SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

bis(pentane-2,4-dionato)calcium

EC No 243-001-3

CAS No 19372-44-2

Evaluating Member State(s): Germany

Dated: 09 July 2021

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Bis(pentane-2,4-dionato)calcium ("$Ca(acac)_2$") was originally selected for substance evaluation in order to clarify concerns about:

- suspected reprotoxic
- sensitiser properties
- exposure of workers
- high (aggregated) tonnage

During the evaluation also another concern was identified:

- consumer uses of plastic and rubber articles

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

None

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

There is need for regulatory follow-up action at EU level.

4.1.1. Harmonised Classification and Labelling

Based on the available information, the eMSCA concluded that the existing information on bis(pentane-2,4-dionato)calcium is sufficient for a harmonised classification as Skin Sens. 1A.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Based on the available information, the eMSCA concluded that the existing information on bis(pentane-2,4-dionato)calcium is not sufficient to identify the substance as SVHC.

4.1.3. Restriction

Based on the available information, for bis(pentane-2,4-dionato)calcium the eMSCA concluded that the risk for workers and consumers is adequately controlled and a restriction is not foreseen at the moment. In the SEV, the registered use status of active registrants on 25th October 2018 is reflected.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Regulatory follow-up action at EU level is required (harmonised classification and labelling).

Table 2

FOLLOW-UP		
Follow-up action	Date for intention	Actor
CLH dossier	2022	German CA

5.2. Other actions

There are no other actions currently foreseen.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Bis(pentane-2,4-dionato)calcium ("$Ca(acac)_2$") was originally selected for substance evaluation in order to clarify concerns about:

- suspected reprotoxic
- sensitiser properties
- exposure of workers
- high (aggregated) tonnage

During the evaluation also another concern was identified:

- consumer uses of plastic and rubber articles

Table 3

EVALUATED ENDPOINTS Endpoint evaluated	Outcome/conclusion
Reproductive toxicity	Concern refuted. No further action.
Skin Sensitisation	Concern confirmed. The eMSCA supports potential classification as Skin Sens. 1A.
Exposure Assessment Human Health - consumers	Exposure assessment performed (see section 7.12.1.2). Clarified and no further action.

7.2. Procedure

On 17 March 2015 ECHA published the CoRAP and initiated a substance evaluation for bis(pentane-2,4-dionato)calcium ($Ca(acac)_2$ or the registered substance). The substance is a substitute for lead in stabilisers for PVC and the eMSCA identified the necessity to evaluate the hazard profile and the exposure situation. During the process of substance evaluation, all data available until November 2018 was considered.

Following evaluation in 2015, the eMSCA submitted a draft decision with further information requirements to clarify the identified concerns. Following registrants' comments and new information provided in registration updates, the eMSCA considered the data sufficient to conclude on the concerns and terminated the decision-making procedure.

Effects on human health

The substance evaluation with respect to human health was comprehensive, addressing all human health endpoints as required according to REACH Regulation, Annex VII-X. Particular emphasis was placed on the evaluation of repeated dose toxicity, reproductive toxicity, and the read-across approach to pentane-2,4-dione. The justification of DNELs was also given particular attention.

The hazard assessment of $Ca(acac)_2$ applies a read-across approach to pentane-2,4-dione ("acetylacetone", EC 204-634-0, CAS 123-54-6) on a case-by-case and endpoint-by-

endpoint basis according to Annex XI of REACH. At physiological pH values which are relevant for toxicity assessment, the substance dissociates largely to calcium ions and pentane-2,4-dione. It is assumed that calcium as a natural constituent of the human body will not significantly contribute to the systemic toxicity in the dose ranges under consideration. Thus, toxicity effects are attributed to pentane-2,4-dione. In general, read-across between similar substances is an effective tool to reduce animal testing according to the 3R principle[2].

Consumer

The evaluation of consumer exposure resulting from the identified uses was based on information provided in the registration dossiers/Chemical Safety Reports (CSRs). In addition, it was based on information given by the registrants in communication with the eMSCA during the substance evaluation process as well as information taken from open data bases, academic literature, and European national product registers.

The consumer exposure was calculated by the eMSCA.

Worker

The following sources were analysed during the initial assessment period to access information on $Ca(acac)_2$ (May, 2015):

- GESTIS-Stoffdatenbank
- ECHA homepage (information on chemicals)
- IFA – Publications
- Patent (Gay,Henrio, 2003)

The exposure scenarios for workers as provided by the registrants in the CSR were checked as to whether they are exhaustive, plausible and well documented with regards to operational conditions (OC) and information about risk management measures (RMMs).

The eMSCA considered the following aspects of particular importance for exposure scenarios for workers:

- Sufficient description of operational conditions and RMMs including personal protective equipment (PPE).
- The priority of implementation for protective and prevention measures shall comply with the order as laid down in Directive 98/24/EG Art.6(2) (EC, 2014).
- The duration of usage of PPE shall not exceed the specified maximum duration.

During substance evaluation, the eMSCA calculated exposure estimates for the inhalation pathway for workers with ECETOC TRA v3 (ECETOC, 2012).

For risk characterisation, a long-term systemic DNEL (inhalation) was derived by the eMSCA and the RCRs for inhalation exposures were checked.

Effects on environment

The effects on the environment were not evaluated during this substance evaluation.

[2] 3R principle: reduce, replace and refine to minimise animal testing

Conclusions

Consumer

On the base of the adapted exposure assessment, no consumer risk was identified.

After having received the draft decision based on Article 46(1) of Regulation (EC) No 1907/2006 for comments the registrants provided additional information on uses, and operational conditions and consumer exposure estimation and updated their registration dossiers in accordance with it. Based on this information the eMSCA performed an exposure assessment reflecting the currently registered identified use (consumer use of plastic articles) and operational conditions.

