Justification for the selection of a candidate CoRAP substance

Substance Name (Public Name):	Succinic anhydride
Chemical Group:	
EC Number:	203-570-0
CAS Number:	108-30-5
Submitted by:	Environment Agency Austria on behalf of the Austrian Competent Authority (Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management)
Published:	20/03/2013

Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

Contents

1 IDENTITY OF THE SUBSTANCE

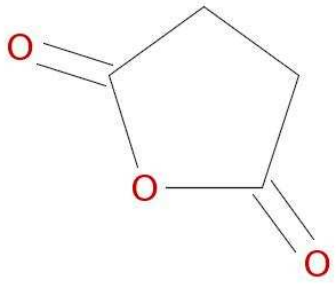
1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	Succinic anhydride
EC number:	203-570-0
EC name:	Succinic anhydride
CAS number (in the EC inventory):	108-30-5
CAS number:	108-30-5
CAS name:	Butanedioic anhydride
IUPAC name:	Oxolane-2,5-dione
Index number in Annex VI of the CLP Regulation	607-103-00-5
Molecular formula:	C4H4O3
Molecular weight or molecular weight range:	100.07
Synonyms:	---

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



2 CLASSIFICATION AND LABELLING

2.1 Harmonised Classification in Annex VI of the CLP

Table 2: Classification according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 (1st ATP, Commission Regulation (EC) No 790/2009)

International Chemical Identification	EC No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
		Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
succinic anhydride	203-570-0	Acute Tox. 4 * Eye Irrit. 2 STOT SE 3	H302 H319 H335	GHS07 Wng	H302 H319 H335		* Eye Irrit. 2; H319: C ≥ 1 % STOT SE 3; H335: C ≥ 1 %	

H302 Harmful if swallowed; H319 Causes serious eye irritation; H335 May cause respiratory irritation

Table 3: Classification according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 (1st ATP, Commission Regulation (EC) No 790/2009

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
607-103-00-5	succinic anhydride	203-570-0	108-30-5	Xn; R22 Xi; R36/37	Xn R: 22-36/37 S: (2-)25-46	Xn; R22: C ≥ 5 % Xi; R36/37: C ≥ 1 %	

R22: Harmful if swallowed; R36/37: Irritating to eyes and respiratory system.

2.2 Proposal for Harmonised Classification in Annex VI of the CLP

None proposed.

2.3 Self classification

In the registration data the following self classification in addition to the harmonized classification is given:

Resp. sens 1 H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.
Skin sens 1 H317 May cause an allergic skin reaction.

C&L inventory additionally includes the following classification: Acute Tox. 3 (H301).

3 JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

3.1 Legal basis for the proposal

☒ Article 44(1) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

3.2 Grounds for concern

☒ (Suspected) CMR	☐ Wide dispersive use	☐ Cumulative exposure
☒ (Suspected) Sensitiser	☐ Consumer use	☒ High RCR
☐ (Suspected) PBT	☐ Exposure of sensitive populations	☒ Aggregated tonnage
☐ Suspected endocrine disruptor	☐ Other (provide further details below)	

The substance Succinic Anhydride (SA) was screened by experts of the Belgian CA. The following grounds for concern are based on the findings of the Belgian CA and extended by findings of the Austrian CA:

Hazard:

SA has a harmonized classification for acute toxicity category 4 (oral), eye irritation and respiratory tract irritation. SA was self-classified for skin and respiratory sensitization on the basis of read-across from maleic anhydride (MA).

The toxicity database for SA is incomplete. It was attempted to close these data gaps by applying read-across from the structurally related substance maleic anhydride (MA) and other cyclic anhydrides for several endpoints. In general this read-across is insufficiently justified.

a) <u>Toxicokinetics</u>

It could be helpful to have a good description of toxicokinetics and why read-across from phthalic anhydride (PA) and hexhydrophthalic anhydride (HPA) is relevant to also assess toxicokinetics of SA. Further the cited toxicokinetic studies on PA and HPA should be presented in more detail. Referring to these data the registrant concluded that SA is expected to show low systemic availability. This is, however, in contrast to the toxicokinetic behavior of MA when referring to the CSR of MA (MA is distributed throughout the body).

