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U.S. EPA High Production Volume (HPV)
Chemical Challenge Program

SUMMARY OF EXISTING DATA, PROPOSED TEST PLAN AND RATIONALE FOR CALCIUM DIPROPIONATE (CASRN 4075-81-4)

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INTRODUCTION

The following document includes a test plan and a summary of existing data for calcium salt of propionic acid (Ca dipropionate) [CASRN 4075-81-4]. The information provided in this document and the attached dossier of robust summaries meets the requirements under the U.S. High Production Volume (HPV) Chemical Challenge. Ca dipropionate is one of 19 sponsored chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. The Coalition member companies sponsoring Ca dipropionate are Kemin Industries and The OM Group (OMG).

USE PATTERNS AND REGULATORY BACKGROUND

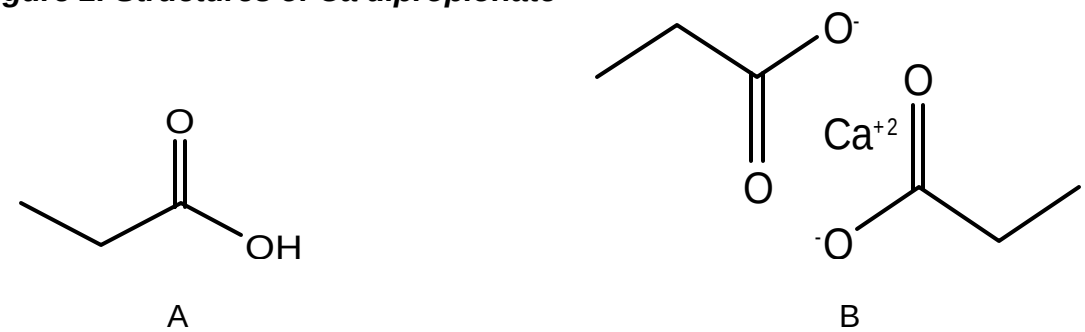
Ca dipropionate, [$2(CH_3CH_2COOH^-)\ Ca^{2+}$] is a metal carboxylic acid, a salt of calcium and the alpha monocarboxylic acid, propionic acid. Ca dipropionate is used in variety of ways including as a common food and feed additive, as a pesticide active ingredient (fungicide), and as an inert ingredient in pesticides. Since 1979 the Code of Federal Regulations (CFR) has listed Ca dipropionate (21 CFR 182.3221), propionic acid [21 CFR 182.3081] and the sodium salt, Na propionate [21 CFR 182.3784] as a generally recognized as safe (GRAS) chemical preservative in food (FASEB 1979). Products such as these are commonly used as additives in cheese and milk products, meats, beverages and other consumer products.

The EPA Office of Pesticide Programs (OPP) recently released a Final Rule exempting from tolerance the residues of these three chemicals in raw agricultural commodities pursuant to section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA). The tolerance for propionic acid (also known as propanoic acid)[1] is found in 40 CFR Part 180 and was announced in the Federal Register August 4, 2004 (Vol. 69, No. 149). Under this exemption, Ca dipropionate residues are permitted to be present in, or added to, any agricultural product with no restriction on the amount of residue present. This tolerance exemption provides a recent affirmation of the status of Ca dipropionate and propionic acid as GRAS. An excerpt of the August 4 *Federal Register* explains:

> *Based on "…the low potential for toxicity of propanoic acid [a synonym for propionic acid] and its calcium and sodium salts for the oral route of exposure, that humans of all ages are highly exposed to propanoic acid from natural sources, and that the human body has a known pathway for metabolizing propanoic acid…EPA concludes that exempting propanoic acid, and its calcium and sodium salts from the requirements of a tolerance will be safe for the public, including infants and children" (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).*

These same compounds have also been evaluated internationally. The safety of these compounds for use in food has been evaluated several times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Propionic acid and three of its simple salts (Ca^{2+}, Na^{+}, K^{+}) have been established internationally as common food additives used as mold inhibitors, preservatives, and flavoring agents. The JECFA concluded as recently as 1997 that there is no safety concern for these compounds at the current levels of use and that their Acceptable Daily Intake (ADI) need not be limited. Propionates are metabolized and utilized in the same way as a normal fatty acid (JECFA, 1962). The toxicology evaluation for these compounds concluded that there is no reason to believe that the propionic acid differs toxicologically from its calcium and sodium salts (JECFA, 1966).

