CATEGORY 3 - 'Rosin Adducts and Rosin Adducts Salts'

UVCB CATEGORY JUSTIFICATION DOCUMENT

1.0 CATEGORY DEFINITION AND ITS MEMBERS

This document describes the Rosin Adducts and Rosin Adducts Salts 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
65997-04-8	266-040-8	Rosin, fumarated
68201-60-5	269-228-8	Resin acids and Rosin acids, maleated, sodium salts
8050-28-0	232-480-4	Rosin, maleated
91722-01-9	294-402-5	Resin acids and Rosin acids, maleated, calcium salts
85409-27-4	287-094-9	Resin acids and Rosin acids, maleated, potassium salts

1.1 Category Definition

1.1.1 Category Hypothesis

The Rosin Adducts category includes rosins or rosin salts that have been chemically reacted with fumaric acid or maleic anhydride(MA).

1.1.1.1 Brief Manufacturing Process Description and Chemistry of adducted rosin

Rosin is a UVCB derived from wood. Rosin and rosin derivatives consists of gum rosin, wood rosin and tall oil rosin while rosin derivatives include hydrogenated rosin and polymerized rosin (also referred to as dimerized rosin or rosin oligomers).

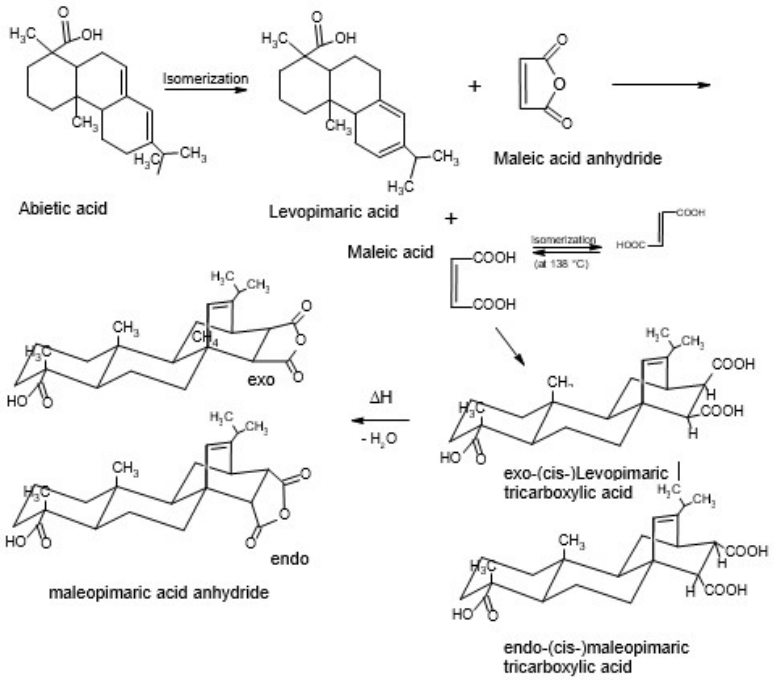
The Diels-Alder reaction involves reaction of an α,ß-unsaturated carbonyl compound, such as maleic anhydride, maleic acid or fumaric acid, with a conjugated double bond; it therefore occurs only with resin acids such as levopimaric acid. However, even under the most favourable of reaction conditions, the majority of the resin acid molecules present in rosin remain unadducted simply because they are unable to undergo this reaction due to their structure.

