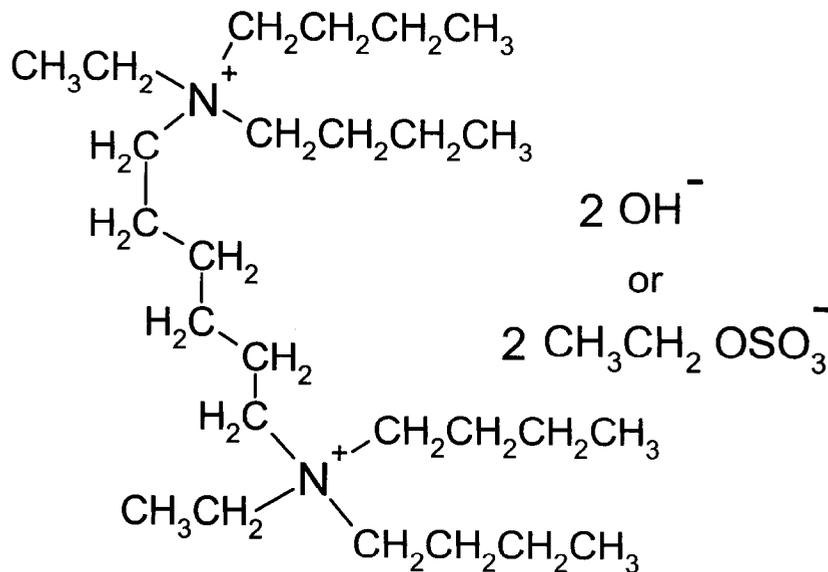


201-15773A

1,6-Bis(dibutylethylammonium)hexane hydroxide
and
1,6-Bis(dibutylethylammonium)hexane ethylsulfate

CAS Number 111960-92-0 & 68052-49-3



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**U.S. EPA HPV Challenge Program
Submission**

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Executive Overview

1,6-Bis(dibutylethylammonium)hexane hydroxide (BQAOH), CAS no. 111960-92-0 and 1,6-Bis(dibutylethylammonium)hexane ethylsulfate (BQAES), CAS no. 68052-49-3 are aliphatic quaternary amines that are produced by Solutia for internal use at only one site. All BQAES is converted to BQAOH that is used as a process aid in the manufacture of adiponitrile, which is an intermediate in Solutia's manufacturing process for nylon-6,6. Solutia produces BQAOH and BQAES at only one site and both are consumed at that site. Some of the BQAOH is disposed by processing in a wastewater treatment plant. This represents the only opportunity for the material to leave the manufacturing site; however, analytical determinations indicate that BQAOH is not discharged, nor processed in high enough concentration to interfere with the bacterial flora in the wastewater treatment plant. Worker exposure is minimized by the use of closed systems and mandated personal protective equipment.

These materials are known to be corrosive to skin and eyes and potentially lethal upon dermal exposure and, based on SAR, are assumed toxic to aquatic species in the environment and to the bacterial flora in a wastewater treatment plant at high levels. Because of these nefarious properties, a high standard of engineering controls, personal-protection requirements and wastewater treatment safeguards have been implemented to protect workers and the environment.

As produced and handled, both BQAOH and BQAES are aqueous solutions containing approximately 4 to 50% of quaternary amine salt. Both are colorless liquids with freezing points slightly below 0°C and boiling points slightly above 100°C. The quaternary amine salts themselves are solids with high melting points and very low vapor pressures. Both salts are water-soluble and the quaternary compounds have an estimated $K_{o/w}$ of 0.13, which indicates little potential for bioaccumulation in the environment. The solutions are clear liquids with a slight amine odor. BQAOH and BQAES both have very low volatility (estimated vapor pressure less than 0.00000001 hPa @ 25°C) and are water-soluble.