Figure 1: Structures of Ca dipropionate



A) Propionate (as the free acid) B) Ca dipropionate

Ca dipropionate is considered a “simple” salt due to the presence of calcium. This divalent metal action is not considered toxicologically significant. Calcium is an essential element that is absorbed mainly through active transport. The amount absorbed is regulated according to the current needs of the body with the participation of vitamin D, parathormone, and calcitonin. Normal calcium absorption requires the presence of vitamin D, a Ca-binding protein and amino acid (lysine and L-arginine).

One characteristic of Ca dipropionate and other metal carboxylates is that they are ion pairs, which readily dissociate in water. The dissociation constants show that at the low pH of the stomach, the important moieties from a toxicological standpoint are the unionized free acid and ionized metal. Because of this, mammalian toxicity data for the free acid, or that for a simple salt of the acid (e.g., the sodium salt or the calcium salt), can serve as surrogate data for the acid component of respective metal carboxylates such as Ca dipropionate. Table 1 shows how similar the acute toxicity data is for the salt, Ca dipropionate, and the free acid, propionate. Under these conditions, the contribution of the metal ion (Ca^{+2}) to any observed toxicity is considered minimal or insignificant. This is

supported by the treatment of the acid and the Ca and Na salts as equivalent in the recent Exemption of Tolerance decision by the EPA (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).

Table 1. Comparison of acute toxicity values for Ca dipropionate and its carboxylic acid, propionate

Acute Mammalian Toxicity[a]	**Ca dipropionate**	**Propionate**
Acute oral toxicity (LD50 in mg/kg bw)	3920-4380	2600-4290
Acute inhalation toxicity (LC50 in mg/L)	>5.4	>4.9
Acute dermal toxicity (LD50 in mg/kg bw)	500	500

[a] See Table I

For this reason the data for the free acid, propionate, are clearly delineated as supporting data and summarized and referenced in the appropriate "Remarks" sections for each data element in the robust summaries of Ca dipropionate. These data are also presented in Tables I.

EXISTING DATA FOR CA DIPROPIONATE – SUMMARY

Physicochemical Properties

Available physicochemical property data for this compound and its carboxylic acid are shown in Table I and briefly summarized below.

Physicochemical properties are well characterized for Ca dipropionate. Data for all five physicochemical endpoints are available for either Ca dipropionate or propionic acid (Table I) (IUCLID 2000b).

Melting Point

The melting point was not applicable (NA) for the Ca salt, but was reported as 22.4^{o}C for the acid.

Boiling Point

Boiling point was evaluated in a GLP study in 2004, but could not be measured under the test conditions (RCC 2003). The reported values for the boiling point of propionic acid are 140.7 to 141.6^{o}C (IUCLID 2000b).

Density

Density for Ca dipropionate is reported as 400 mg/m^3 (IUCLID 2000a)

Vapor Pressure

Vapor pressure was not considered applicable for Ca dipropionate, but was reported as 5 hPa at 20°C for the acid (IUCLID 2000b).

Partition Coefficient

The Log octanol/water partition coefficient for the acid was reported to be very low at 0.25-0.33, but was not evaluated for the Ca dipropionate salt, which is not a pure substance (IUCLID 2000b).

Water Solubility

Ca dipropionate was reported to have a substantial solubility of 260g/L at 20°C (IUCLID 2000a) and the acid has a reported water solubility of 55.8 g/100ml @100°C (HSDB 2002).

Environmental Fate and Transport

Available environmental fate and transport data for Ca dipropionate and propionic acid are shown in Table I and summarized below.

