ACUTE TOXICITY Fatty acids, C8-18 and C18-unsatd., mixed esters with C18-unsatd. fatty acid dimers, decanoic acid, octanoic acid and trimethylolpropane (CASRN: 2411231-33-7)

The polyol esters category comprises of 51 aliphatic esters of polyfunctional alcohols containing two to six reactive hydroxyl groups and one to six fatty acid chains. The category contains mono constituent, multi-constituent and UVCB substances with fatty acid carbon chain lengths ranging from C5 - C28, which are mainly saturated but also mono unsaturated C16 and C18, polyunsaturated C18, branched C5 and C9,branched C14 – C22 building mono-, di-, tri-, and tetra esters with an alcohol (i.e.polyol).

The available data allows for an accurate hazard and risk assessment of the category and the category concept is applied for the assessment of environmental fate and environmental and human health hazards. Thus, where applicable, environmental and human health effects are predicted from adequate and reliable data for source substance(s) within the group by interpolation to the target substances in the group (read-across approach) applying the group concept in accordance with Annex XI, Item 1.5, of Regulation (EC) No 1907/2006. In particular, for each specific endpoint the source substance(s) structurally closest to the target substance is/are chosen for read-across, with due regard to the requirements of adequacy and reliability of the available data. Structural similarities and similarities in properties and/or activities of the source and target substance are the basis of read-across.

A detailed justification for the grouping of chemicals and read-across is provided in the technical dossier (see IUCLID Section 7.1 and 13) and within Chapter 5.1 of the CSR.

Acute Oral Toxicity

There are several reliable acute oral toxicity studies available within the polyol esters category.

CAS 97281-24-8

An acute oral toxicity study Fatty acids, C8-10, mixed esters with neopentyl glycol and trimethylolpropane (CAS 97281-24-8) was performed similar to OECD Guideline 401 (standard acute method, limit test) and in compliance with GLP (Potokar, 1988). The test item was administered by gavage to five Wistar rats per sex at a dose of 2000 mg/kg bw. The animals were subjected to daily observations for clinical signs, and twice daily for morbidity and mortality. Body weights were determined weekly on test Days -1, 2, 7, and 14 and macroscopic examinations were performed after terminal sacrifice. No mortality occurred and no clinical signs of toxicity were observed during the study period. No effects on body weights were noted. Necropsy revealed for males; haemangioma of the left renal lymph node in 1/5 animals, and mild hypoplasia of the right testis in 1/5 animals. 1/5 females showed high grade hydrometra and haemangioma of the left renal lymph node. The oral LD50 value in rats was determined >2000 mg/kg bw.

CAS 11138-60-6

A reliable acute oral toxicity study was conducted with Fatty acids, 8-10 (even numbered), di- and triesters with propylidynetrimethanol according to OECD Guideline 401 (standard acute method, limit test). Upon treatment of male and female rats with 2000 mg/kg bw of the test substance no mortality or enduring adverse effect was observed during the 14 d observation period. The animals had normal weight gain until the end of the observation period (Clouzeau, 1990). The LD50 value was therefore determined to be > 2000 mg/kg bw.

CAS 91050-89-4

An acute oral toxicity study was performed with Fatty acids, C8-10, triesters with trimethylolpropane (CAS 91050-89-4) comparable to OECD 401 (limit test) (Kästner, 1983).Only limited documentation was available but all relevant data were given. The test substance was administered by gavage to 5 male and female Wistar rats at 2000 mg/kg bw. Animals were subjected to daily observations and weekly determination of body weight. No treatment related clinical signs of toxicity were observed up to the end

of the 14-day observation period. In addition no effect on body weight was noted. Thus, the oral LD50 value in rats was found to exceed 2000 mg/kg bw.

CAS 85005-23-8

An acute oral toxicity study was conducted with Fatty acids, C14-18 and C18-unsatd., branched and linear, esters with trimethylolpropane according to OECD Guideline 423 (Acute Toxic Class Method). Upon treatment of male and female Wistar rats with 2000 mg/kg bw of the test substance no mortality or any adverse effect was observed during the 14 d observation period. The animals had normal weight gain until the end of the observation period (Busschers, 1997). The LD50 value was therefore determined to be > 2000 mg/kg bw.