Worker

As correspondence and communication with industry revealed, no further rise in volume for the registered substance is expected as the substitution process of lead compounds as stabilisers for newly produced PVC with lead-free stabilisers like $Ca(acac)_2$ is almost completed. Registrants and downstream users identified the use of the substance in rigid PVC mostly. Products contain matrix-bound $Ca(acac)_2$ up to a maximum of 10%. According to the registrants, no emissions of acetylacetone have been detected during measurements in climate chambers according to the AgBB scheme (AgBB, 2012). Accordingly, a comparison of these results with the DNELs for workers derived by the eMSCA did not show a risk originating from products containing the substance. Further, the number of production and compounding sites is small and consequently only few workers are potentially exposed. The RMMs communicated in the CSR cover the safe use of the substance and the eMSCA did not identify a risk at the workplace originating from the use of the substance.

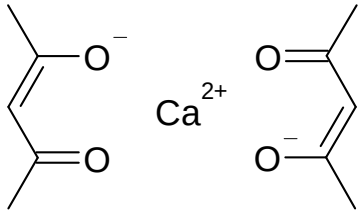
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Bis(pentane-2,4-dionato) calcium
EC number:	243-001-3
CAS number:	19372-44-2
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_{10}H_{14}CaO_4$
Molecular weight range:	238.29 g/mol
Synonyms:	Bis(2,4-pentanedionato)calcium Bis(acetylacetonate)calcium Bis(acetylacetonyl)calcium Bisacetylacetonatocalcium Calcium acetylacetonate Calcium bis(acetylacetonate) Calcium, bis(2,4-pentanedionato)-

Type of substance ☒ Mono-constituent

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	Value
Physical state at 20°C and 101.3 kPa	Off-white powder
Melting/freezing point	Decomposition starting at 205 °C, OECD Test Guidelines 102
Vapour pressure	<0.01 Pa, most likely in the range of $1*10^{-12}$ Pa to $1*10^{-6}$ Pa, DSC according to ASTM E1782-08
Water solubility	12.9 g/L at 20 °C and pH 11, OECD Test Guideline 105
Partition coefficient n-octanol/water (Log $_{Kow}$)	log K_{OW} = 1.1 , flask method according to OECD Test Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method)
Granulometry	d_{10} = 0.94 µm, d_{50} = 5.3 µm and d_{90} = 16.6 µm, in accordance with European Chemicals Agency (ECHA), Guidance on information requirements and chemical safety assessment, Chapter R.7a, Endpoint specific guidance, May 2008
Stability in organic solvents and identity of relevant degradation products	Data waiving; According to the table in REACH Annex IX, column 2, the study on stability in organic solvents can be waived since the stability of the substance is not considered to be critical.
Dissociation constant	pKa = 8.8 at 25 °C, OECD Test Guideline 112

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☒ 10 – 100 t	☒ 100 – 1000 t	☒ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

As of July 2021, there are 10 active registrations submitted as part of one joint submission.

7.5.2. Overview of uses

Table 7

USES	
	Use(s)
Uses as intermediate	None
Formulation	Formulation and (re)packing of the substance and distribution of the substance and mixture PROC 1, 2, 3, 5, 8a, 8b, 9, 15 Industrial formulation of the substance in materials PROC 5, 7, 8b, 10, 13, 14
Uses at industrial sites	Manufacture: PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 15 Industrial use of the substance as a colour stabilising agent in polymer industry (e.g. plastic and rubber) PROC 1, 2, 3, 4, 5, 6, 8a, 8b, 9, 10, 13, 14, 21, 24
Uses by professional workers	None
Consumer Uses	None
Article service life	Registration(s) refer(s) to consumer applications of plastic products in indoor and outdoor wide dispersive uses of long-life articles and materials with low release (ERC 11a, ERC 10a, AC 13)

The information given in Table 7 is taken from the disseminated data from the registration dossiers. The information on the Article Service Life reflects the active registration situation in October 2018. In addition to this, other sources indicate:

- The substance is a heat stabiliser in the formulation of halogenated polymers.
- The substance is an ingredient of Calcium/Zinc (Ca/Zn) stabilisers of halogenated polymers in profile and siding productions (Patent DE 102010020263 A1 (Heris and Uysal, 2011).

Based on Swedish data from 2013, the SPIN Exposure toolbox states a very probable use of the substance in article productions (SPIN database, 2015).

The types of articles produced are linked to the types of plastics/rubbers and the required properties determine the additives used for the production process. An example for potential articles produced from PVC with different stabiliser systems is given below.

Table 8

Applications for Stabilisers - European Market (South East Europe PVC Forum)							
	Stabiliser Type						
Application	Pb	Pb/Ba/Cd	Ba/Cd	Ca/Zn	Ba/Zn	Sn	K/Zn(2)
Non-plasticised PVC							
Pipes	++			++(1)			
Fittings	++					+(1)	
Profiles	++	++		+			

Foil						++	
Bottles				++		++	
Sheet	+			(+)		++	
Plasticised PVC							
Cable Covering	+			++			
Foil and Sheet	+		+	++			
Flooring					++	+	++
Wall Covering				(+)	++	+	++
Medical Use				++			
Tubes and Footwear				+	++		
Food Packaging Film					++		
Fabric Coating				+	++		++

++ Major use + Minor use (+) Occasional use (1) Used for potable water pipe (2) Used as a stabiliser/'kicker' for foamed layers in these products

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classification in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 (EC, 2015).

