CATEGORY 4 - 'Rosin adduct esters'

UVCB CATEGORY JUSTIFICATION DOCUMENT

1.0 CATEGORY DEFINITION AND ITS MEMBERS

This document describes the Rosin adduct esters category and its members as per ECHA guidance R6: QSARs and grouping of chemicals (2008) the ECHA Read-Across Assessment Framework[1] and the specific guidance for UVCBs[2]. Although this format is more applicable to analogue or chemical categories the main headings of the guidance are included for this UVCB category to ensure consistency in reporting.

Table 1: Category UVCB Members

CAS Number	EC Number	Registered Substance Name
92202-14-7	296-047-1	Rosin, fumarated, reaction products with glycerol and pentaerythritol
94581-15-4	305-514-1	Resin acids and Rosin acids, fumarated, esters with pentaerythritol
94581-17-6	305-516-2	Resin acids and Rosin acids, maleated, esters with pentaerythritol-
97489-11-7	307-051-0	Resin acids and Rosin acids, fumarated, esters with glycerol
94581-16-5	305-515-7	Rosin acids and resin acids, maleated, esters with glycerol

1.1 Category Definition

1.1.1 Category Hypothesis

Rosin Adduct Esters are UVCB substances produced by the reaction of resin acids present in rosin with fumaric acid or anhydride maleic followed by esterification with glycerol and/or pentaerythritol. They comprise a group of close structural analogues and are expected to have similar intrinsic toxicological and environmental properties.

1.1.1.1 Brief Manufacturing Process Description

Rosin Adduct Esters are formed when rosin is reacted with maleic anhydride (or maleic acid) or fumaric acid yielding a maleated rosin adduct or a fumarated rosin adduct, respectively, followed by esterification with glycerol or pentaerythritol or a combination of glycerol and pentaerythritol. The adducts are formed via a Diels-Alder reaction in which the single carboxylic acid rosin is converted to a rosin derivative with three carboxylic acid groups following reaction with fumaric acid or maleic anhydride/acid.

1.1.2 Applicability domain (AD) of the category

The chemistry of Rosin and its derivatives is highly complex. H4R has produced a reference document on analytical aspects. It also provides an insight into this chemistry. A copy is also given in the registration dossier.

[1] https://echa.europa.eu/documents/10162/13628/raaf_en.pdf
[2] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

Table 2: Category Constituents

Constituent Types		Rosin, fumarated, reaction products with glycerol and pentaerythritol	Resin acids and Rosin acids, fumarated, esters with pentaerythritol	Resin-acids-and- Rosin-acids,-maleated,-esters-with-pentaerythritol-	Resin acids and Rosin acids, fumarated, esters with glycerol	Rosin acids and resin acids, maleated, esters with glycerol	Category Boundary Conditions
		Typical Range %					
Ester	Mono		<2				0-2
	Di		<5				0-5
	Tri		25				0-25
	Tetra		33				0-33
	Poly		35				0-35
Total Ester		35-99	20-97	<30	60-70	10 -99	0-99
Fumaro-pimaric acid		0-30	0-24	1 - 5	3- 25	0 -25	0-30
Maleo-pimaric acid				1 - 5			0-5
Maleo-pimaric acid anhydride				1 -15			0-15
Non-reacted Acids		0-60	2 -65	30-60	15-20	1 -60	0-65
Fatty Acids				0-5		0 - 5	0-5
Neutral fraction		0-5	0-5	1 -5	0-5	0 - 5	0-5

1.2 Purity / Impurities

The substances in this category are UVCBs and as such are considered to be 100% pure. The term impurity is not relevant for UVCBs. Often, substances will be described by known constituents present at 10% or greater identified by IUPAC name and EC number/CAS number, indicating typical concentrations and/or concentration ranges. However, there are no individual constituents at concentrations > 10%. Consequently, these substances are characterised by their constituent types.