Formerly CAS 85186-89-6

An acute oral toxicity study (limit test) with Fatty acids, C8-10(even), C14-18(even) and C16-18(even)-unsatd., triesters with trimethylolpropane (CAS 85186-89-6) was performed according to OECD Guideline 401 and GLP (Kuszewski, 1996). The test substance was administered by gavage at a concentration of 2000 mg/kg bw to groups of five male and female Hsd/Cpb:WU rats. The animals were observed for 14 days following administration. No mortalities occurred during the study period. No clinical signs of toxicity, only slight changes in body weights for some animals and no differences at macroscopic examination were reported. The acute oral LD50 was found to be greater than 2000 mg/kg bw.

CAS 403507-18-6

An acute oral toxicity study with Fatty acids, C16-18 and C18-unsatd., branched and linear ester with trimethylolpropane (CAS 403507-18-6) was performed comparable to OECD Guideline 423 (acute toxic class method, limit test) and under GLP conditions (Sanders, 2002). The test substance was administered by gavage to three Sprague-Dawley CD (Crl: CD IGS® BR) male and female rats at 2000 mg/kg bw. Animals were subjected to daily observations and weekly determination of body weight. Gross pathology examination was performed after terminal sacrifice (Day 15). No treatment related abnormalities with regard to clinical signs, body weights and necropsy were observed. The oral LD50 value in rats was found to exceed 2000 mg/kg bw.

CAS 91050-90-7

An acute oral toxicity study (limit test) with Fatty acids, C16-18, triesters with trimethylolpropane (CAS 91050-90-7) is available, which was performed according to EU Method B.1 and GLP (Potokar, 1989). The test substance was administered by gavage at a concentration of 2000 mg/kg bw to groups of five male and female Wistar rats. The animals were observed for 14 days following administration, body weights were determined weekly. No mortalities occurred during the study period. No clinical signs of toxicity, no changes in body weight and no differences at macroscopic examination were reported. The acute oral LD50 was found to be greater than 2000 mg/kg bw.

Acute Inhalation Toxicity

CAS 68855-18-5

For acute inhalation toxicity, one study is available within the NPG esters and was considered for assessment of all NPG esters and of two TMP esters and read-across was conducted based on a category and/or weight of evidence approach.

An acute inhalation toxicity study was performed with Heptanoic acid, ester with 2,2-dimethyl-1,3-propanediol (CAS 68855-18-5) according to OECD Guideline 436 (acute toxic class method) under GLP conditions. Three RccHanTM:WIST rats per sex were exposed for 4 hours to 5.22 mg/L (mean achieved concentration) test substance aerosol by nose only inhalation (Griffiths, 2012). The test concentration was chosen based on the outcome of a preliminary test with two rats at a dose of 2.14 mg/L. In the main study, the animals were subjected to daily observations for clinical signs, and twice daily for morbidity

and mortality. Body weights were determined prior to treatment and afterwards on test Days 1, 3, 7, and 14. After terminal sacrifice the animals were submitted to full external and internal observation. Detailed macroscopic examination of the respiratory tract was performed to determine signs of irritancy or local toxicity. No mortality occurred throughout the study period. Signs of hunched posture and pilo-erection were commonly seen in animals for short period on removal from the chamber following 4-h inhalation studies. Wet fur was commonly recorded both during and for a short period after exposure. These observations were considered to be associated with the restraint procedure and, in isolation, were not indicative of toxicity. In addition, an increased respiratory rate was noted in all animals. On removal from the chamber and 1 h post-exposure, all animals exhibited increased respiratory rate and ataxia. One day after exposure, all animals still showed increased respiratory rate and also hunched posture as well as occasional instances of pilo-erection. All animals recovered to appear normal from Days 5 to 8 post-exposure. All animals showed the expected body weight gain during the study, except for one female which not gained weight during the final week of the 14-day observation period. In addition, one male exhibited a slight loss in body weight on the first day of exposure. Necropsy revealed no treatment-related findings. The inhalation LC50 value in rats was determined >5.22 mg/L.

For acute inhalation toxicity, one study is available within the TMP esters. Heptanoic acid, ester with 2,2-dimethyl-1,3-propanediol (CAS 68855-18-5) and Fatty acids, C5-10, esters with pentraerythritol (CAS 68424-31-7) were used for assessment of the TMP esters and read-across was conducted based on a category approach.

CAS 78-16-0

An acute inhalation toxicity study was performed with 2-ethyl-2-[[(1-oxoheptyl)oxy]methyl] propane-1,3-diyl bisheptanoate (CAS 78-16-0). 5 male and female rats (strain not specified) were exposed for 1 hour to 20 mg/L test substance vapour (Anonimous, 1978). The test substance caused no clinical signs, body weight changes or abnormalities in necropsy during the 15 day study period. Only one animal died on day 14. The LC50 was therefore found to be greater than 20 mg/L air, however since the original report is not available and because of only one hour of exposure this study is found insufficient for hazard assessment.