Photolysis

Photolysis was not measured for Ca dipropionate, but was measured for the free acid. The rate of degradation was 1.22-1.60 E^{-12} CM^{3}/mole/s @298°K (Adkinson 1993).

Dissociation in water

One key characteristic of any metal carboxylate is that they readily dissociate from an ion pair into free metal and free acid as the pH is decreased. The equilibrium constants from a recent GLP dissociation study with Ca dipropionate can be seen in Table 2 (below), and the pKb values for propionate from the scientific literature are very consistent with the measured pKb2 value from the dissociation study (see bolded values).

Table 2 Comparison of pK values for Ca dipropionate, the metal carboxylate salt, and respective carboxylic acid[a]

Chemical Tested	Equilibrium Constants	
	pKb1	pKb2
Propionate	**4.87**	
Ca dipropionate	6.67	**4.75**

[a] See Table I and the Robust Summaries for additional details.

Biodegradation

The calcium salt of propionic acid is readily biodegradable and, as is the case for the acid, does not persist for long periods in water. The salt is 100% degraded after 7 days (Lezotte 2003) and the acid shows a similar rate of degradation of 95% in 10 days (IUCLID 2000b).

Monitoring data

Residues in foods, measured as propionic acid range from approximately 1100 to 2000 ppm (IUCLID 2000b, FASEB 1979).

Transport data

Estimation of environmental transport is not available since fate models generally used do not accurately predict salts such as metal carboxylates. Further, the product is approved for use in food and feed at substantial levels.

Ecotoxicity

Fish Toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with the reported 96-h LC50 value for *Leuciscus idus* reported as >10,000 mg/L (Table I) (BASF AG 1990). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for salmon and trout, respectively (IUCLID 2000b).

Invertebrate toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with reported 48-h LC50 value of > 500 mg/L (Table I) for *Daphnia* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for *Daphnia sp*., respectively (IUCLID 2000b).

Algal toxicity

The calcium salt of propionic acid is practically non-toxic toward algal species with reported 96-h IC50 value of > 500 mg/L (Table I) for *Scenedesmus subspecatus* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 43.0 to 45.8 mg/L for *Scenedesmus subspecatus* (IUCLID 2000b).

Propionic acid is slightly toxicity to fish, invertebrates and algae with LC50 values ranging from 22.7 to 85.3 mg/L. The higher toxicity of the acid appears to be mainly due to the effects of low pH, as toxicity is greatly reduced under neutralized conditions.

Human Health Effects

Propionic acid is a normal intermediary metabolite in animals and humans. There is an extensive mammalian toxicity database available for this compound and the salt, Ca dipropionate.

Acute Mammalian Toxicity

Acute toxicity data is available Ca dipropionate for five of five acute endpoints (i.e., oral toxicity, inhalation, dermal toxicity, skin irritation and eye irritation) and two endpoints for the acid as presented and referenced in Table I (Kobayashi et al. 1976, BASF AG 1980, Patty Ind. Hyg. Toxicol. 1982, Symth et al. 1962, BASF AG 1979). Ca dipropionate shows a low order of acute toxicity and no irritation. The same order of toxicity is reported for propionate. The acid has a low acute toxicity in animal studies (Table I), and is not reported to be corrosive or irritating to skin and eyes. Oral, inhalation and dermal LD50 or LC50 values are 3920-4380 mg/kg (rat), >5.6 mg/L (4 hrs., rat), and 500 mg/kg bw (rabbit). Reported acute toxicity in the rat exposed to propionic acid range from 2600 to 4290 mg/kg and >4.9 mg/L (4 hrs.) for oral and inhalation routes, respectively (IUCLID 2000b). Ca dipropionate is reported to be “not irritating”, to either the skin or eye in rabbits using the Draize test (BASF AG 1979).