7.6.2. Self-classification

- In the registration(s):

  The following information is provided by the lead registrant and presented as joint entry in the C&L Inventory:

Acute Tox. 4	H302: Harmful if swallowed.
Acute Tox. 3	H311: Toxic in contact with skin
Acute Tox. 3	H331: Toxic if inhaled
Skin Sens. 1A	H317: May cause an allergic skin reaction.
Eye Dam. 1	H318: Causes serious eye damage.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Acute Tox. 3	H311: Toxic in contact with skin.
Acute Tox. 4	H312: Harmful in contact with skin.
Acute Tox. 3	H331: Toxic if inhaled.
Acute Tox. 4	H332: Harmful if inhaled
Skin Sens. 1A	H317: May cause an allergic skin reaction.
Skin Sens. 1B	H317: May cause an allergic skin reaction.
Skin Sens. 1	H317: May cause an allergic skin reaction.
Skin Irrit. 2	H315: Causes skin irritation.
Eye Irrit. 2	H319: Causes serious eye irritation.
STOT SE 3	H335: May cause respiratory irritation.

Repr. 2	H361: Suspected of damaging fertility or the unborn child.
Repr. 2	H361(d): Suspected of damaging fertility or the unborn child.

7.7. Environmental fate properties

Environmental fate properties have not been evaluated during this substance evaluation.

7.8. Environmental hazard assessment

The effects on the environment were not considered during this substance evaluation.

7.9. Human Health hazard assessment

The lead registrant used data from the read-across substance pentane-2,4-dione to assess the developmental toxicity and repeated dose toxicity endpoints of $Ca(acac)_2$. The eMSCA agrees with the argument that bis(pentane-2,4-dionato)calcium hydrolyses at a lower pH compared to pentane-2,4-dione. Therefore, the use of studies on pentane-2,4-dione to read across the developmental toxicity and repeated dose toxicity for $Ca(acac)_2$ is accepted by the eMSCA.

7.9.1. Toxicokinetics

No toxicokinetic data are available on $Ca(acac)_2$.

Dermal absorption

The lead registrant presented assumptions according to the ECHA guidance on information requirements and chemical safety assessment (Chapter R 7C). The molecular weight is 238.294 g/mol, the substance is soluble in water up to 12.9 g/L and the log P_{ow} of -1.1 is moderate. The registrant concluded that the substance may be significantly absorbed via the skin based on the values above. With respect to dermal absorption, only two experiments have been performed in animals with $Ca(acac)_2$. An acute dermal toxicity study did not show any mortality or relevant clinical symptoms at the limit dose of 2000 mg/kg bw. A study on skin irritation did not show any effects either.

It seems likely that the substance undergoes partial hydrolysis, thereby yielding the read-across compound pentane-2,4-dione. However, in contrast to the acute dermal toxicity testing with pentane-2,4-dione (LD_{50} of 790 and 1370 mg/kg bw), no lethality was observed with the test compound.

The eMSCA concludes that some amount of $Ca(acac)_2$ will likely be absorbed via the skin, but it is unclear to what extent.

Inhalation absorption

Considering that the test compound is a very fine powder with 47.9 % < 5 µm the registrants concluded that the substance may be significantly absorbed via inhalation. The acute inhalation toxicity with the limit dose of 5 mg/L did not show any mortality or relevant clinical symptoms.

A partial hydrolysis of the substance yielding the read-across compound pentane-2,4-dione appears likely.

The eMSCA concludes that it is possible for $Ca(acac)_2$ to be absorbed by inhalation.

Oral absorption

Acute oral toxicity indicate that with an LD_{50} of 1250 mg/kg bw, $Ca(acac)_2$ was absorbed.

The eMSCA concludes that very likely $Ca(acac)_2$ is hydrolysed to the read-across compound pentane-2,4-dione, which, in turn, can be absorbed.

7.9.2. Acute toxicity and Corrosion / Irritation

The registrants concluded that $Ca(acac)_2$ has an oral LD_{50} of 1250 mg/kg bw requiring a self-classification of Acute Tox. 4 (harmful if swallowed). Based on the results of the studies for dermal and inhalation acute toxicity, no classification is required. Based on the available information the eMSCA supports these conclusions.

Irritation

The registrants concluded that $Ca(acac)_2$ is not irritating to the skin. Based on the available information the eMSCA supports this conclusion.

Corrosivity

The registrants concluded that $Ca(acac)_2$ caused severe irritation to the eye. The substance has been classified by the registrant as corrosive to the eyes (Eye Dam. 1, H318: Causes serious eye damage). Based on the available information the eMSCA supports this conclusion.

7.9.3. Sensitisation

The results of the sensitisation study on bis(pentane-2,4-dionato)calcium can be found in Table 9.

Table 9

Results of the sensitisation study			
Method / Guideline	Results	Remarks	Reference
OECD 406 (Skin Sensitisation) Guinea pig (Dunkin-Hartley) Guinea pig maximisation test Control group: 3 animals Test group: 5 animals Induction 0.5 % in FCA emulsion (injection) Induction 60 % in petrolatum (topical) Challenge 60 % in petrolatum No information if the challenge was done under occlusion or for how long	Sensitising Control group: 1st read.: 0 out of 3 24 h after challenge 2nd read.: 0 out of 3 48 h after challenge Test group: 1st read.: 5 out of 5 24 h after challenge 2nd read.: 5 out of 5 48 h after challenge	2 (reliable with restriction) Key study $Ca(acac)_2$	Study report, 1999

The registrants noted that the number of animals was limited (in comparison to the standard requirements of OECD Test Guideline 406) but the validity of the study was not questioned since all (5/5) animals of the test group showed a positive reaction. Based on the intradermal induction concentration of 0.5 % and the observation of ≥60 % positive animals (Table 3, Annex I: 3.4.2.2.3.2 of the CLP Regulation) it can be concluded that $Ca(acac)_2$ warrants a classification as Skin Sens. 1A. The eMSCA also notes that the study did not meet the minimum requirements of the OECD test guideline with 10 animals in the treatment group and 5 animals in the control group. However, since the results showed a clear effect in all of the animals treated, the eMSCA supports the overall conclusion-classification as Skin Sens. 1A.

