thyphimurium reverse mutation assay	40385211	unacceptable (neg.)
870.5395	In vivo mouse micronucleus assay	41296804	acceptable (neg.)
870.6200	Neurotoxicity screening battery	R[5]	TGAI
870.5550	Unscheduled DNA synthesis in mammalian cells	41296804	unacceptable (neg.)
870.8700	Immunotoxicity	R[6]	TGAI

The current risk assessment for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride is presented using the available Toxicology data for this chemical. RASSB has conducted this risk assessment using conservative assumptions based upon the lack of an adequate data base for assessing risks to infants and children from exposure to this chemical (i.e. only a single developmental toxicity study was conducted).

3.0 Hazard Characterization

As stated, the Toxicology database for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride is inadequate to fully assess the hazard; conservative assumptions regarding hazards to infants and children as well as the extent of dermal absorption have been made. In addition, the mutagenicity of 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride is not fully characterized. Only one study has been determined to be acceptable by the Agency.

Acute toxicity data for a 50% formulation of 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride show low acute toxicity for single exposures by the oral, dermal, and inhalation routes. However, severe toxicity is observed with respect to skin and eye irritation of this active ingredient. This type of toxicity could be of concern especially in light of the registrant's desire to market this active ingredient for application by homeowners.

In a subchronic dermal toxicity study conducted in rats In a 90-day subchronic dermal toxicity study (MRID 41339403), groups of 10 male and 10 female Sprague-Dawley rats were treated with 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride (81.08%, Lot No. BN029263) at doses of 0, 100, 500, or 1000 mg/kg/day (doses based on range-finding study MRID 41339402). A vehicle control group was treated with 1000 mg/kg/day propylene glycol and an additional sham control group was included in the study. Animals were treated by dermal occlusion for 6 hours/day, 5 days/week for 90 days.

There were no treatment-related deaths or signs of systemic toxicity and no treatment-related effects on body weight, food consumption, hematology, clinical chemistry, organ weight, or histopathology at any dose level tested. No evidence of skin irritation was observed.

The dermal NOAEL is ≥1000 mg/kg/day based on a lack of dermal effects. The dermal LOAEL is > 1000 mg/kg/day. The systemic NOAEL is ≥ 1000 mg/kg/day (highest dose tested). The systemic LOAEL is > 1000 mg/kg/day. This study has been classified as unacceptable, but may be upgraded to acceptable pending the submission of stability, homogeneity, and concentration analysis data of the dosing suspensions.

In a developmental toxicity study in rats (MRID # 41438003), 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride (81.08% a.i., in corn oil) was administered by gavage to pregnant Sprague-Dawley rats (25/sex/dose) on days 6 through 15 of gestation at dose levels of 0, 100, 300, and 1000 mg/kg/day. Group mean liver weight was increased 6% in maternal animals at 1000 mg/kg/day compared to vehicle control. There was no significant treatment-related effect on body weights or food consumption in maternal animals. There were no significant treatment-related effects on cesarean section observations or on the incidence of fetal skeletal or soft tissue malformations or variations at any dose level. Although maternal liver weight was increased by 7% at the 1000 mg/kg/day dose, this effect was not accompanied by any other signs of liver toxicity, and is thus not considered treatment-related. The maternal NOAEL is considered to be ≥ 1000 mg/kg/day, and the Maternal LOAEL is >1000 mg/kg/day. The developmental toxicity NOAEL is considered to be ≥ 1000 mg/kg/day, and the developmental toxicity LOAEL is > 1000 mg/kg/day. This study is classified as acceptable and satisfies the guideline requirement (870.3700) for a developmental toxicity study in rats. Although this was the only developmental toxicity study available for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride , the data show no evidence of increased susceptibility to offspring of rats following *in utero* exposure up to and including a limit dose (1000 mg/kg/day). However, for the proposed uses of this active ingredient, a second developmental toxicity study should be conducted to better characterize the potential susceptibility of offspring to the effects of this chemical. The requirement for a 2-generation reproduction study is held in reserve.