Genetic Toxicology - Mutation Assays

Neither Ca dipropionate nor propionic acid is mutagenic in *in vitro* Ames Tests. Genetic Toxicity Studies are available for Ca dipropionate and the carboxylic acid, propionate. *In vitro* Ames bacterial assays have been used to evaluate Ca dipropionate, including at least 11 strains with and without activation and with standard strains (e.g., TA 98, TA100, TA1535, TA1537, and TA1538) being evaluated in multiple studies (Altman et al. 1988a, Ohta et al. 1980, Litton Bionetics, Inc. 1974, Ishidata et al. 1984). All studies were negative for mutagenicity of Ca dipropionate. Similar *in vitro* studies with propionic acid and Na propionate were all negative. Similar results were observed in an *in vitro* study with Chinese hamster lung cells (without activation) and in sister chromatid exchange assays, using V79 cells (with and without activation) (Basler et al. 1987).

Genetic Toxicology – Clastogenic

Ca dipropionate is negative in cytogenetic or dominant lethal assays (Table I). Propionic acid is negative in a micronucleus test. In *in vivo* studies, Ca dipropionate showed no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutations were observed (Litton Bionetics 1974). In the mouse exposure to Ca dipropionate resulted in increased reversion

frequency, in one of three strains, but this was not dose-related. Propionic acid is reported to be negative in a micronucleus test (Basler et al. 1987).

In summary, all genetic toxicity studies using bacterial and mammalian cells, *in vitro* or *in vivo* are consistently negative.

Repeated Dose

There is extensive toxicity data for Ca dipropionate including several long-term repeated dose studies. This salt has a low order toxicity and it is typically less toxic that the acid alone, likely due to its lower acidity.

Repeated dose studies were conducted in rats and dogs with study periods ranging from 4 weeks to 90 days and exposure levels ranging up to 3320 mg/kg/day. No abnormalities in clinical or hematological examinations were observed. These changes were largely reversible. Changes in the fore stomach (e.g., hyperkeritosis and hyperplasia) were observed. These changes were observed to occur equally with Ca and Na propionate, but were more marked with exposure to propionic acid. The changes were largely reversible, attributed to the acidity of the compound, and were not related to any systemic toxicity of the compound. Studies with Na propionate and propionic acid are also available. Some of these were conducted in parallel with Ca dipropionate (Altman et al. 1988a, Altman et al. 1988b, Harshbarger 1942).

Developmental Studies

Developmental studies have been conducted with five species (mouse, rabbit, hamster, rat, and chicken) (Food and Drug Research Labs Inc. 1972, Miss. State Univ. 1973). All five studies are rated as “Reliable with Restriction”. In the four studies with mammalian species, no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls. Parameters monitored including food and water consumption; body weight during early gestation; numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses; body weights of live pups; dam urogenital tract examination; examination of all fetuses for gross abnormalities and one third for visceral abnormalities; and one third of fetuses were preserved, stained and examined for skeletal defects. In the study with chickens, Ca dipropionate was not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg pre-incubation or at 96 hours via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered pre-incubation via the yolk caused a high mortality rate (FASEB 1979).

Reproduction Studies

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure to propionate, no reproduction data is recommended.

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Table I: Summary of existing data for Ca dipropionate and its carboxylic acid

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate[a]
Physicochemical Properties			
Melting Point		NA[1]	22.4°C
Boiling Point		….[b]	140.7–141.6 °C
Density		400 mg/m^3 [c]	
Vapor pressure		NA	5 hPa at 20 °C
Log Partition Coefficient		….[2]	0.25-0.33
Water Solubility		260 g/L at 20°C[c]--	49 g/100 ml at 0°C; 55.8 g/100 ml at 100°C[d]
Environmental Fate Parameters			
Photodegradation		--	1.22-1.60 E^{-12} cm^3/mol/s at 298°K[e]
Dissociation in water		pKb 6.7 and 4.75 at 20°C[f]	pKb 4.78
Monitoring Data	Food[3]		Ca 1100 to 2000 ppm[c,g]
Transport	NA[c]	--	
Biodegradation		100% degraded after 7 days [h]	40% removal after 24 hrs. and 95% removal after 10 days.
Ecotoxicity			
Fish toxicity (96-h)	Bluegill Trout	>10,000 mg/L[i] (*Leuciscus idus)*	96-h LC50 for trout and salmon are 85.3 and 67.1 mg/L respectively
Invertebrate toxicity (48-h)	*Daphnia*	> 500 mg/L in (*Daphnia)*[j]	Ranged from 22.7 to 50 mg/L (*Daphnia)*
Algae toxicity (96-h)		>500 mg/L (Scenedesmus subspicatus)[j]	43 to 45.8 mg/L (Scenedesmus subspicatus)
Human Health Effects			
Acute	Oral LD50, rat	3920-4380 mg/kg bw[k]	3470, 4290, and 2600 mg/kg bw
	Inhalation LC50, rat	>5.6 mg/L (4 hrs.)[l]	>4.9 mg/L (4 hrs.)
	Dermal LD50, rabbit	500 mg/kg bw[m,n]	---
	Skin irritation, rabbit	Not irritating in Draize Test[o]	---
	Eye irritation	Not irritating[o]	---