For acute inhalation toxicity, three studies are available from the PE esters within the polyol esters category. Fatty acids, C5-10, esters with pentraerythritol (CAS 68424-31-7), Fatty acids, C5-9, mixed esters with dipentaerythritol and pentaerythritol (CAS 85536-35-2) and Fatty acids, C5-9 tetraesters with pentaerythritol has been investigated in rats in two studies (CAS No. 67762-53-2) were used for assessment of the PE esters and read-across was conducted based on a category and/or weight of evidence approach.

CAS 67762-53-2

The acute toxicity via the inhalation route of Fatty acids, C5-9 tetraesters with pentaerythritol has been investigated in rats in two studies (CAS 67762-53-2).

The first study was conducted comparable to OECD Guideline 403 and according to GLP. 10 male and female Sprague-Dawley rats were exposed for 4 hours to 0.48 or 4.06 mg/L test substance aerosol by whole body inhalation exposure (Mekitarin, 1990). No mortality, clinical signs, body weight changes or abnormalities in necropsy were observed during the 15 day study period in any group. The LC50 was therefore found to be greater than 4.06 mg/L.

In the second study 10 male and 5 female CD Sprague-Dawley rats were exposed for 4 hours to 5.5 mg/L test substance aerosol by nose/head only inhalation (Hoffman, 1999). No mortalities occurred during the study period. Nasal discharge was noted as the only sign of clinical toxicity. The test group females lost weight during the first week after the test material exposure, but gained weight during the second week after exposure. In all other animals no effect on body weight was noted. Necropsy examination revealed no substance-related findings. The LC50 was therefore found to be greater than 5.50 mg/L.

In summary, the LC50 of Fatty acids, C5-9 tetraesters with pentaerythritol is greater than 5.5 mg/L.

CAS 68424-31-7

An acute inhalation toxicity study was performed with Fatty acids, C5-10, esters with pentraerythritol (CAS 68424-31-7) comparable to OECD Guideline 403. 5 male and female Alpk:APfSD rats were exposed for 4 hours to 5.0 mg/L test substance aerosol by nose only inhalation (Parr-Dobrzanski, 1994). The test substance caused no mortality, body weight changes or abnormalities in necropsy during the 15 day study period. Some clinical signs were noticed, which consisted of hunched position, chromodacryorrhea, piloerection, staining around nose and wet fur. These signs however occurred during or just after exposure and were clearly consistent with the use of restraint for exposure. The LC50 was therefore found to be greater than 5.1 mg/L.

CAS 85536-35-2

An acute inhalation toxicity study was performed with Fatty acids, C5-9, mixed esters with dipentaerythritol and pentaerythritol (CAS 85536-35-2) comparable to OECD Guideline 403. 5 male and female Alpk:APfSD rats were exposed for 4 hours to 5.0 mg/L test substance aerosol by nose only inhalation (Parr-Dobrzanski, 1994). The test substance caused no mortality, body weight changes or abnormalities in necropsy during the 15 day study period. Clinical signs during and immediately after exposure included hunched posture, chromodacryorrhea, piloerection, stains around the nose and wet fur. In general, animals showed a rapid recovery from these effects by Day 2, although, hunched posture and piloerection persisted in few animals to Days 4 and 8, respectively. No effect on body weight was noted. Necropsy and histopathological examination revealed non substance-findings. The LC50 was therefore found to be greater than 5.0 mg/L.

Acute Dermal Toxicity

For acute dermal toxicity, one study is available for the NPG esters and was considered for assessment of 2,2-dimethyl-1,3-propanediyl dioleate (CAS 42222-50-4). No reliable studies on the acute dermal toxicity are available for NPG esters within the polyol esters category. In regard to the estimated low dermal absorption calculated with DERMWIN (v 2.0, 2011, see toxicokinetic chapter), dermal uptake of the sub-category members is considered as low. Therefore, dermal exposure for the NPG esters within the polyol esters category is not expected to be associated with any adverse effects on human health as dermal absorption can be considered as nearly negligible.