Dermal absorption data are only available for HPA from 5 human volunteers. On the basis of these data a value of 5% is derived for dermal absorption of SA. This value has to be further substantiated. Dermal absorption should also be considered in relation to the irritant properties of the substance (damaged skin can be penetrated more easily than intact skin).

b) <u>Acute toxicity:</u>

One oral acute toxicity test is available. According to Annex VIII of REACH a second route should be tested.

It has to be checked whether it is really feasible to waive inhalation testing ➔ justification is based on not inhalable/respirable particles; this has to be demonstrated by appropriate data on particle distribution, further it might be possible that the substance enters the gaseous phase depending on its vapour pressure ➔ Regarding this option, the given vapour pressure in the dossier appears to be too low. This could be a reason, why gaseous release was disregarded. Significantly higher vapour pressures can be found in literature and are also predicted by QSAR-models like MPBPWIN (Episuite v.4.1). Besides, elevated process temperatures for some uses are considered to be possible/likely (resulting in higher vapour pressures e.g. 1.2hPa at 92°C(found in literature)), as the processes and the temperatures were not specified in detail

Justification to waive a dermal acute toxicity study is insufficient and the value of 5% for dermal absorption is not sufficiently justified (see above).

c) Irritation:

In the registration dossier it is stated that read-across from MA was applied for this endpoint. SA has a harmonized classification for Eye irritation and STOT SE 3 (respiratory tract irritation). Data supporting this classification should be presented.

Therefore the data which were the basis for the harmonized classification should be identified and presented.

d) Sensitisation:

Read-across from MA and other cyclic anhydrides is supported by a positive LLNA with SA and by the structural similarity to the group of cyclic anhydrides, both for respiratory and skin sensitization. It is stated that the LLNA study for SA is of insufficient quality to derive a quantitative DNEL. On the basis of data from other cyclic anhydrides it is not possible to derive a quantitative DNEL for SA. A qualitative risk assessment should therefore be carried out for the sensitizing properties of SA.

e) Repeated dose toxicity:

Only one oral 13 wk study for SA is available. Route-to-route (RTR) extrapolation to dermal & inhalation route is proposed. For systemic effects RTR extrapolation from oral to inhalation route seems justifiable. However, for dermal absorption it is necessary to first substantiate the dermal absorption value of 5% (see also dermal acute toxicity).

f) Reproductive toxicity:

Regarding the reproductive toxicity there are indications for effects. The available studies have severe deficiencies. It is stated that potential developmental toxicity could be related to the acetylating properties of SA. This concern needs clarification.

In the following section a summary of the Belgian CA highlighting the deficiencies of reproductive toxicity studies is given:

Generally the available tests are poorly reported.

→ Available tests on Fertility toxicity

Short RD, Johannsen FR, Levinskas GJ, Rodwell DE, and Schardein JL. (1986); Two-Generation Reproduction Toxicity Study (equivalent or similar to OECD Guideline 416) - Read-across with maleic anhydride

10 males and 20 females were used per dose group. The NOAEL was established at 55 mg/kg/day for the F2, maleic anhydride was toxic to parents at 150 mg/kg/day.

The fertility was significantly reduced at some occasions although no patterns within the generation suggest a treatment-related effect.

No adverse effects on litter size or pup survival were noted in F1a or F1b litters from parents treated at up to 150 mg/kg/day and up to 55 mg/kg bw/day in the F2a and F2b litters (the high dose group was terminated due to treatment-related mortality in adults).

There is no examination on the oestrus cycle, the sperm measures or parameters.

→ Available tests on developmental toxicity

Short RD, Johannsen FR, Levinskas GJ, Rodwell DE, and Schardein JL. (1986); Prenatal Developmental Toxicity Study (equivalent or similar to OECD Guideline 414) - Read-across with maleic acid

It seems that it was conducted at the same time than the fertility study but there are problems with the description of the test and the identification of the substance in the IUCLID file: "maleic anhydride" in the title of the study and in the executive summary but "maleic acid" under test material identity section.