If released into the environment, based on physicochemical properties, neither has significant potential to bioaccumulate ($\text{Log } K_{o/w}$ 0.13) and both will distribute primarily to water. Both materials are considered water stable but neither is expected to be resistant to biodegradation. Although volatilization to the atmosphere is not anticipated, the cations are expected to react rapidly with atmospheric hydroxyl radicals with a half-life of about 1.3 hours. Toxicity to aquatic species is predicted to be low using the ECOSAR model but testing is recommended to determine actual toxic potential.

The acute oral toxicity of BQAOH is moderate with an LD_{50} value of around 350 mg/kg found in a rat gavage study. BQAOH displayed a high degree of dermal toxicity in experimental animals giving a dermal LD_{50} in rabbits of only 22.5 mg/kg. Based on the high-level of acute toxicity and a presumed mechanism as a ganglionic blocker, repeated-dose, reproductive and developmental, and genotoxicity hazard assessments are derived using a "read-across" approach from similar compounds. These indicate little specific reproductive, developmental or genetic toxicity hazard. No studies have been conducted or proposed for BQAES as it is only a variation in the salt and, except for temporary storage, is not isolated.

It is concluded that the available information on the compounds and surrogates adequately fills all the data elements of the HPV Program for BQAOH and BQAES except for the biodegradation and aquatic toxicity endpoints. Studies to provide experimental data for these endpoints are recommended.

Testing Plan and Rationale

Testing Plan in Tabular Format

CAS No. 111960-92-0 BQAOH	Information Available?		OECD Study?		GLP Study?		Supporting Information?		Estimation Information?		Acceptable Method?		Testing Recommended?	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
HPV Endpoint														
Physical Chemical														
Melting Point	Y	N	N	N	Y	Y	N							
Boiling Point	Y	N	N	N	Y	Y	N							
Vapor Pressure	Y	N	N	N	Y	Y	N							
Partition Coefficient	Y	N	N	N	Y	Y	N							
Water Solubility	Y	N	N	Y	N	Y	N							
Environmental & Fate														
Photo-Degradation	Y	N	N	N	Y	Y	N							
Water Stability	Y	N	N	Y	Y	Y	N							
Transport	Y	N	N	N	Y	Y	N							
Biodegradation	N	N	N	Y	N	N	Y							
Ecotoxicity														
Acute Fish	Y	N	N	N	Y	N	Y							
Acute Invertebrate	N	N	N	N	N	N	Y							
Acute Algae	N	N	N	N	N	N	Y							
Toxicity														
Acute	Y	N	N	Y	N	Y	N							
Repeated Dose	Y	N	Y	Y	Y	Y	N							
Genetic Toxicology "in vitro"	Y	N	Y	Y	Y	Y	N							
Genetic Toxicology "in vivo"	Y	N	Y	Y	Y	Y	N							
Reproductive	N	N	Y	Y	Y	Y	N							
Developmental	Y	N	Y	Y	Y	Y	N							

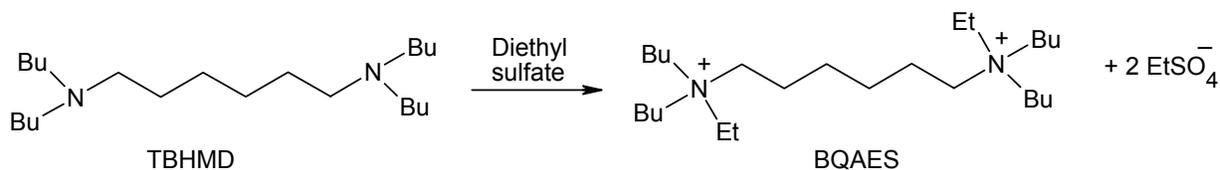
disposed by processing in a wastewater treatment plant. This represents the only opportunity for the material to leave the manufacturing site; however, analytical determinations indicate that BQAOH is not discharged, nor processed in high enough concentration to interfere with the bacterial flora in the wastewater treatment plant. Worker exposure is minimized by the use of closed systems and mandated personal protective equipment.