CAS 403507-18-6

An acute dermal toxicity (limit test) was performed on Fatty acids, C16-18 and C18-unsatd., branched and linear ester with trimethylolpropane (CAS 403507-18-6) according to OECD Guideline 402 and GLP (Sanders, 2004). 5 male and female Sprague-Dawley CD (Crl: CD IGS® BR) rats each were exposed to 2000 mg test substance /kg bw for 24 hours on the back skin under semiocclusive conditions. The observation period was 14 days. No mortality, clinical signs of systemic toxicity and changes in body weight were noted in any animal during the study period. Necropsy at study termination revealed no abnormalities. Thus, the acute dermal LD50 in rats for Fatty acids, C16-18 and C18-unsatd., branched and linear ester with trimethylolpropane was found to exceed 2000 mg/kg bw.

For acute dermal toxicity, two studies are available for the PE esters and were considered for assessment of members of PE esters within the polyol esters category and read-across was conducted based on a category and/or approach.

CAS 62125-22-8

An acute dermal toxicity test (limit test) was performed on 2,2-bis[[(1-oxoisooctadecyl)oxy]methyl]-1,3-propanediyl bis(isooctadecanoate) (CAS 62125-22-8) according to OECD Guideline 402 and GLP (Debets,

1984). 5 male and female Wistar rats each were exposed to 2000 mg test substance /kg bw for 24 hours on the back skin under occlusive conditions. The observation period was 14 days. No mortality and clinical signs of systemic toxicity were noted in any animal during the study period. Body weight gain and necropsy at study termination revealed no abnormalities. Thus, the acute dermal LD50 in rats 2,2-bis[[(1-oxoisooctadecyl)oxy]methyl]-1,3-propanediyl bis(isooctadecanoate) was found to exceed 2000 mg/kg bw.

Conclusion for acute toxicity

Several studies are available investigating the acute oral toxicity of polyol esters category members resulting in oral LD50 values greater than 2000 mg/kg bw. Five reliable studies investigating the acute inhalation toxicity within the polyol esters category are available resulting in LC50 values > 5.0 mg/L. Seven reliable acute dermal toxicity studies consistently showed no effects at the limit dose of 2000 mg/kg bw.

Thus, the available data indicate a very low level of acute toxicity for the category members and thus, no hazard for acute oral, inhalation and dermal toxicity was identified.

Data matrix for acute toxicity

CAS	Acute toxicity oral	Acute toxicity inhalation	Acute toxicity dermal
NPG esters			
68855-18-5 (a)	LD50 > 2000 mg/kg bw	LC 50 > 5.22 mg/L air	Waiver
31335-74-7	LD50 > 2000 mg/kg bw RA: CAS 68855-18-5 RA: CAS 85711-80-4	RA: CAS 68855-18-5	Waiver
67989-24-6 (b)	LD50 > 2000 mg/kg bw	--	--
85711-80-4	LD50 > 2000 mg/kg bw	--	--
70693-32-2	RA: CAS 97281-24-8	RA: CAS 68855-18-5	Waiver
former CAS 85186-86-3	RA: 85186-86-3	RA: CAS 68855-18-5	Waiver
85186-86-3	LD50 > 2000 mg/kg bw	RA: CAS 68855-18-5	Waiver
85186-95-4	RA: CAS 85711-80-4 RA: CAS 85005-25-0	RA: CAS 68855-18-5	Waiver
85116-81-0	RA: CAS 85711-80-4 RA: CAS 85005-25-0	RA: CAS 68855-18-5	Waiver
91031-27-5	RA: CAS 85711-80-4 RA: CAS 85005-25-0	RA: CAS 68855-18-5	Waiver
42222-50-4	LD 50 > 2100 mg/kg bw RA: CAS 67989-24-6	RA: CAS 68855-18-5	LD50 > 2000 mg/kg bw
85005-25-0	LD50 > 2000 mg/kg bw	RA: CAS 68855-18-5	Waiver
TMP esters			
78-16-0 (a)	LD50 > 5000 mg/kgbw	LC50 > 20 mg/L	LD50 > 2000 mg/kg bw