7.9.4. Repeated dose toxicity

The results of the repeated dose toxicity study using the read-across substance pentane-2,4-dione are presented in Table 10.

Table 10

Studies on repeated dose toxicity after inhalation exposure				
Method/ Guideline	Test organism/ Strain, Dose levels	Results	Remarks	Reference
Equivalent or similar to OECD 413 (Subchronic inhalation toxicity: 90-Day)	Rat (Fischer 344), male/ female 20 animals per sex per dose, half of the animals were investigated after 4 weeks recovery. An additional 10 males were added to the highest dose group and the control group for examination of the sciatic nerve Whole body inhalation Exposure levels: 0, 100, 300, 650 ppm corresponding to 0, 420, 1260, 2730 mg/m^3 Exposure: 6h/day, 5 days/week	LOAEC: 300 ppm NOAEC: 100 ppm All female rats of the 650 ppm group died, 10 of 30 male rats of the 650 ppm group died. Animals died between the second and the sixth week of treatment. At 650 ppm animals showed general signs of toxicity and sensory irritancy. At 300 ppm female animals had slightly but significantly decreased body weight gains from day 45. Red blood cells (-4 %) and haematocrit were significantly decreased in females, mean corpuscular volume was significantly increased.	Key study, reliable without restriction Test material: pentane-2,4-dione	Dodd et al., 1986

Four groups of Fischer 344 rats (20 m/f) were exposed via inhalation route for six hours per day, five days a week, for 14 weeks to the read-across compound pentane-2,4-dione vapour at concentrations of 0, 100, 300, or 650 ppm (corresponding to 0, 420, 1260 and 2730 mg/m^3). In addition, 10 males were added to the 650 and 0 ppm groups for subsequent microscopic examination of sciatic nerves. Severe toxicity was observed at 650 ppm, with all of the females and 10 out of 30 males dying between the second and sixth week of exposure. Subacute degenerative changes in the deep cerebellar nuclei, vestibular nuclei and corpora striata, as well as acute lymphoid degeneration of the thymus were reported in these animals. Surviving animals had gliosis and malacia in the brain, minimal squamous metaplasia in the nasal mucosa, decreased body and organ weights, lymphocytosis, and minor alterations in serum and urine chemistry. No effects were observed at the lowest dose level of 100 ppm (NOAEC) and only mild signs of toxicity such as body weight changes, minor changes in haematology, urinalysis and histopathology were reported at the mid dose of 300 ppm. Despite the fact that these (mid dose) effects were all reversible after 4 weeks post-exposure and considering the significance of the body weight reduction in female rats, this concentration was considered as lowest observed adverse effect level (LOAEC).

The registrants concluded that the effects at 300 ppm and 650 ppm corresponding to 1260 and 2730 mg/m^3 did not qualify for a classification according to STOT RE.

The eMSCA agrees with this conclusion of the registrants as the LOAEL is above the guidance value for classification as STOT RE 2 of 1000 mg/m^3.

7.9.5. Mutagenicity

Not evaluated in this SEv

7.9.6. Carcinogenicity

No information is available for the substance. It is the conclusion of the eMSCA that no information on carcinogenicity is necessary for the substance.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Fertility

The registrants waived the information requirement. It was argued that investigations on sub-chronic and developmental toxicity were performed with the read-across compound pentane-2,4-dione. The results of the sub-chronic toxicity study gave no relevant evidence for toxicity on reproductive organs.

Considering the results of the sub-chronic toxicity study, according to which hitherto no effects were identified, which reveal concerns in relation to reproductive toxicity, further testing on reproductive toxicity is not triggered for the Annex IX tonnage band. Therefore the eMSCA concludes that an extended one-generation reproductive toxicity study is not required.

Developmental toxicity

The results of the key study on the read-across substance penta-2,4-dione are compiled in the following table.

Table 11

Studies on developmental toxicity				
Method/Guideline	Test organism/Strain dose levels	Results	Remarks	Reference
Equivalent of similar to OECD 414 (Prenatal Developmental Toxicity)	Rat (Fischer 344), females, 25 time-pregnant animals per dose Whole body inhalation Exposure levels: 0, 53, 202, 398 ppm (corresponding to 0, 223, 848, 1672 mg/m^3) Exposure: 6h/day, gestation day 6 to 15	NOAEC (maternal toxicity): 53 ppm NOAEC (foetotoxicity): 53 ppm LOAEC (maternal toxicity): 202 ppm, based on increased liver weight LOAEC (foetotoxicity): 202 ppm, based on reduced foetal weights (all foetuses and males beginning at 202 ppm, females at 398 ppm). Reduced foetal ossifications at 398 ppm	Key study, reliable with restriction Test material: pentane-2,4-dione	Tyl et al., 1990

Timed-pregnant Fischer 344 rats were exposed to the read-across substance pentane-2,4-dione on gestational days 6–15 for 6 h/d to vapour concentrations of 0, 53, 202 and 398 ppm (corresponding to 0, 223, 848 and 1672 mg/m^3). Maternal toxicity (reduced body

weight of 6.5 % at day 18) and fetotoxicity (reduced foetal weight of 10 % at day 21 and delayed ossification) was observed at the high dose. No embryotoxicity or teratogenicity was reported at any concentration, and there was fetotoxicity (reduced foetal weight) at 202 ppm. The NOAEC for both maternal and developmental toxicity was set at 53 ppm (223 mg/m^3) and used as POD to calculate a DNEL for developmental toxicity (see section 7.9.9).

The eMSCA concludes that the minor foetal weight reduction at 202 ppm in the range of 3 to 3.3 % is not sufficient for a classification as Repro 2.

7.9.8. Hazard assessment of physico-chemical properties

According to the registrants, the test compound dissociates to at pH=2 with >99.9 % to Ca^{2+} and pentane-2,4-dione, at pH=5 with 99.7 % and at pH=7 with 78.3 %.