These materials are known to be corrosive to skin and eyes and potentially lethal upon dermal exposure and, based on SAR, are assumed toxic to aquatic species in the environment and to the bacterial flora in a wastewater treatment plant. Because of these nefarious properties, a high standard of engineering controls and personal-protection requirements have been implemented to protect workers and the environment. Exposure in industrial applications is limited by process controls, stringent protective equipment requirements and a very low vapor pressure. The number of workers possibly exposed to these chemicals is limited to about three per work shift.

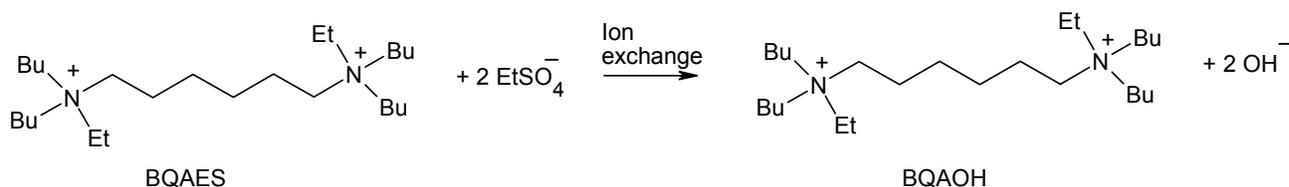
No studies have been conducted or proposed for BQAES as it is only a variation in the salt and, except for temporary storage, is not isolated.

Chemistry of Manufacture

BQAES is produced by the reaction of N,N,N',N'-tetrabutylhexamethylene diamine (TBHMD) with ethyl sulfate as shown below.



BQAOH is made by an ion exchange reaction to convert the sulfate to the hydroxide.



All the BQAES produced is converted to BQAOH and all the BQAOH produced is used on site as a production aid in the manufacture of adiponitrile. Although there is some temporary storage of BQAES in a holding tank, it can be considered essentially a closed-system intermediate and BQAOH can be considered a site-limited intermediate. After its use as a production aid, about half the BQAOH is burned as part of an organic waste stream and about half goes with a wastewater stream to the on-site wastewater treatment plant.

Physicochemical Data

Physicochemical data for BQAES and BQAOH are available from the manufacturer and from estimates.

Table 1: Physicochemical Properties of BQAES and BQAOH		
Parameter	BQAES	BQAOH
Melting Point	ca. 300-350° C as solid (3) ca. -6° C as aqueous soln (4)	ca. 300-350° C as solid (3) ca. -3° C as aqueous soln (4)
Boiling Point (aqueous solution)	ca. 100-102°C @ 1027 hPa (5)	ca. 100-101°C @ 1027 hPa (5)
Vapor Pressure	negligible @ 25° C (6)	negligible @ 25° C (6)
Partition Coefficient Cation	Log $K_{o/w}$ = 0.13 (7)	Log $K_{o/w}$ = 0.13 (7)
Water Solubility	>10,000 mg/L @ 25° C (8)	>10,000 mg/L @ 25° C (9)

These properties indicate that at ambient temperatures both BQAES and BQAOH are non-volatile solids with high water solubility. The values of the partition coefficients, suggests that both will partition preferentially into water; therefore, on the basis of only the octanol-water partition coefficient, BQAES and BQAOH are considered to have minimal potential for bioaccumulation. As both materials are handled and used as aqueous solutions, the estimated boiling and melting point of the solutions were calculated from the solute concentration and given in Table 1. As organic salts, in the anhydrous form neither is expected to have a distinct boiling point as most organic salts decompose before boiling.

Regarding BQAES, which is an ethylsulfate salt, the values for the $K_{o/w}$, melting point and vapor pressure were independently calculated for the cation and anion. Only the values for the cation (quaternary amine) are shown in the table, while both values are given in the robust summaries.

Recommendation: No additional physicochemical studies are recommended. The available data fill the HPV required data elements.