1.2.1 Substances with CLP Implications

None of the members of Category 4 are classified for reproductive or developmental toxicity or for Specific Target Organ Toxicity, repeated exposure (STOT-RE) according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008 or UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Category 4 Rosin Adduct Esters are classified according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008 as:

- "Skin Sensitiser Category 1" and assigns the hazard statement H317: May cause an allergic skin reaction.
- "Eye Irritant Category 2" and assigns the hazard statement H319: May cause serious eye irritation.
- "Aquatic Chronic 4" and assigns the hazard statement H413: May cause long lasting harmful effects to aquatic life.

1.2.2 Toxicity Classification Overview

The sensitisation potential of the substances included in this category is well understood and is based upon the results from six local lymph node assays and a guinea pig maximisation test. The LLNA results indicate that members of Category 4 have a moderate potential to cause skin sensitisation. Results obtained from a guinea pig maximisation test indicated that Resin acids and rosin acids,

fumarated esters with pentaerythritol was not a skin sensitiser. Although some anomalous results were obtained, the overall weight of evidence suggests that the members of Category 4 have a moderate potential to cause skin sensitisation.

The ocular irritancy of two members of Category 4 (Resin acids and rosin acids, fumarated, esters with glycerol; Resin acids and rosin acids, maleated, esters with pentaerythritol) was determined in primary eye irritation studies with rabbits. All treated eyes were normal by the 7-day examinations. Based on the scoring and classification system used in these studies, these Category 4 substances were irritating to rabbit eyes and classified for eye irritation according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008 and UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Eye Irritation Category 2.

2.0 CATEGORY JUSTIFICATION

2.1 Composition

See Table 2.

2.2 Physico-Chemical

All the substances in this category are solids at ambient temperature, with similar densities and low vapor pressures. Melting points are in a similar range (72.4 – 145°C) and all substances decompose before boiling. Solubility and partition coefficient values are likely to be similar for individual constituents within the UVCB substances, however, as the proportion of different constituents varies between category members measured results for the whole substances are variable.

Table 3: Phys-chem data for Category Members of Rosin adduct esters

Registered Substance Name and CAS	Physical state	Melting point (°C)	Boling point (°C)	Density (kg/m3)	Vapour pressure (mbar)	Partition coeffcient (log Pow)	Water Solubility (mg/L)
Rosin, fumarated, reaction products with glycerol and pentaerythritol (92202-14-7)	Solid	72.4 - 77.2	ca 225 (decomposition temperature)	1,039 (at 25 °C)	0.07 (at 20 °C)	4.58	10
Resin acids and Rosin acids, fumarated, esters with pentaerythritol (94581-15-4)	Solid	86.4 - 126.9	163 (decomposition temperature)	1,065 (at 20 °C)	<1	3.41	≤1
Resin-acids-and-Rosin-acids,-maleated,-esters-with-pentaerythritol-(94581-17-6)	Solid	80 – 87	ca 138 (decomposition temperature)	1, 120 (at 21.6°C)	0.0000043	4.39 - >6.5	19.3 Loading 1,000
Resin acids and Rosin acids, fumarated, esters with glycerol (97489-11-7)	Solid	145	283 (decomposition temperature)	1,170 (at 21.6°C)	0.0000068 (at 25°C)	2.44 - > 6.5	1.37
Resin acids and Rosin acids, maleated, esters with glycerol (94581-16-5)	Solid	Tg around 70°C (Tg: Glass transition)	no vaporization and no decomposition up to 300°C	1.01 Kg/m3	0.2273 Pa	> 6.5	$1.00x10^{-9}$ @20°C

2.3 Environmental

Ready biodegradation studies have been conducted for the following members of the rosin adduct esters category: Rosin, fumarated, reaction products with glycerol and pentaerythritol and Resin acids and rosin acids, fumarated esters with pentaerythritol. Members of this category have not been shown to be readily biodegradable in biodegradation screening tests.