No hazardous physico-chemical properties were identified for the substance during this evaluation.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

According to Section R.8.4 of the REACH Guidance (ECHA, 2012), a DNEL for the leading health effect needs to be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible. Initially, the lead registrant provided DNELs which were intended to protect workers from long-term systemic effects caused during inhalation and dermal exposure to $Ca(acac)_2$. In a subsequent dossier update from 30 March 2015, the lead registrant removed the previously calculated DNELs stating that:

"…The substance is classified as Category 1A skin sensitizer and thus falls in the high hazard band according to the Guidance on information requirements and chemical safety assessment (Part E). Handling of such substances should be strictly contained and controlled in order to avoid dermal contact and inhalation exposure. Accordingly, no DNELs are derived for long-term and short-term exposure and a qualitative risk characterisation is performed."

The eMSCA is of the opinion that handling of dangerous substances under strictly contained/controlled conditions does not eliminate the need for a quantitative risk assessment, in particular for other routes than the dermal route and for other (systemic) effects than the skin sensitising property. According to REACH (Annex I, 1.1.2), a qualitative or semi-quantitative risk characterisation is performed only for human health effects for which no DNEL(s) can be derived (e.g. non-threshold carcinogenicity, sensitising effects, etc.). Two repeated-dose studies on systemic toxicity are available with the read-across substance pentane-2,4-dione. For the general population, the most sensitive endpoint was developmental toxicity (Tyl et al., 1990). For workers, a NOEC of 100 ppm (417 mg/m^3) for general systemic toxicity (Dodd et al., 1986) was selected as the most appropriate POD for DNEL calculation and risk characterisation at the workplace.

7.9.9.1. Workers

Quantitative dose-response data on systemic toxicity is available from a reliable 90-day inhalation toxicity study with the read-across substance pentane-2,4-dione (Dodd et al., 1986; details described in section 7.9.4).

In this study, no exposure-related effects were observed at the lowest dose level of 100 ppm (NOEC), and only mild toxicity signs such as body weight changes, minor changes in haematology, urinalysis and histopathology were reported at the mid-dose of 300 ppm. Although effects at 300 ppm are considered minor and transient, the very steep dose-response profile of pentane-2,4-dione (i.e., doubling the exposure level of 300 ppm leads to massive mortality in females and severe toxicity in males) justifies the use of 100 ppm as the conservative and more appropriate POD for DNEL calculation (cf. Table 12).

Relevant scenarios for worker exposure are long-term inhalation exposure and long-term dermal exposure. The NOAEC obtained from the 90-day inhalation toxicity study with the read-across substance pentane-2,4-dione needs to be adjusted for relevant occupational exposures scenarios (Table 13). The standard modifying factors applied to adjust for the

respiratory conditions and for duration of exposure at the workplace are outlined in Chapter R8 of the REACH Guidance (ECHA, 2012).

It should be noted in this context that in an earlier assessment of pentane-2,4-dione performed by the German Committee on Hazardous Substances (AGS) the mid-dose of 300 ppm was considered a NOAEC and used as a starting point to calculate a national legally-binding OEL (Arbeitsplatzgrenzwert, AGW) of 30 ppm (126 mg/m³). Here, assessment factors of 2 for time extrapolation and 5 for both inter- and intraspecies variability were applied (a total of 10). AGW values are published in Technical Rule for Hazardous Substances (TRGS) No. 900 ((AGS, 2015)).

Table 12

Detailed overview of the derivation of the DNEL (worker, inhalation, long-term, systemic) for the read-across substance pentane-2,4-dione (based on 90-day subchronic inhalation toxicity study Dodd et al., 1986)		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	NOAEC: 417 mg/m³	Based on a 90-day inhalation study in rats with pentane-2,4-dione
Modification of the relevant dose descriptor	6 h/d → 8 h/d 6.7 m³ → 10 m³	Inh. study in rats vs. workers exposure Resp. volume (8h) normal (6.7 m³) to light activity (10 m³)
Corrected dose descriptor	NOAEC(corr.) = 417 mg/m³ x 6/8 x 6.7/10 = 209.5 mg/m³	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	1	
Interspecies (remaining differences)	2.5	
Intraspecies	5	worker
Exposure duration	2	Subchronic to chronic
Dose-response	1	Steepness of dose response considered by selection of conservative POD.
Quality of whole database	1	
DNEL for pentane-2,4-dione	209.5 mg/m³ / (1 x 2.5 x 5 x 2 x 1 x 1) = 8.4 mg/m³	

Considering the ratio of 1.2 in the molecular weights of $Ca(acac)_2$ (238.3 g/mol) and the $(acac)_2$ moiety (198.2 g/mol) which is released under conditions of physiological pH, a long term systemic DNEL (inhalation) of 10 mg/m³ can be calculated for $Ca(acac)_2$:

DNEL = 8.4 x 1.2 = 10 mg/m³

Using the inhalation DNEL of 10 mg/m³ as a starting point, a long-term systemic dermal DNEL of 1.4 mg/kg bw/day can be calculated by multiplying the DNEL by 10 m³ (the volume of air breathed in a 8-hours working day) and divided by 70 kg (the standardised average worker's body weight); equal rate of respiratory and dermal absorption is assumed. The long term systemic DNEL (dermal) can be derived as follow:

DNEL = 10 mg/m³ x 10 m³ /70 kg bw = 1.4 mg/kg bw/day

According to APPENDIX R. 8-12 of the REACH Guidance (ECHA, 2012), a DNEL value for effects on fertility as well as for developmental toxicity should be derived if data for these endpoints are available. No reproductive toxicity study was performed so far with the registered substance. The developmental toxicity of the read-across substance pentane-2,4-dione was investigated in a prenatal developmental toxicity study (Details in 7.9.7; Tyl et al., 1990). In this study, the NOAEC for both maternal and developmental toxicity was set at 53 ppm (223 mg/m³) and used as POD to calculate a DNEL for developmental toxicity (Table 14). Here, no assessment factor for duration of exposure was applied.