In an Ames salmonella assay (MRID # 40385211), 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride did not cause an increase in number of revertant colonies in *Salmonella typhimurium* strains TA1535, 1537, 98, and 100 when tested at concentrations of 50, 100, 250, or

500 μg/plate in the absence or presence of metabolic activation. This study was classified as unacceptable due to the lack of testing to cytotoxic levels.

In a mouse micronucleus assay (MRID # 41296803), 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride was administered to groups of five male and female mice at dose levels of 500, 2500, or 5000 mg/kg. No compound related toxicity was observed in either sex at the top dose, and there were no significant increases in the percentage of micronucleated polychromatic erythrocytes in bone marrow cells harvested at 24, 48, or 72 hours following exposure to the test material. There was also no evidence of compound induced cytotoxicity in the target cells. This study was classified as acceptable.

In an unscheduled DNA synthesis assay (MRID # 41296804), 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride was used in two independent assays (dose range of 0.025 - 1.02 μg/ml in the first assay; 0.063-2.01 μg/ml in the second assay). The first assay was considered invalid because of the high frequency of net nuclear grain counts in the solvent control group. The second assay was also compromised by the lack of a defintive cytotoxic effect at the high concentration of 2.01 μg/ml. Although reduced cell survival was observed at this concentration (23.3% reduction), the evidence for cytotoxicity is questionable based on the statement in the report that severe cytotoxicity, which prevented the scoring of hepatoytes, was observed at doses greater than 1.02 μg/ml. This study is classified as unacceptable and does not satisfy the requirement for a UDS assay.

3.1 FQPA Considerations

The determination of the appropriate safety factor for assessing potential risk to infants and children under the Food Quality Protection Act is presented below as an interim determination, pending submission of a second developmental toxicity study and formal assessment of 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride by the Health Effects Division's Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee. It is recommended that the FQPA Safety factor be **reduced to 3x** because:

- there was no evidence for increased susceptibility in the prenatal developmental toxicity study in rats, and there was no evidence for neurotoxicity to the offspring.
- there is potential for significant contact of infants and children though the proposed homeowner uses for this active ingredient
- there is a lack of a developmental toxicity study in a second species for this active ingredient and a lack of a 2-generation reproduction toxicity study.

The FQPA safety factor should be applied to all populations which include infants and children for residential risk assessments. The FQPA safety factor is appropriate for these populations since the potential for residential exposures exists, and the database characterizing the developmental and reproductive toxicity of 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride is incomplete.

3.2 Endpoint Selection

Table 2. Summary of Doses and Endpoints Selected for 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride Risk Assessments.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13+)			
		This risk assessment is not required.	
Acute Dietary (general population)			
		This risk assessment is not required.	
Chronic Dietary			
		This risk assessment is not required.	
Short-,intermediate-, and long-term (Dermal)	This risk assessment is **not required** based upon the lack of any toxicological effects up to and including a limit dose (1000 mg/kg) from available data.		
	UF = 100 ; FQPA UF = 3 (10% dermal absorption)[a]		
Dermal absorption	10% (default value based on determination for ADBAC)		

a = The use of a 10% dermal absorption rate is selected as a default value based on the structure, molecular weight, ionized state, and lack of lipophilicity.

Conclusions

The available Toxicology data for 3-(Trimethoxysilyl)propyl dimethyl octadecyl ammonium chloride showed a lack of toxicological effects at dose levels up to and including a limit dose (i.e. 1000 mg/kg/day). The Agency recognizes as a matter of policy that chemicals which do not show any significant effects when tested to a limit dose do not require endpoint selection and risk assessment, based upon the existence of effects only at very high and unrealistic exposures. Therefore, for the proposed amended registration of Bioshield AM500 containing 3-(Trimethoxysilyl)propyl dimethyl octadecyl ammonium chloride as the active ingredient, RASSB at this time has no risk concerns for this chemical.

However, it is to be noted that this conclusion does not apply to any future amended registrations or new uses for this active ingredient, for which a risk assessment may be necessary.