Environmental Fate and Pathways

Photodegradation was estimated by examination of the structure for chromophores that would indicate direct photolysis and indirect photolysis was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to

calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced an estimated rate constant of $98.4 \text{ E-12 cm}^3/\text{molecule-sec}$ for the quaternary amine, which is the same in BQAOH and BQAES. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of the quaternary amine portion of the molecule with hydroxyl radical, the estimated half-life of BQAOH vapor in air is approximately 1.3 hours (see accompanying robust summary for full details). In the case of BQAOH the anion is hydroxide, which will not further photolytically degrade. In the case of BQAES, the anion is ethylsulfate. The half-life of ethylsulfate (as the sodium salt) was estimated with the AOPWIN program as 13 days based on the default hydroxyl radical concentrations and an estimated rate constant of $0.82 \text{ E-12 cm}^3/\text{molecule-sec}$ for reaction with atmospheric hydroxyl radical. It should be noted that since both materials have insignificant vapor pressures and high water solubilities, it is unlikely that release of vapor into the atmosphere will be significant for either material under plausible release scenarios.

Water stability has not been quantitatively determined for BQAOH or BQAES. Quantitative stability determinations (e.g. OECD 111) are considered unnecessary for compounds containing only non-hydrolysable groups. Under these conditions, the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available in the literature that BQAOH or BQAES are unstable in water and they are in fact handled, stored and used as aqueous solutions. Regarding the quaternary amine cation, no specific data were found for water stability of similar quaternary amines. Assuming the reaction products of hydrolysis is the tertiary amine and either butanol or ethanol, the enthalpy of the reaction can be calculated using standard bond energies. As the number of reactants (2) is the same as the number of products (2), it can be assumed that entropy changes will be a minor consideration in the free energy change resulting from the hydrolysis reaction and the feasibility and rate of reaction can be estimated from enthalpy estimates. Conducting this calculation using standard bond energies and the hydrolysis reaction was estimated to be endothermic by more than 400 kJ/mole (see robust summary). With this scale of energy requirement, it can be assumed that the quaternary amine moiety will be hydrolytically stable under environmental conditions (that is it may be considered non-hydrolysable).

Regarding the anions, the BQAOH anion is the hydroxyl ion, which is considered fully hydrolyzed. The BQAES anion is monoethylsulfate and since it is known that diethyl sulfate hydrolyzes to ethanol and sulfate with a half-life of 1.7 hours (10), and because monoethylsulfate is an intermediate in this reaction, the hydrolysis half-life of this anion can safely be estimated as less than 1 day under environmental conditions (see robust summary for details).

Except for data showing ready biodegradation of diethyl sulfate in the MITI test (11), no definitive biodegradation data has been located for BQAOH or BQAES. Biodegradation studies of quaternary amines are limited as many of these materials are biocidal surfactants and are difficult to study using standard protocols. In the extensive book "Surfactant Biodegradation", Swisher (12) only devotes a short section to a discussion of the biodegradation of alkyl quaternary amines. This review, directed toward monoamino quaternary amines, notes that difficulties have been encountered due to bacterial toxicity. Biodegradation results for the alkyl quaternary amines are mixed but indications are that most of the ones tested are "ultimately biodegradable". As BQAOH and BQAES are

comprised primarily of linear alkyl groups and are not anticipated, based on their structures, to have significant surfactant or biocidal properties, they are anticipated to be biodegradable and this is confirmed by analytical investigations of wastewater at the plant. Definitive determination of the relative rate of biodegradation, however, will require testing; hence, biodegradation testing of BQAOH is recommended. As the quaternary amine structure of BQAOH and BQAES are identical and as diethylsulfate is known to be biodegradable, testing of only BQAOH is considered sufficient.

Theoretical Distribution (Fugacity) of BQAOH and BQAES in the environment was estimated using the MacKay EQC level III model found in EPIWIN set to estimate distribution after 100% release to water, which is the most likely scenario. The EPIWIN model was allowed to estimate physicochemical and fate parameters used in the calculations; however, these were verified for appropriateness before the final calculation was accepted. Because BQAES is a salt and is expected to dissociate in the environment, the cationic and anionic portions of the salt were independently modeled. (see robust summaries).