Based on the NOAEC of 53 ppm from the above study as the most sensitive toxicity endpoint for pentane-2,4-dione, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) proposed a MAK value of 84 mg/m³ (20 ppm) in 2006 (MAK, 2006).

Table 13

Detailed overview of the derivation of the DNEL (worker, inhalation, long-term, development) for the read-across substance pentane-2,4-dione (based on a prenatal developmental toxicity study by (Tyl et al., 1990))		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	NOAEC: 223 mg/m³	Based on reduced foetal weights from a PND study in rats with 2,4-pentanedione
Modification of the relevant dose descriptor	6 h/d → 8 h/d 6.7 m³ → 10 m³	Exposure schedule in rats vs. workers Resp. volume (8h) normal (6.7 m³) to light activity (10 m³)
Corrected dose descriptor	NOAEC(corr.) = 223 mg/m³ x 6/8 x 6.7/10 = 112 mg/m³	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	1	
Interspecies (remaining differences)	2.5	
Intraspecies	5	worker
Exposure duration	1	No time extrapolation for effects on reproduction
Dose-response	1	
Quality of whole database	1	
DNEL for pentane-2,4-dione	112 mg/m³ / (1 x 2.5 x 5 x 1 x 1 x 1) = 10 mg/m³	

Considering the stoichiometry of pentane-2,4-dione and its calcium salt as detailed above, the following DNELs for $Ca(acac)_2$ can be calculated:

DNEL = 10 x 1.2 = 12 mg/m³ *(inhalation, reproductive toxicity),* and

DNEL = 12 x 10m³/70kg bw = 1.7 mg/kg/day *(dermal, reproductive toxicity)*

As above, equal rates of absorption are assumed for both inhalation and dermal routes of exposure.

Both DNEL values for systemic and reproductive toxicity are very similar indicating that in occupational settings no developmental effects have to be expected unless the DNEL for systemic toxicity is exceeded.

An overview of the calculated DNELs can be found in Table 14.

Table 14: An overview of the calculated DNELs for workers

CRITICAL DNELS/DMELS					
Endpoint of concern	Type of effect	Critical studies	Corrected dose descriptor(s)	DNEL/ DMEL	Justification/ Remarks

			(e.g. NOAEL, NOAEC)		
Repeated dose toxicity, Inhalation	Systemic toxicity	Dodd et al., 1986	NOEC = 209.5 mg/m³	10 mg/m³	
Repeated dose toxicity, Dermal	Systemic toxicity	Dodd et al., 1986		1.4 mg/kg bw/day	
Repeated dose toxicity, Inhalation	Developmental toxicity	Tyl et al., 1990	NOAEC = 112 mg/m³	12 mg/m³	
Repeated dose toxicity, Dermal	Developmental toxicity	Tyl et al., 1990		1.7 mg/kg bw/day	

7.9.9.2. Consumers

All exposure scenarios were assessed for the general population. The POD was the NOAEC of 53 ppm (corresponding to 223 mg/m³), derived from a prenatal developmental toxicity with the read-across substance pentane-2,4-dione.

Bis(pentane-2,4-dionato)calcium is a skin sensitising substance, a property which is generally regarded as a threshold effect. However, based on the available experimental data it was not possible to derive an appropriate DNEL to compare it with exposure levels resulting from the use of the compound in consumer products.

Table 15

Detailed overview of the derivation of the DNEL (general population, inhalation, long-term, systemic) for the read-across substance pentane-2,4-dione		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	NOAEC: 223 mg/m³	Based on reduced foetal weights from a PND study in rats with 2,4-pentanedione
Modification of the relevant dose descriptor	6 h/d → 24 h/d	Exposure schedule in rats vs. general population
Corrected dose descriptor	NOAEC(corr.) = 223 mg/m³ x 6/24 = 55.8 mg/m³	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	1	
Interspecies (remaining differences)	2.5	
Intraspecies	10	General population
Exposure duration	1	POD: Developmental toxicity, therefore no extrapolation for duration
Dose-response	1	
Quality of whole database	1	
DNEL for pentane-2,4-dione	55.8 mg/m³ / (1 x 2.5 x 10 x 1 x 1 x 1) = 2.23 mg/m³	

Considering the ratio of 1.2 in the molecular weights of the test compound (238.3 g/mol) and the $(\text{pentane-2,4-dione})_2$ moiety (198.2 g/mol) which is released under conditions of physiological pH, the following DNEL (inhalation) can be calculated for the test compound:

DNEL = 2.23 x 1.2 = 2.68 mg/m³ *(inhalation, reproductive toxicity)*

According to the Guidance on information requirements and chemical safety assessment, Chapter R.8., Version 2.1 (November 2012), example R.8-1 the corrected dose descriptor was calculated with 55.8 mg/m³ x 1.15 m³/kg bw = 64.1 mg/kg bw.