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate
Repeated dose	90-day oral	Reversible changes in stomach mucosa, but no mortality, no abnormalities following clinical and hematological examination and no change in organ weights were observed following exposures up to 3320 mg/kg/day[pqr]	pH related lesions in mucosal wall following 21 to 28 day exposures at 3320 mg/kg/day
Genetic Toxicology – mutation assay	Ames bacterial reversion assay	Negative[p,s,t,u]	Negative[v]
Genetic Toxicology – Clastogenic	Cytogenetic and dominant lethal assay	Negative (No increased chromosomal aberrations in bone marrow cells)[t]	Negative (micronucleus test)[v]
Reproductive		NA	NA
Developmental		No teratogenic effects in five species tested[x,y]	NA

[a] IUCLID 2000b; [b] RCC 2003; [c] IUCLID. 2000a; [d] HSDB. 2002; [e] Adkinson. 1993; [f] Lezotte 2003; [g] FASEB 1979; [h] BASF AG 1989b; [i] BASF AG 1990; [j] BASF AG 1988; [k] Kobayashi et al. 1976; [l] BASF AG 1980; [m] Patty Ind. Hyg. Toxicol. 1982; n Symth et al. 1962; [o] BASF AG 1979; [p] Altman et al. 1988a, [q] Altman et al. 1988b; [r] Harshbarger 1942; [s] Ohta et al. 1980; [t] Litton Bionetics, Inc. 1974; [u] Ishidata et al. 1984; [v] Basler et al. 1987; [x] Food and Drug Research Labs 1972; [y] Mississippi State University (1973).

[1.] Boiling Point could not be measured under conditions of GLP Test

[2] The octanol/water partition coefficient was not measured for any of the metal carboxylates because they are salts which dissociate into ionized substances and they are not pure substances.

[3] Estimated levels reported to be found in baked goods.

TEST PLAN AND RATIONALE FOR CA DIPROPIONATE

Propionic Acid, Calcium Salt	CASRN 4075-81-4

The Test Plan for Ca dipropionate is presented in Table II with supporting data for the carboxylic acid, propionate. The rationale for the Test Plan is based upon existing data as summarized above and in Table I. Some data is older, but this entire dataset has consistently served as an adequate basis for addressing food safety concerns by FDA, WHO, and most recently by the EPA (Office of Pesticide Programs). Furthermore, key studies have a rating of [1] reliable without restriction or [2] reliable with restrictions.

Physicochemical Properties

Data is available for all five SIDS endpoints listed in Tables I and II for either Ca dipropionate or propionic acid. The melting point and vapor pressure studies were considered not applicable and data was available for the free acid. A GLP boiling point study (OECD 103) was conducted, but the BP could not be determined under the conditions of the test (RCC 2003). The rationale for not conducting an octanol/water partition coefficient study with Ca dipropionate is based on the impurity of the compound (i.e. a salt), and an ionizeable substance. Using a compound with these characteristics to measure the partition coefficient is inappropriate. This would yield erroneous data. Data is available for the acid, which shows the Log Kow to be very low. No additional testing is recommended for any of the physicochemical endpoints.