[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

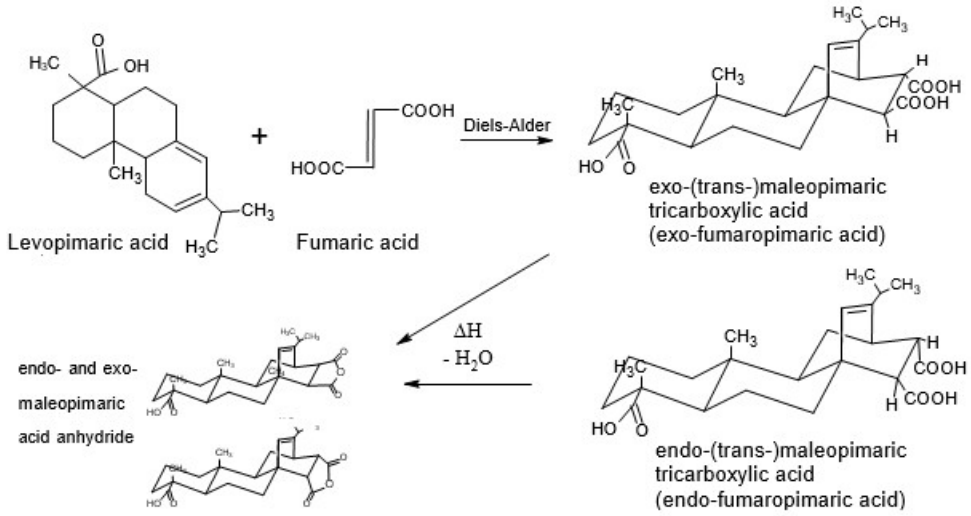
1: Reaction with maleic acid anhydride or maleic acid (Soltes and Zinkel, 1989)

The Diels-Alder reaction of levopimaric acid with maleic anhydride or maleic acid results in the formation of maleopimaric anhydride or acid and the (cis-) maleopimaric tricarboxylic acid. The reaction is highly quantitative. The tricarboxylic form is unstable, readily dehydrating to the anhydride.



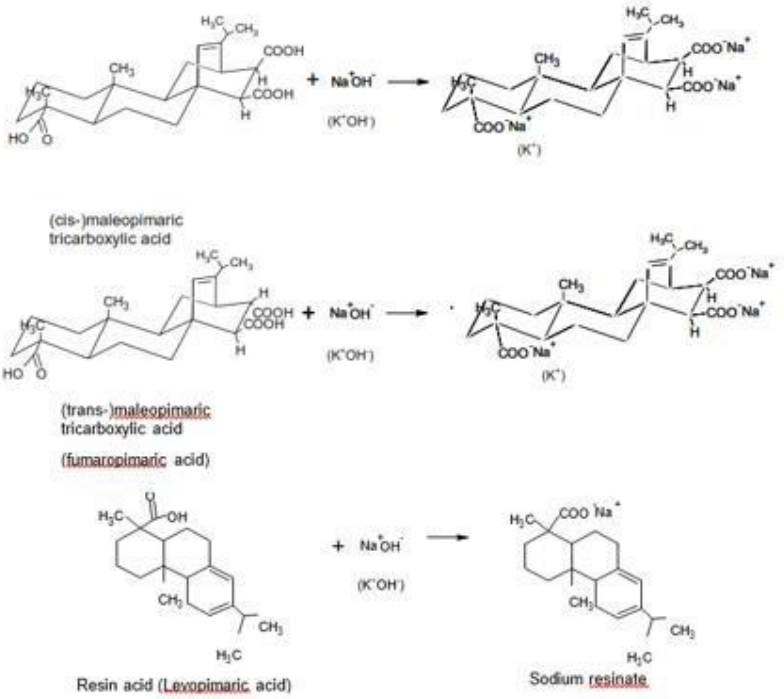
2: Reaction with fumaric acid (Soltes and Zinkel, 1989)

The Diels-Alder reaction of levopimaric acid with fumaric acid results in the formation of fumaropimaric tricarboxylic acid (the trans-maleopimaric tricarboxylic acid) and maleopimaric acid anhydride. The reaction is highly quantitative.



3: Rosin adduct salts (Soltes and Zinkel, 1989)

The sodium, potassium and calcium salts are produced by the reaction of maleated/fumarated rosin with NaOH, KOH or Ca(OH)2. The underlying chemistry is illustrated below for the monovalent salts.



1.1.2. Applicability domain (AD) of the category

This category applies to rosins or rosin salts that have been chemically reacted with either fumaric acid or maleic anhydride.

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.