The study was conducted through two generations. The study design is explained as such: rats in groups of 10 males and 20 females were treated at 0, 20, 55 or 150 mg/kg bw/day (F0), Treatment began when the F0 rats were 5-6 weeks old, continued for at least 80 days prior to mating and continued to termination. For the F1 animals treatment began on Day 22, continued for at least 80 days prior to mating and then continued to termination (Daily). However the section "no. of animals per sex per dose" refers to 25 mated females per dose.

Slight foetal bodyweight reductions were noted in low and high dose groups. Malformations were observed in one foetus from one control litter, two foetuses from two litters in the low dose group. Three foetuses from three separate litters in the high dose group showed isolated changes with no consistency and no evidence of dose-related increase. Foetal variations were comparable in both type and frequency for control and treated groups.

Fabro S, Schull G, and Brown NA (1982); equivalent or similar to in vivo teratology screen

Pregnant CD-1 mice given ip injections of succinic anhydride on days 8-10 of gestation showed malformations at doses nearly lethal to adults (10 animals/dose, doses of 0.31 mmol and lower). Only major structural defects were included in the evaluation of teratogenic potential . The median effective teratogenic dose, tD50, was established at 0.8 mmol/kg/day and the minimum teratogenic dose, tD05, was established at 0.3 mmol/kg/day.

Melnick, R. (1990a); equivalent or similar to in vivo teratology screen

Refers to two other studies: Fabro et al (1976) and Brown et al (1978). In both pregnant CD-1 mice were administered succinic anhydride by ip injections on gestational days 8-10 or 11-13. There are no data regarding the vehicle, the mating procedure, the duration of the test, the number of animal per sex per dose, the study design, the maternal/foetal examination, the ovaries and uterine content, the statistics and the maternal toxic effects.

Fabro et al (1976): no increases in resorptions or decreases in birth weight occurred at dose level of 50 mg/kg/day but 23.3% of the viable pups exhibited branched ribs, fused vertebrae or cleft palate.

Brown et al (1978): significant increase in defects was seen after administration of 0.25 mmol/kg succinic anhydride on GD 11-13.

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g) Derived no effect levels

- DNEL long term & acute, inhalation, systemic: 10 mg/m^3

A DNEL of 14mg/m^3 was derived based on the NOAEL from the oral sub-chronic study for SA. As this value exceeds the TWA of 10mg/m^3 for non-toxic dust this value (10mg/m^3) was used instead. The applied AFs were however not in line with the recommendations of the REACH guidance on IR & CSA. If AFs are reduced from the default this has to be justified adequately. This justification is missing.

Further this DNEL was based on systemic long-term effects and therefore does not cover the sensitising effects of SA for which no quantitative DNEL can be derived.

- DNEL long term & acute, inhalation, local: 0,41 mg/m^3

This value is based on read-across from MA. It is based on the evaluation by the German MAK commission who used a 6 months study where local irritating effects were observed in rats, hamsters and rhesus monkeys to derive this value.

Two case reports of occupational respiratory sensitisation with unclear exposure (MA as well as phthalic anhydrate) lead the MAK commission to review their MAK value, however, they concluded not to change their value. The MAK commission stated, however, that there exists no reliable quantitative information on MA concentrations which can be related to sensitisation or elicitation. Therefore, the sensitising effects of MA and in consequence also of SA are not covered by this DNEL.

AFs: see above.

- DNEL acute, dermal, local & systemic: 167mg/kg bw/day

The value of 5% for dermal absorption needs better justification in order to increase reliability of this DNEL for systemic effects. It is not clearly demonstrated that also local irritant effects are covered by this DNEL.