The results for both the cation and anion are similar, except for about 0.2% distributing to sediment, all the material remains in the water column. (13). A summary of these results is shown below in Table 2:

Environmental Compartment	Species Modeled	
	BQAOH and BQAES Cation	Sodium ethylsulfate
○ Air	< 0.01%	< 0.01%
○ Water	99.8%	99.8%
○ Soil	< 0.01%	< 0.01%
○ Sediment	0.2%	0.2%

Table 2. Distribution Estimates from EQC Level III Model

Recommendation: Considering the uncertainty in the ease of biodegradation for the BQAOH quaternary amine cation, an OECD 301 or 302 series study is recommended. No additional fate studies are recommended. The available data fill all other HPV required elements.

Ecotoxicity

No definitive data on the ecotoxicity of BQAOH or BQAES could be found. Although the EPA ECOSAR program estimated the LC₅₀ for fish at 23,000 mg/L using the cationic surfactants model, the similarity of the

structure to cholinergic blocking agents suggests that there is a potential for acute toxicity to fish should the material be bioavailable. Regarding the ethylsulfate anion, since it is readily biodegradable and hydrolysable and will rapidly hydrolyze under environmental conditions to sulfate and ethanol, it may be considered well characterized. It is recommended that OECD-guideline fish, invertebrate and algal toxicity assays be conducted using BQAOH. Studies should use neutralized conditions to best represent actual environmental conditions. As the material is considered to be stable and highly soluble in water the use of nominal concentrations and static conditions is recommended for this screening-level hazard assessments.

Recommendation: Acute fish, invertebrate, and algal toxicity studies of BQAOH are recommended to provide information adequate for the purpose of the HPV program.

Health Effects

Acute Toxicity

Oral Exposure

The oral LD₅₀ of BQAOH was determined to be approximately 350 mg/kg in Sprague-Dawley rats dosed by gavage with a 28% solution of BQAOH. Clinical signs in decedents were reported as rapidly increasing weakness, collapse and death occurring between 30 minutes and 120 minutes of administration. No clear cause of death could be identified at necropsy; the principle necropsy finding was hemorrhagic lung and liver. (14)

Dermal Exposure

The dermal LD₅₀ of BQAOH was determined to be approximately 22.5 mg/kg in New Zealand white rabbits dosed with a 28% solution of BQAOH. Clinical signs in decedents were reported as rapidly increasing weakness, collapse and death occurring about 2 hours after administration. No clear cause of death could be identified at necropsy; the principle necropsy finding was hemorrhagic lungs. Furthermore, all six rabbits died after application of 0.5 ml of 28% aqueous solution in a skin-irritation study in which the solution was determined to be corrosive to skin. (14)

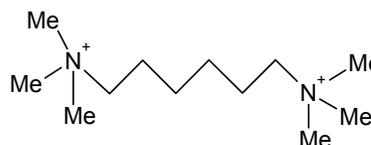
Relative to acute toxicity, the greater sensitivity of test animals by dermal exposure than by oral exposure is noted. This can be explained several ways including species difference, limited oral absorption or first-pass metabolism of the test material by the liver of rats. The most probably explanation is thought to be limited oral absorption as it is established that the absorption of quaternary compounds from the enteric tract is “incomplete and unpredictable” (15). Hexamethonium bromide, which has a similar structure and was FDA approved for treatment of hypertension between 1951 and 1972, shows a similar toxicity profile for oral versus subcutaneous treatment of rats. Its oral LD₅₀ is 2891 mg/kg while the subcutaneous LD₅₀ is only 200 mg/kg (RTECS). Another quaternary compound that is fatal at low dermal doses is tetramethylammonium hydroxide, which has an oral LD₅₀ of 34-50 mg/kg in rats (16) and is fatal to rabbits when applied as a 2.75% solution (17) (estimated dermal LD₅₀ <20 mg/kg). This demonstrates that charged quaternary ammonium compounds can be absorbed through the skin and cause mortality at very low dose levels.