Table 16

Detailed overview of the derivation of the DNEL (general population, oral, long-term, systemic) for the read-across substance pentane-2,4-dione		
Descriptor	Value	Remarks
Relevant dose descriptor	55.8 mg/m³	Inhalative NOAEC will be transformed with factor 1.15 m³/kg bw into oral NOAEL
Corrected dose descriptor	NOAEL (corr) = 55.8 mg/m³ x 1.15 m³/kg bw = 64.1 mg/kg bw	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	4	allometric scaling factor rat/human
Interspecies (remaining differences)	2.5	
Intraspecies	10	General population
Exposure duration	1	
Dose-response	1	
Quality of whole database	1	
DNEL for pentane-2,4-dione	64.1 mg/kg bw / (4 x 2.5 x 10 x 1 x 1 x 1) = 0.64 mg/kg bw	

Considering the stoichiometry of pentane-2,4-dione and its calcium salt as detailed above, the following DNELs for the test compound can be calculated:

DNEL = 0.64 mg/kg bw x 1.2 = 0.77 mg/kg bw *(oral, reproductive toxicity)*

According to the Guidance on information requirements and chemical safety assessment, Chapter R.8., Version 2.1 (November 2012), example B. 5, the oral NOAEL will be transformed into a dermal NOAEL (in order to account for systemic (reproductive) effects after chronic dermal exposure) according to the following formula:

NOAEL (dermal) = NOAEL (oral) x (Abs oral-rat/Abs derm-human)

It is assumed, that the oral absorption in the rat is 100 % since the test compound will hydrolyse completely at gastric pH. In the following table two scenarios will be calculated setting the dermal absorption in humans at 10 % and 100 %.

Table 16

Detailed overview of the derivation of the DNEL (general population, oral, long-term, systemic) for the read-across substance pentane-2,4-dione		
Descriptor	Value	Remarks
Relevant dose descriptor	NOAEL: 64.1 mg/kg bw	Oral NOAEL will be transformed into two different dermal NOAEL, assuming human dermal absorption with 10 % and 100 %.
Modification of the relevant dose descriptor	a) x (100/10) b) x(100/100)	a) human dermal abs = 10 % b) human dermal abs = 100 %
Corrected dose descriptor	a) NOAEL(derm) = 64.1 mg/kg bw x (100/10) = 641 mg/kg bw b) NOAEL(derm) =	

	64.1 mg/kg bw x (100/100) = 64.1 mg/kg bw	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	4	
Interspecies (remaining differences)	2.5	
Intraspecies	10	General population
Exposure duration	1	
Dose-response	1	
Quality of whole database	1	
DNEL for pentane-2,4-dione	a) 641 mg/kg bw / (4 x 2.5 x 10 x 1 x 1 x 1) = 6.41 mg/kg bw b) 64.1 mg/kg bw / (4 x 2.5 x 10 x 1 x 1 x 1) = 0.64 mg/kg bw	

Considering the stoichiometry of pentane-2,4-dione and its calcium salt as detailed above, the following DNELs for the test compound can be calculated:

DNEL = 6.41 mg/kg bw x 1.2 = 7.69 mg/kg bw *(dermal 10 %, reproductive toxicity)*

DNEL = 0.64 mg/kg bw x 1.2 = 0.77 mg/kg bw *(dermal 100 %, reproductive toxicity)*

Table 17: Overview of calculated DNELs for consumers

CRITICAL DNELS/DMELS					
Endpoint of concern	Type of effect	Critical study(ies)	Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)	DNEL/ DMEL	Justification/ Remarks
Repeated dose toxicity, inhalation	Developmental toxicity	Tyl et al., 1990	NOAEC = 55.8 mg/m³	2.68 mg/m³	
Repeated dose toxicity, oral	Developmental toxicity	Tyl et al., 1990		0.77 mg/kg bw	
Repeated dose toxicity, dermal	Developmental toxicity	Tyl et al., 1990	Human derm abs = 10 %	7.69 mg/kg bw	
Repeated dose toxicity, dermal			Human derm abs = 100 %	0.77 mg/kg bw	

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

The lead registrant used data on the read-across substance pentane-2,4-dione for developmental toxicity and repeated dose toxicity. The eMSCA follows the argument that bis(pentane-2,4-dionato)calcium hydrolyses at lower pH to pentane-2,4-dione. Therefore, the use of studies on developmental toxicity and repeated dose toxicity with pentane-2,4-dione is accepted by the eMSCA.

Some amount of $Ca(acac)_2$ will be absorbed via the skin but is unclear to what extent. Some test compound will be absorbed by inhalation. It is very likely that the test compound is after oral absorption hydrolysed to the read-across compound pentane-2,4,dione which in turn can be absorbed.

$Ca(acac)_2$ requires a self-classification of Acute Tox. 4 (H 302: harmful if swallowed) and causes severe irritation to the eye and requires a self-classification of Eye Dam 1 (H318: Causes serious eye damage).

Based on an OECD Test Guideline study, $Ca(acac)_2$ can be classified as skin sensitiser (> 60% positive animals after an intradermal induction at a concentration of 0.5%). Based on the data on skin sensitisation $Ca(acac)_2$ warrants a self-classification of Skin Sen 1A (H317: May cause an allergic skin reaction). The eMSCA endorses a proposal for a harmonised classification for this endpoint.

An inhalation repeated dose toxicity study with the read-across compound pentane-2,4-dione did not yield relevant toxicity sufficient for classification as STOT RE.

$Ca(acac)_2$ showed no potential for mutagenicity or genotoxicity. No information is available on the carcinogenic potential of $Ca(acac)_2$, however, the eMSCA believes no additional information is necessary.

An inhalation developmental toxicity study with the read-across compound pentane-2,4-dione showed some effects on the foetal weight. However, it was concluded that the foetal weight reduction of 3 to 3.3% is not sufficient for a classification as Repro. 2.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated during this substance evaluation.

7.10.2. Endocrine disruption - Human health

No relevant information was found by the eMSCA for endocrine disruption – human health, therefore no evaluation of human ED properties was performed by the eMSCA.