AFs: see above

- DNEL long-term, dermal, local & systemic: 0,04 mg/cm^2

As the LLNA for SA is not suitable for quantitative risk assessment this DNEL is based on read-across from MA. The value is derived from an EC_3 value from a LLNA on MA. The information presented in the registration dossier is insufficient to conclude whether this value was derived correctly. An EC_3 value can be regarded as a LOAEL value. The REACH guidance on CSA & IR chapter R.8 recommends to apply several AFs (vehicle or matrix effects: 1-10, occasionally higher; exposure conditions: 1-10, occasionally higher; interspecies difference: 1-10, occasionally higher) in order to derive DNELs from EC_3 values. Not a single assessment factor (AF) was applied to derive this DNEL, and no justification was provided for that.

Based on the available information it is not sure if MA and SA have a comparable potency with regard to their sensitising properties. Therefore it cannot be concluded that the DNEL of 0.04 mg/cm^2 is sufficiently low to cover the sensitising effects of SA.

The registrant applied the above DNELs in the risk characterisation. As the resulting RCRs are below 1 (though quite close to 1 in some cases) the registrant concluded that the applied RMMs and PC are sufficient to guarantee safe use conditions. However, it seems that the sensitising properties of MA are not adequately covered by this approach.

h) General remarks:

Reference list is incomplete for example Batke et al. (2010), and more references are missing.

For some studies insufficient information is presented in the IUCLID file.

3.3 Information on aggregated tonnage and uses

☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 50,000 tpa	☐ 50,000 – 100,000 tpa
☐ 100,000 – 500,000 tpa	☐ 500,000 – 1000,000 tpa	☐ > 1000,000 tpa
☐ Confidential		
Please provide further details		

☒ Industrial use	☒ Professional use	☐ Consumer use	☒ Closed System

For further information (see http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances)

Industrial use as intermediate for production of substances or other intermediates
Industrial use as monomer for production of resins
Manufacture of Succinic anhydride
Laboratory Use

3.4 Other completed/ongoing regulatory processes that may affect suitability for substance evaluation

☐ Compliance check	☐ Dangerous substances Directive 67/548/EEC
☐ Testing proposal	☐ Existing Substances Regulation 793/93/EEC
☒ Annex VI (CLP)	☐ Plant Protection Products Regulation 91/414/EEC
☐ Annex XV (SVHC)	☐ Biocidal Products Directive 98/8/EEC
☐ Annex XIV (Authorisation)	☐ Other (provide further details below)
☐ Annex XVII (Restriction)	

The registered substance is classified according to Annex VI (CLP), see section 2.1.

3.5 Information to be requested to clarify the suspected risk

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☒ Information on exposure
☐ Information on ecotoxicological properties	☒ Information on uses
☐ Other (provide further details below)	

The applied read-across from MA and other cyclic anhydrides needs to be better justified. This should be included in an up-date of the registration dossier.

As a result of the evaluation it might become necessary to request further data on reproductive toxicity.

More data on human exposure of workers and the intended uses are needed. It has to be checked, if the proposed operational conditions and risk management measures in the ESs, which are targeted on the quantitative hazard assessment, also meet the required safety standard for covering the sensitizing effects. In order to cover the sensitizing properties exposures should be reduced to the extent possible (goal: no contact at all), if it proves correct that the available information is insufficient to derive a quantitative DNEL for skin and respiratory sensitization. Information on common practice regarding the intended uses and cases of illnesses have to be further evaluated, in order to prove if the derived ESs are safe enough for the workplace situation.

3.6 Potential follow-up and link to risk management

☒ Restriction	☒ Harmonised C&L	☒ Authorisation	☐ Other (provide further details)

Depending on the outcome of the substance evaluation the most effective Risk Management Option can be chosen.

Depending on the result of the evaluation of the single human health hazards it might be necessary to prepare a CLH dossier.
If all questions are properly resolved and exposure is shown to be sufficiently low in order to avoid the critical effects, it may be decided that the use of SA is well controlled and presents no risks. In contrast if unacceptable risks are identified the substance evaluation may result in the preparation of an Annex XV dossier for SVHC identification under Art 57f, or a restriction dossier for the use of SA in certain products and/or applications.