QSAR predictions conducted with Episuite's BIOWIN model show that di- and tri- adduct ester constituents screen as potentially persistent (BIOWIN 3 value <2.2 and BIOWIN 6 or BIOWIN 2 <0.5). Tetra-ester constituents are also considered to be potentially P, but these constituents could not be run through the model due to issues processing the SMILES notation. In addition, the tetra-ester constituents are outside the model domain.

Mono-ester constituents do not screen as persistent based on BIOWIN results. Resin acids are the main components of rosin (>85%) and based on measured ready biodegradation studies with rosin these constituents are considered to be readily biodegradable and not persistent.

No measured bioaccumulation data is available for rosin adduct ester substances. Measured Kow values are available for all members of this category, however, results are variable due to the difficulties with testing these substances, with log Kow values ranging from 2.44 - >6.5. The wide range of measured Kow values are considered to reflect the differences in partitioning behavior between constituents.

Based on QSAR predictions using Episuite's KOWWIN and BCFBAF models (regression-based estimates), di- and tri- ester constituents are not considered to be bioaccumulative as their large molecular size and very high predicted log Kow values (9.82 – 16.51) mean that these constituents are unlikely to be taken up by organisms. Predicted BCF values are therefore low (3.16 L/kg ww, log BCF 0.5, regression-based estimate). Structures for tetra-ester constituents could not be run through the model, but as these constituents have an even larger molecular size than the di-esters they are also unlikely to bioaccumulate.

Mono-ester constituents are considered to be potentially bioaccumulative based on predicted log Kow values (log Kow 3.75 – 4.23), although predicted BCF values for these constituents are still low (3.16 L/kg ww, log BCF 0.5, regression-based estimate). Resin acid constituents are also present in rosin adduct esters and these are not bioaccumulative based on measured data for fish, with BCF values between <25 and 130 (Niimi and Lee 1992) and for mussels, with BCF values between 110 and 330 L/kg (Burggraaf et al. 1996).

Measured toxicity data are available for *Daphnia magna* for all category members (Laus 2013a, Laus 2013b, Harlan Laboratories 2010a, Harlan Laboratories 2010b, Water Quality Institute 1993) for algae for resin acids and rosin acids, fumarated esters with glycerol and resin acids and rosin acids, maleated esters with pentaerythritol (Laus 2013a, Laus 2013b, Water Quality Institute 1993) and for fish for resin acids and rosin acids, maleated, esters with pentaerythritol (Water Quality Institute 1993). In all studies the EL50 value was determined to be above the highest concentration tested.

2.4 Mammalian Toxicology

Based on similarity in structure and molecular weight (>500), these substances are expected to be poorly absorbed and relatively non-hazardous with regulatory classifications limited to eye irritation and dermal sensitisation potential. This assumption is supported by results from toxicological testing which demonstrated that Rosin Adduct Esters are not acutely toxicity via ingestion and demonstrate limited uptake from the gastrointestinal tract following oral administration to rats. They are not irritating to the skin and produce moderate reversible eye irritation. Results of *in vitro* genotoxicity testing revealed no mutagenic activity in microbial or mammalian cells, both in the absence and presence of exogenous metabolic activation. Results of 90- and 28-day repeated dose studies, developmental toxicity studies and screening reproductive toxicity studies provided no data to trigger reproductive, developmental or specific target organ toxicity classifications.

3.0 CONCLUSIONS FOR CLASSIFICATION & LABELLING, PBT/vPvB

3.1 Classification & Labelling

3.1.1 Physico-chemical Hazard Assessment

There are no hazardous properties.

3.1.2 Human Health Hazard Assessment

Mammalian toxicity will be influenced by the degree to which the Rosin Adduct Esters are capable of being absorbed via the appropriate route of exposure. The high molecular weights coupled with log Kow values of approx. 4 suggest that these substances have limited absorption potential.