Environmental Fate Parameters

Adequate data is available for three SIDS endpoints (i.e., photodegradation, dissociation and biodegradation) for Ca dipropionate and/or propionic acid. Data for transport in the environment is not provided and is not considered necessary. Standard models used for estimating transport do not accurately predict salts or ionized substances. Adequate biodegradation data are currently available for propionic acid component of the salt. The acid rapidly biodegrades (IUCLID 2000b). Further, aerobic degradation data already exists for Ca dipropionate and shows that it rapidly biodegrades. Because propionic acid is known to occur naturally and to readily be metabolized and degraded *in vivo,* and in the environment, estimating the environmental transport is considered unnecessary.

Ecotoxicity

Sufficient data is available for Ca dipropionate and for the carboxylic acid, propionic acid, for all three types of organisms (i.e., fish, invertebrates and algae). Based on the low order of toxicity for both the Ca salt and the acid for all three endpoints no additional studies are recommended.

Human Health Effects

Acute toxicity studies

Acute oral toxicity data is available for the Ca dipropionate and dissociation product propionic acid for five acute toxicity endpoints (oral toxicity, inhalation, dermal toxicity and skin and eye irritation) (Table I). No additional studies are recommended for acute toxicity endpoints.

Genotoxicity studies

Existing data for Ca dipropionate and the carboxylic acid, propionate are all negative (Table I). No additional genetic toxicity studies are proposed.

Higher tiered studies

Numerous repeated dose studies with Ca dipropionate, Na propionate, and the free acid, propionate, show a consistent lack of effects with the exception of changes in the digestive tract mucosa. These changes are largely reversible and attributed to generic pH effects and not to systemic toxicity. No additional repeated dose studies are recommended.

Developmental studies were conducted with four mammalian species and consistently showed a lack of teratogenic effects. There were no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival. A study with chickens also showed a lack of teratogenicity. These studies were conducted in the early 1970's by the Food and Drug Research Labs and Litton Bionetics prior to the establishment of guidelines. They are rated as [2] Reliable with Restrictions. No additional studies are recommended.

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure of organisms to propionate via diet, no additional testing is recommended.

Table II: Test Plan Matrix: Ca dipropionate

	Information available	Ca Dipropionate	Propionate	GLP Study	Acceptable	Testing recommended
PHYSICOCHEMICAL PROPERTIES						
Melting Point	Y	Y	N	Y	Y	N
Boiling Point	Y	Y	Y	Y	Y	N
Vapor pressure	Y	N	Y	N	Y	N
Partition Coefficient	Y	N	Y	Y	Y	N
Water Solubility	Y	Y	N	N	N	N
ENVIRONMENTAL FATE PARAMETERS						
Photodegradation	Y	N	Y	--[C]	--	N
Dissociation in water	Y	Y	N	Y	Y	N
Transport	--	Y	--	--	--	N
Biodegradation	Y	Y	Y	--	Y	N
ECOTOXICITY						
Fish toxicity (96-h)	Y	Y	Y	Y	Y	N
Invertebrate toxicity (48-h	Y	Y	Y	Y	Y	N
Algae toxicity (72-h)	Y	Y	Y	--	N	N
HUMAN HEALTH EFFECTS						
Acute						
Oral LD50, rat	Y	Y	Y	N	Y	N
Inhalation LC50, rat	Y	Y	Y	N	Y	N
Dermal LD50, rat	Y	Y	N	N	Y	N
Skin Irritation	Y	Y	N	N	Y	N
Eye Irritation	Y	Y	N	N	Y	N
Repeated dose	Y	Y	Y	Y	Y	N
Genetic Toxicology – mutation assay	Y	Y	Y	Y	Y	N
Genetic Toxicology – chromosomal aberration	Y	Y	Y	Y	Y	N
Reproductive	N	N	N	N	Y	N
Developmental	Y	Y	N	Y	Y	N

[A] U = undetermined
[B] Study currently being conducted
[C] -- means not applicable