Table 2: Category Constituents

Constituent Types	Rosin, fumarated	Resin acids and Rosin acids, maleated, sodium salts	Rosin, maleated	Resin acids and Rosin acids, maleated, calcium salts	Resin acids and Rosin acids, maleated, potassium salts	Category Boundary Conditions
	Typical Range %					
Fumaro-pimaric acid	5 - 24	1 – 24	1 - 5	>0-24	1- 24	**0-24**
Maleo-pimaric acid	1 - 10	1 – 24	1 - 18	>0-24	1 -24	**0-24**
Maleo-pimaric anhydride	1 - 30	1 - 10	1 - 25	0-<5	0 -10	**0-30**
Non-reacted-Acids	35-85	35-85	35 - 85	70-95	35 -85	**35-95**
Fatty acids	0-5	0-5	0-5	0-5	0 -5	**0-5**
Neutral fraction	1 - 5	1 - 09	1 - 05	1 - 5	1 - 9	**1 -10**

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 characterized by their constituent types.

1.2.1 Substances with CLP Implications

None of the members of Category 3 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 3 Rosin Adduct and Rosin Adduct Salts 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 1" and assigns the hazard statement H318: Causes serious eye damage.

For environmental endpoints rosin maleated and resin and rosin acids, maleated sodium salts are classified as Aquatic Chronic Category 2. Resin acids and rosin acids, maleated, calcium salts and rosin fumarated are classified as Aquatic Chronic Category 4. Note that classifications are completed based on data for the substance itself rather than using read-across.

1.2.2 Toxicity Classification Overview

Adequate information exists to characterise the skin sensitisation and eye irritation potential of Rosin Adducts and Rosin Adducts Salts.

Eye irritation

The eye irritation potential of Rosin, fumarated was evaluated after instillation of 0.1 g into the eye of one New Zealand White rabbit (Life Science Research, 1991c). The animal was observed and then terminated 5 hours after application. After 5 hours, the substance was found to be a severe eye irritant, and further testing was therefore not warranted.

Skin sensitisation

The data available to characterise the skin sensitisation potential of Rosin Adducts and Rosin Adducts Salts includes:

- Three Local Lymph Node Assays (LLNA, OECD 429) in mice with Rosin, fumarated, Rosin, maleated and Rosin, fumarated, reaction products with formaldehyde
- One Guinea Pig Maximisation Test with Rosin, maleated
- One Guinea Pig Buehler assay with Rosin, maleated

Based on the LLNA (OECD 429) results, Rosin, fumarated, Rosin, maleated and Rosin, fumarated, reaction products with formaldehyde were considered to be a skin sensitizer in mice and Rosin, maleated Rosin, maleated was a skin sensitizer in the guinea pig in both the Buehler and GPMT assays.

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 vapour pressures. 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 Adducts and Rosin Adducts Salts

Substance / CAS No.	Physical state	Melting point (°C)	Boiling point (°C)	Density (kg/m3)	Vapour pressure (mbar)	Partition coefficient (log Pow)	Water Solubility (g/l)
Rosin, fumarated (65997-04-8)	Solid	75.8-82.4	215 (decomposition temperature)	1,029 (at 20°C)	0.03 (at 20°C)	2.8 - 7	9
Resin acids and Rosin acids, maleated, sodium salts (68201-60-5)	Solid (Paste)	Gradually softens from a sticky solid to a viscous liquid, but it was not possible to determine a melting point.	>400	1,250 (at 23°C)	<0.00097 (at 25°C)	3.42 - >6.5	Expressed as Percentage Loading rate:50% w/w Loading 10,000; 47% w/w Loading 1,000
Rosin, maleated (8050-28-0)	Solid	95.9 - 115.5	> 300	1117 (at 20°C)	0.04 (at 20°C)	1.5 – 7.6	1.38
Resin acids and Rosin acids, maleated, calcium salts (91722-01-9)	Solid	From 120 °C - Fused from a powder to a sticky, immobile solid and on further heating continued gradually to a viscous fluid	ca 313 (decomposition temperature	1,130(21.4°C	0.00022(at 25°C	4.69 –5.84	55.8 Loading 10,00015.8 Loading 1,000
Resin acids and Rosin acids, maleated, potassium salts (CAS 85409-27-4)	Solid (paste)	NA (1)	NA (1)	NA (1)	<0.000097 Pa at 25°C(2)	1.4 to >6 (7.9) in media adjusted to pH 2.	Mutually miscible with water at ambient laboratory temperature (21.1°C).