The similarity of the structure of BQAOH to the prototypical ganglionic blocking drug hexamethonium is obvious by examination of the structures below. The muscle paralyzing activities of quaternary amines were first described by Marshall in 1913 who described the “nicotine paralyzing” activity of tetraethylamine on ganglia (18). More than 30 years passed before the bis-quaternary ammonium salts were independently studied and developed by Barlow and Ing and reported in a 1948 publication (19) and by Paton and Zaimis in a 1952 publication (20). Hexamethonium was the “prototypical” agent described and was reported to have potent ganglionic blocking activity but minimal neuromuscular or muscarinic activity. In the subsequent years, many specific ganglionic and neuromuscular blocking agents have been developed and used, especially as an adjunct to anesthetic agents in surgery. Hill reviewed many of the active compounds and discussed structure–activity relationships (21); subsequently, a review in 2001 by Lee (22) extended the review and discussed conformational

contributions to specific activity. These reviews discuss several structural features that affect the nicotinic activity of amines. Relative to this discussion, important observations are that a very wide variety of structures have activity at the nicotinic receptor. The specific mode of activity can be depolarizing or non-depolarizing with bulkier compounds tending to be non-depolarizing. The amines do not have to be quaternary to have activity; potency generally follows the order: bis quaternary amines > bis amine with one nitrogen tertiary and one quaternary > bis tertiary amines > quaternary mono-amines. Depending on the structure, other cholinergic receptors can be affected most notably those of the cardiovascular system. An important determinant of the activity type (ganglionic or neuromuscular junction) and potency is the distance between the two charged nitrogen atoms. As both BQAOH and hexamethonium share a hexamethylene bridge between the quaternary nitrogens, they are anticipated to have similar pharmacological specificity. It is logical to speculate that BQAOH will show clear ganglionic blocking activity and is anticipated to cause mortality by blocking respiration at sufficiently high dose levels. This hypothesis is supported by the data showing rapid mortality in rats after oral administration and in rabbits after dermal administration with a lack of delayed deaths in both species. The low LD₅₀ of BQAOH in rabbits also supports a specific pharmacological activity after dermal administration. It can therefore be concluded that the toxicity of BQAOH is most probably mediated by its activity as a ganglionic blocking agent.



BQAOH



Hexamethonium

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet all requirements of current OECD guidelines in all cases, the weight of evidence shows that the oral toxicity is significant and that the dermal toxicity is remarkably high.

Repeat Dose Toxicity

Repeated-dose studies have not been conducted on BQAOH or BQAES. Although chemicals produced at this volume within Solutia generally have a more complete data set, there are sound reasons why repeated-dose have not been conducted with these materials:

- ❑ These materials are highly toxic after acute exposure producing lethality and severe burns.
- ❑ These materials already carry the strongest possible label warnings.
- ❑ A high level of personal protective equipment is required when handling the materials.
- ❑ These materials are produced and consumed entirely on site.
- ❑ Findings of repeated-dose studies would not change handling procedures.
- ❑ Conduct of additional studies would unnecessarily expose laboratory workers to these acutely toxic materials.

For these reasons, and because additional mammalian testing would result in pain (the material is corrosive) and death of laboratory animals, additional mammalian testing cannot be recommended. For the purposes of the HPV program it recommended that surrogate compounds that already have data be used for filling the endpoints.

Quaternary ammonium compounds (QACs) are a recognized group of industrial chemicals used for their activity as surfactants and bactericides. EPA suggested in 1988 that the QACs could be divided into four groups and that toxicity studies would be facilitated by selecting a representative compound from each group for testing (23)

- ❑ Group I: Straight-chain alkyl or hydroxyalkyl QACs
- ❑ Group II: Alkyl dimethyl benzyl ammonium compounds
- ❑ Group III: Alkyl [di- and tri- chlorobenzyl] dimethyl ammonium compounds
- ❑ Group IV: Heterocyclic ammonium compounds

BQAOH and BQAES fall in Group I, although data from Group II QACs may still be applicable. Several observations lend support to using Group I and II QACs as surrogates for BQAOH and BQAES (24).