	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	
91050-88-3 (b)	RA: 85186-89-6	RA: CAS 68424-31-7	RA: CAS 11138-60-6
97281-24-8	LD50 > 2000 mg/kg bw	--	--
11138-60-6	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	LD50 > 2000 mg/kg bw
91050-89-4	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	RA: CAS 11138-60-6
	RA: 85186-89-6	RA: CAS 68424-31-7	RA: CAS 11138-60-6
85566-29-6	RA: 403507-18-6	RA: CAS 68855-18-5	
	RA: 91050-90-7		
(Formerly 85186-89-6)	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	RA: CAS 11138-60-6
403507-18-6	LD50 > 2000 mg/kg bw	--	LD50 > 2000 mg/kg bw
	RA: 85005-23-8	RA: CAS 68424-31-7	RA: CAS 11138-60-6
68002-79-9	RA: 403507-18-6	RA: CAS 68855-18-5	
	RA: 91050-90-7		
(Formerly 85005-23-8) EC 931-531-4	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	RA: CAS 11138-60-6
91050-90-7	LD50 > 2000 mg/kg bw	--	--
	RA: CAS 85186-89-6		
68002-78-8	RA: CAS 91050-90-7	RA: CAS 68855-18-5	RA: CAS 403507-18-6
	RA: CAS 403507-18-6		
(Formerly 57675-44-2) EC 931-461-4	LD50 > 2000 mg/kg bw	RA: CAS 68424-31-7	RA: CAS 11138-60-6
	RA: (Formerly 57675-44-2)		
85186-92-1	EC 931-461-4	RA: CAS 68424-31-7	RA: CAS 11138-60-6
	RA: (Formerly 85005-23-8)	RA: CAS 68855-18-5	RA: CAS 403507-18-6
	EC 931-531-4		
	RA: CAS 85186-89-6		
68541-50-4	RA: CAS 91050-90-7	RA: CAS 68855-18-5	RA: CAS 403507-18-6
	RA: CAS 403507-18-6		
	PE esters		
15834-04-5 (b)	RA: CAS 67762-53-2 RA:68424-31-7 RA: 85116-93-4	RA: CAS 67762-53-2 RA: CAS 68424-31-7	RA: CAS 71010-76-9
85116-93-4	LD50 > 2000 mg/kg bw	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8

	RA:68424-31-7RA: CAS 19321-40-5		
85711-45-1 (a)	RA: CAS 19321-40-5 RA: CAS 85186-89-6 RA: CAS 85116-93-4	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8
25151-96-6	RA: CAS 19321-40-5	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8
67762-53-2	LD50 > 2000 mg/kg bw	LC50 > 5.50 mg/L	RA: CAS 71010-76-9
(Formerly 68441-94-1)	RA: CAS 71010-76-9 RA: 68424-31-7 RA: 85116-93-4	RA: CAS 67762-53-2 RA: CAS 68424-31-7	RA: CAS 71010-76-9
(Formerly 68424-30-6)	RA: CAS 71010-76-9 RA: 68424-31-7 RA: 85116-93-4	RA: CAS 67762-53-2 RA: CAS 68424-31-7	RA: CAS 71010-76-9
68424-31-7 (c)	LD50 > 2000 mg/kg bw RA: CAS 67762-53-2 RA: 85116-93-4	RA: CAS 68424-31-7	RA: CAS 71010-76-9
68424-31-7 (d)	LD50 > 2000 mg/kg bw RA: CAS 67762-53-2 RA: 85116-93-4	RA: CAS 68424-31-7	RA: CAS 71010-76-9
68424-31-7 (e)	LD50 > 2000 mg/kg bw RA: CAS 67762-53-2 RA: 85116-93-4	RA: CAS 68424-31-7	RA: CAS 71010-76-9
71010-76-9	LD50 > 2000 mg/kg bw	RA: CAS 67762-53-2	LD50 > 2000 mg/kg bw
85586-24-9	LD50 > 4800 mg/kg bw RA: CAS 71010-76-9 RA: 68424-31-7	RA: CAS 67762-53-2 RA: CAS 85536-35-2 RA: CAS 67762-53-2	RA: CAS 71010-76-9 RA: CAS 71010-76-9
85049-33-8	RA: 85116-93-4 RA: CAS 85186-89-6	RA: CAS 68424-31-7	RA: CAS 62125-22-8
91050-82-7	RA: CAS 19321-40-5	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8
19321-40-5	LD50 > 2000 mg/kg bw	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8
68604-44-4	RA: CAS 19321-40-5 RA: CAS 85186-89-6	RA: CAS 67762-53-2 RA: CAS 85536-35-2	RA: CAS 62125-22-8
62125-22-8	LD50 > 5000 mg/kg bw	RA: CAS 67762-53-2 RA: CAS 85536-35-2	LD50 > 2000 mg/kg bw

68440-09-5 85536-35-2	RA: CAS 19321-40-5 RA: CAS 71010-76-9 --	RA: CAS 67762-53-2 RA: CAS 85536-35-2 LC50 > 5.0 mg/L	RA: CAS 62125-22-8 RA: CAS 71010-76-9 --

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