(1) The study will be available 27/06/2018
(2) RA CAS 68201-60-5

2.3 Environmental

Ready biodegradation studies have been conducted for the following members of the rosin adduct and rosin adduct salts category: Rosin maleated and rosin fumarated. Members of this category have not been shown to be readily biodegradable in biodegradation screening tests. The structural differences between maleated and fumarated category members are not considered to affect biodegradation potential and it is considered to be appropriate to read across biodegradation data between all members of the category.

Bioaccumulation studies have not been conducted for any category member due to the analytical difficulties with conducting such a study with UVCB substances containing constituents with differing, and often low, solubility. 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 1.5 - >6.5. The wide range of measured Kow values are considered to reflect the differences in partitioning behaviour between constituents.

The available ecotoxicity results indicate that there may be differences in environmental toxicity between substances reacted with fumaric acid and substances reacted with maleic anhydride. For Rosin fumarated no effects were observed at the highest loading rate tested in any of the acute toxicity studies.

The ecotoxicity of maleated substances is affected by the solubility of the test item, with more soluble substances rosin, maleated (lowest EC50 value 9.3 mg/L for fish) and resin acids and rosin acids, maleated sodium salts (lowest EC50 from these studies is 4.8 mg/L for fish) showing higher aquatic toxicity compared to the poorly soluble substance resin acids and rosin acids, maleated calcium salts (no effects were observed at the highest loading rate tested in any of the acute toxicity studies).

2.4 Mammalian Toxicology

Mammalian toxicity will be influenced by the degree to which the Rosin Adducts are capable of being adsorbed via the appropriate route of exposure. The high molecular weights (~418) coupled with a low log Kow (values range from 0.4 to 7.6) suggest that these substances will have limited absorption potential.

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

Based on the similar structures and molecular weights of category members, these materials 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 Adducts are not acutely toxicity via ingestion and demonstrate limited uptake from the gastrointestinal tract following oral administration to rats. Results of *in vitro* genotoxicity testing reveal no activity in microbial or mammalian cells in the absence or presence of exogenous metabolic activation. However, Rosin Adducts are classified as eye irritants and dermal sensitisers based on experimental data obtained for Rosin, fumarated, Rosin, maleated and Rosin, fumarated, reaction products with formaldehyde.

The systemic toxicity of the Rosin Adducts and Rosin Adducts Salts category was evaluated in two 90 day (OECD 408) oral dietary studies with Rosin maleated and Rosin fumarated, two OECD 422 combined repeated dose, reproductive/developmental toxicity screening studies with Rosin maleated and Rosin fumarated and an OECD 414 developmental toxicity study with Rosin maleated. The lowest NOAEL for systemic effects from all of these studies was 1500 ppm (equivalent to a mean dosages of 99.5 and 120.4 mg/Kg bw/day for males and females, respectively), obtained from the OECD 408 study with Rosin, maleated, and was based on reduced bodyweight gains and food consumption and adverse histopathological changes in the urinary bladder of both sexes exposed to a dietary concentration of 3000 ppm of Rosin, maleated. In comparison, the NOAEL for systemic effects in the OECD 408 study with Rosin, fumarated was considered to be 10000 ppm, the highest dietary exposure level in both sexes (equivalent to 704.6 mg/kg bw/day for males and 843.4 mg/kg bw/day for females). None of the NOAELs for systemic effects observed in these studies triggered classifications 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).

However, in view of the substantial difference in the NOAELs for systemic toxicity and the types of effects observed in the OECD 408 studies with Rosin fumarated and Rosin maleated, the H4R Consortium considered that the proviso noted in ECHA's final decision letter of August 14 2014 (Decision number TPE-D0000004371-81-07/F) was satisfied (proviso was that: "*An additional pre- natal developmental toxicity study will be proposed by the Registrant for the substance subject to this decision if the results from the proposed sub-chronic toxicity (90 days; OECD Guideline 408) studies or available/on-going combined repeated dose toxicity study with the reproduction/developmental toxicity screening (OECD Guideline 422) studies on this substance indicate differences in toxicity relative to Rosin, maleated (CAS No. 8050-28-0)*"). Consequently, the H4R Consortium informed ECHA on June 26 2017 that an OECD 414 study with Rosin, fumarated was initiated at Envigo's Barcelona, Spain laboratory. The study has now started and the final report is expected by Q4 2017. This was acknowledged by ECHA in their communication to H4R of July 3 2017.