- ❑ Some produce remarkably higher toxicity by sq or ip routes than by oral administration
- ❑ Some show curare-like activity resulting in muscle paralysis causing rapid death without CNS effects
- ❑ Among the alkyl dimethyl benzyl ammonium compounds, shorter (e.g. C8) alkyl carbon chain compounds were more toxic than those with longer carbon chains and increase in carbon chain length beyond C16 markedly reduced toxicity.
- ❑ The rat oral LD₅₀'s for most QAC's are in the range of 250-1000 mg/kg
- ❑ Most QACs are strong skin and eye irritants in aqueous solutions.

This spectrum of activity is consistent with the acute toxicity data from BQAOH, suggesting commonality of mechanism for BQAOH with the Group I and Group II QAC's. Based on this, it is proposed that data from other QACs can be reasonably used to assess the potential health effects of BQAOH and BQAES.

Didecyltrimethylammonium chloride, CASNO 7173-51-5 (DDDMAC) has been designated by EPA as the representative chemical for toxicology studies for all dialkyl quaternaries. As BQAOH and BQAES have multiple alkyl groups associated with the quaternary nitrogen (two butyl and one ethyl) and as the empirical formulas for the cationic portion of BQAOH and BQAES ($C_{26}H_{58}N_2$) is similar to DDDMAC ($C_{22}H_{48}N$), DDDMAC was also selected as the principle surrogate for BQAOH and BQAES. Several other surrogates, however, are available and provide confirmatory evidence for the health effects assessment (25).

Oral Exposure

Didecyltrimethylammonium chloride, CASNO 7173-51-5, DDDMAC was incorporated in the diet and fed to groups of 60 Sprague-Dawley rats of each sex for 104 weeks at 0, 300, 750, or 1500 ppm. Decreased bodyweight gain and food consumption was observed in each sex at 1500 ppm. Increased incidence in mesenteric lymph node pathology (blood in sinuses, hemosiderosis and histiocytosis) occurred in both sexes at 1500 ppm. Bile duct hyperplasia occurred in females at 1500 ppm. Treatment-related oncogenicity was not observed. The chronic NOEL was determined to be 750 ppm for rats of each sex (26).

Recommendation: No additional repeated-dose studies are recommended. The available data fill the HPV required endpoint for repeated-dose toxicity.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one test sensitive for point mutation and one sensitive for chromosomal aberrations. In the case of these materials, adequate tests using various surrogate compounds have been conducted that cover both of these endpoints. As in the case of the repeated-dose assessment, the lack of potential exposure, the warning label and level of protective equipment utilized, the commonality of the quaternary amine groups in normal biochemical processes and the availability of consistently negative data on a variety of analogous compound indicate there is no need to conduct genotoxicity studies on BQAOH or BQAES. DDDMAC studies are proposed as a surrogate for filling the HPV genotoxicity data elements.

Genetic Toxicology in vitro

DDDMAC was tested in a CHO/HGPRT forward mutation assay at concentrations of 0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 or 10.0 µg/ml without metabolic activation trial and at concentrations of 0, 1.0, 5.0, 10.0, 13.0, 15.0, 18.0, 20.0, 22.0 or 25.0 µg/ml with metabolic activation. Cell survivals were in an acceptable range. Neither assay showed an increase in mutant frequency (27).

DDDMAC was tested in an in vitro cytogenetic assay in the presence of activation (+S9) with Chinese Hamster ovary cells in duplicate at concentrations of 0, 2, 4, 8, or 16 µg/ml. In the absence of activation (no S9), concentrations for the first replicate were 0, 0.25, 0.5, 1.0, and 2.0 µg/ml and because these levels did not produce the expected toxicity and levels for the second replicate were increased to 0, 1.0, 2.0, 4.0, or 8.0 µg/ml. No adverse effects were reported either with or without S9 (28).