Based on similarity in structure and molecular weight (>500), these substances are expected to be poorly absorbed and relatively non-hazardous with regulatory classifications limited to eye irritation and dermal sensitisation potential. This assumption is supported by results from toxicological testing which demonstrated that Rosin Adduct Esters are not acutely toxicity via ingestion and demonstrate limited uptake from the gastrointestinal tract following oral administration to rats. They are not irritating to the skin and produce moderate reversible eye irritation. Results of *in vitro* genotoxicity testing revealed no mutagenic activity in microbial or mammalian cells, both in the absence and presence of exogenous metabolic activation. However, Rosin Adduct Esters are classified as dermal sensitisers based on positive findings in several LLNA assays and as eye irritants based on findings in two primary eye irritation studies with rabbits.

Information exists to characterise the repeated dose toxicity of Rosin adduct esters, which are formed after modification of rosin with either fumaric acid or maleic anhydride followed by esterification with glycerol and/or pentaerythritol, and hence the adduct ester products exhibit close structural similarities. The available data includes results from three 90-Day dietary OECD 408 studies with Category 4 members: Resin acids and rosin acids, fumarated, esters with glycerol; Resin acids and rosin acids, fumarated, esters with pentaerythritol; and Resin acids and rosin acids, maleated, esters with pentaerythritol. The NOAEL of Resin acids and rosin acids, fumarated, esters with glycerol was 18000 ppm for female rats and 7500 ppm for male rats; the NOAEL of Resin acids and Rosin acids, fumarated, esters with pentaerythritol was 18000 ppm for both sexes and the NOAEL for Resin acids and rosin acids, maleated, esters with pentaerythritol was 3000 ppm. None of the observations from these 90 day studies triggered STOT RE-1 or STOT-RE-2 classifications.

Adequate information is also available to characterise the reproductive toxicity of Rosin adduct esters. This includes results obtained from OECD 422 studies with Resin acids and rosin acids, maleated, esters with pentaerythritol; Resin acids and rosin acids, fumarated, esters with glycerol; and Resin acids and rosin acids, fumarated, esters with pentaerythritol. The developmental toxicity of Category 4 was also assessed in an OECD 414 study with Resin acids and Rosin acids, fumarated esters with Glycerol. None of the reproductive or developmental toxicity studies with Cat 4 members provided data to trigger a reproductive toxicity classification.

3.1.3 Environmental Hazard Assessment

No effects were observed at the highest loading rate tested in any of the acute toxicity studies for fish, *Daphnia magna* or algae. Substances in this category would not therefore be classified for acute environmental hazards. However, as these substances are of low solubility, are not readily biodegradable and have log Kow values of >4. a "safety net" classification of Chronic Category 4 is assigned to substances in this category.

3.2 Conclusion for PBT / vPVB

Members of the category rosin adduct esters are not considered to be PBT or vPvB.

Whole substance screening level data are available for the assessment of biodegradation and bioaccumulation for rosin adduct esters. However, assessing the substances as a whole is not considered to be the most appropriate method for assessing the PBT potential of complex UVCB substances such as these, as different constituents will have different environmental fate properties.

Assessing rosin adduct esters based on constituents within the UVCBs using QSAR predictions:

- Mono adduct esters are considered to be not P but potentially B and therefore not PBT or vPvB.
- Di-, tri- and tetra- adduct ester constituents are potentially P but not B and therefore not PBT or vPvB.
- Free resin acids are not P or B.

Measured toxicity data are available for *Daphnia magna* for all category members, for algae for resin acids and rosin acids, fumarated esters with glycerol and resin acids and rosin acids, maleated esters with pentaerythritol and for fish for resin acids and rosin acids, maleated, esters with pentaerythritol. In all studies the EL50 value was determined to be above the highest concentration tested.

None of the substances included in H4R Category 4 are classified as carcinogenic (cat. 1A or 1B), germ cell mutagenic (cat. 1A or 1B), toxic to reproduction (cat. 1A, 1B or 2), STOT RE 1, or STOT RE 2.

Based on whole substance data none of the substances in the category are T. Therefore, none of the constituents in rosin adduct ester substances are PBT or vPvB.

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