The results from the OECD 414 study with Rosin, maleated demonstrated that developmental effects occurred at dietary concentrations below those that produced systemic toxicity in the parental animals. However, it should be noted that this study was performed with Rosin, maleated containing
20 parts of MA (16.7% w/w in terms of raw material balance), and the SIP (Substance Identity Profile) for Rosin, maleated has since changed from Rosin, maleated 20 parts MA to Rosin, maleated 10 parts MA. H4R members do not consider that the OECD 414 study conducted with Rosin, maleated 20 parts MA accurately reflect the developmental toxicity hazards of Rosin, maleated 10 parts MA, which reflects the composition of products on the market. Consequently, on July 11 2017, H4R submitted an additional testing proposal to ECHA for an OECD 414 study to be conducted with Rosin, maleated 10 parts MA. This testing proposal is pending review and approval by ECHA.

3.1.3 Environmental Hazard Assessment

The available ecotoxicity results indicate that there may be differences in environmental toxicity between substances reacted with fumaric acid and substances reacted with maleic anhydride.

The ecotoxicity of maleated substances is affected by the solubility of the test item, with more soluble substances rosin, maleated and resin acids and rosin acids, maleated sodium salts showing higher aquatic toxicity compared to the poorly soluble substance resin acids and rosin acids, maleated calcium salts.

Therefore, environmental classification of this category is completed based on data for the substance itself rather.

Acute fish, *Daphnia magna* and algal studies are available for fumarated substances in this category. The EL50 values from these studies are all >100 mg/L. However, as substances in this category 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 rosin fumarated.

Two acute *Daphnia magna* studies and one acute fish study are available for rosin, maleated. The lowest EC50 value for this substance is 9.3 mg/L. As this result is >1 mg/L an acute environmental classification is not appropriate for this substance. However, a chronic category 2 classification is assigned to this substance as it is not readily biodegradable and has an EC50 value between 1 and 10 mg/L.

Acute fish, *Daphnia magna* and algal studies are available for resin acids and rosin acids, maleated, sodium salts. The lowest EC50 from these studies is 4.8 mg/L, for fish. As this result is >1 mg/L an acute environmental classification is not appropriate for this substance. However, a Chronic category 2 classification is assigned to this substance as it is not considered to be readily biodegradable and has an EC50 value between 1 and 10 mg/L.

No effects were observed at the highest loading rate tested in any of the acute toxicity studies for fish, *Daphnia magna* or algae for Resin acids and rosin acids, maleated calcium salts. However, as the substance is of low solubility, is not readily biodegradable and has a log Kow values of >4. a "safety net" classification of Chronic Category 4 is assigned to resin acids and rosin acids, maleated, calcium salts.

3.2 Conclusion for PBT/vPVB

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

A PACT assessment was published by the Finnish Competent Authority, Tukes, which carried out a PBT assessment for rosin, maleated (Tukes 2015). The assessment includes information on both maleopimaric acid / anhydride and fumaropimaric acid and therefore the assessment is relevant for both fumarated and maleated substances within this category. The PACT assessment reviewed both measured data and conducted QSAR predictions for representative constituents.

QSAR predictions conducted using Episuite's BIOWIN model for constituents maleopimaric acid / anhydride and fumaropimaric acid indicate the persistence criteria may be met, and the substance is potentially persistent (P).

For bioaccumulation, the PACT assessment reports predicted logD (pH specific log Kow values) and these indicate that at environmentally relevant pH, log Kow values for these constituents are <4.5. Predicted log BCFs are also low. The PACT assessment concludes that rosin, maleated is not bioaccumulative (B) or very bioaccumulative (vB) and this conclusion is considered to be appropriate for other category members as well.

The PACT assessment concludes that rosin, maleated is not toxic (T), based on measured data from studies conducted with the whole substance and Ecosar predictions for maleopimaric acid/anhydride. The lowest acute ecotoxicity result is a 96-hour EC50 of 4.8 mg/L for fish exposed to resin acids and rosin acids, maleated, sodium salts. This result also supports that members of this category are not T.

None of the substances included in H4R Category 3 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.

The assessment concluded that "*…the substance is not considered to meet the PBT/vPvB criteria based on the available, mainly screening level, information. This conclusion covers the relevant constituents*."

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