Genetic Toxicology in vivo

Metaphase chromosomes obtained from the bone marrow of CD rats treated with DDDMAC by gavage at doses of 0 or 600 mg/kg were analyzed for adverse effects at sampling times of 6, 24, and 48 hours. The positive control cyclophosphamide was administered at 40 mg/kg and bone marrow was sampled at 24 hours post treatment. No treatment-related effects to metaphase chromosomes were observed and positive controls gave the expected result (29).

A large number of genotoxicity studies, have been reported on other related QACs indicting a general lack of genotoxicity (30)

Recommendation: The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted on related materials using acceptable protocols. No additional genotoxicity testing is recommended.

Reproductive Toxicity

As described under *Repeated Dose*, a surrogate chemical is recommended to fill this HPV endpoint.

A two-generation reproductive of DDDMAC was conducted by dosed feed using Sprague-Dawley (CD) rats (28/sex/dose) treated through two generations with 2 litters per generation at dose levels of 0, 300, 750, or 1500 ppm. Treatment began 10 weeks prior to mating. At 1500 ppm, reduced bodyweight gains and food consumption were observed for parental animals and pups displayed reduced bodyweight gain. The parental and maternal NOAL was 750 ppm.

Recommendation: No additional reproductive testing is recommended. The available data are sufficient to assess the reproductive toxicity of this material.

Developmental Toxicity

As described under *Repeated Dose*, a surrogate chemical is recommended to fill this HPV endpoint.

DDDMAC was tested for developmental toxicity in a rabbit study using 16 animals per group and doses of 0, 1.0, 3.0 or 10.0 mg/kg-day administered by gavage on days 6 - 18 of gestation. In this study, the maternal NOEL was determined to be 1.0 mg/kg. There were 4 deaths accompanied by labored respiration, gasping, sloughing of esophageal lining and stomach, and decreased weight gain at 10.0 mg/kg. At 3.0 mg/kg, audible respiration, hypoactivity and decreased weight gain was observed in the dams. The developmental NOEL was 3.0 mg/kg. At 10 mg/kg-day, there was an increased number of dead fetuses/litter and decreased fetal body weight.

Other QACs with similar structures have been tested for developmental toxicity and reported in the “Fatty Nitrogen Derived Cationics Category “ and none have given positive results (30). In addition, developmental toxicity of the neuromuscular drugs has been reviewed by Schardein and found to be largely devoid of developmental toxicity (31).

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of this material.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that the available information fills all of the requirements for physicochemical parameters, and acute toxicity. As the materials have a high degree of acute toxicity after dermal administration (dermal rabbit LD₅₀ of 22 mg/kg), and likely act at peripheral cholinergic sites to cause muscle paralysis, and are site-limited intermediates, additional health effect studies are not recommended. Additional studies would not impact the warning label, handling recommendation, or requirements for personal protective equipment that are already in place for these acutely toxic materials. It is proposed that rather than expose testing laboratory personnel to the known hazards of BQAOH and BAQES, the HPV data elements for repeated dose toxicity, reproductive and developmental toxicity and genotoxicity be filled using data from surrogate quaternary amines. It is recommended, however, that the HPV data elements of biodegradation and aquatic toxicity be filled by appropriate OECD-guideline testing on BQAOH.

References

- 1 Chemical Information System (CIS) file Database File: SANSS [Chemical Nomenclature, Formulas, Structures] CAS Registry Number: 111960-92-0, Source of Information: TSCA Inventory, CIS Record ID.: SA-00472956
 - 2 Chemical Information System (CIS) file Database File: SANSS [Chemical Nomenclature, Formulas, Structures] CAS Registry Number: 27090-63-7, Source of Information: TSCA Inventory, CIS Record ID.: SA-00177616
 - 3 MPBPWIN (v1.40) program as found in EPIWIN 3.05, Syracuse Research Corporation, ES EPA Version 2000
 - 4 Calculated using freezing-point depression method. See robust summary for details.
 - 5 Calculated using boiling-point elevation method. See robust summary for details
 - 6 MPBPWIN (v1.40) program using modified Grain method as found in EPIWIN 3.05, Syracuse Research Corporation, ES EPA Version 2000
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