7.11. PBT and VPVB assessment

Not considered during this substance evaluation.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Route of exposure: dermal

The registrant provided a qualitative exposure assessment for the dermal exposure route. This approach is plausible, since $Ca(acac)_2$ is classified (by the registrant) as Skin Sens. 1A. For this human health endpoint, it is not possible to determine a DNEL as no quantitative data are available that would allow for setting a threshold for sensitisation. Annex I 6.5 of REACH states that "*For those human effects … for which it was not possible to determine a DNEL …, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out.*" *How to undertake a qualitative human health assessment and document it in a chemical safety report* is described in ECHAs Practical Guide of the same name (ECHA, 2012). The qualitative risk assessment of the registrant is in accordance with this practical guide. The registrant concludes that the likelihood of exposure is "high" (caused by the high dustiness of $Ca(acac)_2$) and chose the substance hazard band "high" for $Ca(acac)_2$ (due to sensitisation). With these parameters, the resulting risk is "high". To control this risk at the workplace a combination of several OCs and RMMs is stipulated by the registrant. These OCs and RMMs, of course, do have influence on both exposure pathways, dermal and inhalation.

Route of exposure: inhalation

The registrant did not provide any exposure assessment related to the inhalation exposure route.

The self-classification of the registrant does not include hazard classes for which the inhalation exposure is of great importance. However, according Annex I of Reach the exposure assessment has to cover all hazards which were identified. The ECHA Guidance

on Information Requirements and Chemical Safety Assessment Part B Chapter 8.1, describes this more precisely. Identified hazards necessitating exposure assessment are amongst others "*…hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified".* The toxicological studies with $Ca(acac)_2$ show that there are systemic effects, but the concentration where severe effects occur is lower than the criteria for classification. The 14-week repeated dose toxicity study with pentane-2,4-dione shows mortality and severe systemic toxicity at vapour concentrations of 650 ppm (2711 mg/m^3; (Dodd et al., 1986)). To fulfil the criteria for classification as STOT RE Cat.2, however, severe effects should be seen between 200 and 1000 mg/m^3 as vapour. Both dose levels of 300 and 650 ppm are outside of this range and warrant no classification for target organ toxicity.

Therefore, the registrant should derive a DNEL for this endpoint and perform a quantitative exposure assessment for the inhalation exposure route.

In order to examine if there is a risk regarding the inhalation exposure, the eMSCA carried out an exposure assessment with ECETOC TRA v3 with the parameters given in the CSR. To detect any potential risk whatsoever, conservative assumptions, such as full 8-hour shift, substance as such (100 %), indoors with basic general ventilation, no local exhaust ventilation (LEV), no respiratory protection (RPE) were used for the calculation. The model estimation yielded the highest inhalation exposure value for PROC 8a. For this PROC the estimate is about 5 times higher, than the DNEL derived by the eMSCA.

The OCs and RMMs mandated by the registrant do not allow the "open use" of $Ca(acac)_2$. Containment shall only be interrupted temporary for short times, e.g. for taking samples. In these cases where complete containment is not verified, appropriate respiratory protection is necessary. ECETOC TRA v3 assumes for the effectiveness of RPE at least an *Assigned Protection Factor* (APF) of 10. This is equivalent to a reduction of exposure of 90 %. The combination of PROC 8 with RPE would yield an inhalation exposure which is about half the DNEL.

7.12.1.2. Consumer

Consumer utilise various kinds of plastic and rubber articles in their daily life. Substances bound onto or into their matrix may still migrate to the surface and then evaporate or be removed through contact with the human skin, when handled or washed. The potential to migrate from plastic depends on the physical-chemical characteristics of the substance including their solubility in the plastic (Hansen et al., 2014). According to Hansen et al. (2014) the ability to migrate differs between substances used as cross-linkers, hardeners and catalysts and no general rules can be presented. For stabilisers the behaviour differs between substances as well. Most substances can be assumed to migrate, with a low rate leaving most of the product in the article (Hansen et al., 2014).

All exposure assessments by the eMSCA were performed with ECETOC TRA Version 3.

This low-tier model allows assessing broad "sentinel" categories (AC 10 or AC 13) based on default scenarios. Technically, this output equals the highest exposure value obtained for a given route among all sub-categories within the AC in the model. The contents in the respective default scenarios for AC 10 and AC 13 are higher than 5 %, which is the maximum content indicated for stabilisers in production processes for different plastic types (e.g. rigid or flexible PVC) in the Emission Scenario Document On Plastic Additives (OECD, 2009) and Emission Scenario Document On Additives In Rubber Industry (OECD, 2004). In lack of more detailed information on the use conditions of the substance (e.g. maximum remaining content of substance, type of plastic and type of article produced) the exposure assessment was originally based on these default scenarios but with a refinement of the remaining content to 5 %.

Table 18 summarises the highest exposure value obtained among all sub-categories within the AC in the model for a given route.

Table 18

Exposure values	AC 10 (rubber articles)	AC 13 (plastic articles)
Oral, mg/kg/d	0.5	0.08
Dermal, mg/kg/d	1.74	7.29
Inhalation, mg/kg/d	0.00176	0.00176
Inhalation, mg/m³	0.00962	0.00962

In the registration the Environmental Release Categories ERC 10a and 11a have been assigned (see section 7.5.2 Overview of uses). In accordance with these the OECD ESD (OECD, 2004) and (OECD, 2009) indicates a small release potential for the substance into the environment. As already explained above, Hansen et al. (2014) suggests that a small fraction of stabilising substances migrates from plastic materials and subsequently causes a low consumer exposure not further defined. Therefore, the exposure calculated in Table 18 could be an overestimation. However, the extent of the deviation remains unclear for all cases where detailed data on the precise conditions of use for the identified uses and physical-chemical characteristics of the substance including their solubility in the produced plastic or on its diffusion or migration potential from it are missing. These would allow establishing a more graduated exposure scenario and performing exposure estimations with more refined model concepts.

In the course of the substance evaluation process, the eMSCA communicated with the registrants asking for more detailed information on the conditions of exposure (such as types of articles and materials produced as well as the maximum content of the substance in the production process). Several registrants replied to this informal information request, enabling the eMSCA to perform a further iteration for their registrations of the Substance. It was performed by exchanging the maximum content to 1 %, which was the highest value reported by voluntarily replying registrants. The corresponding data are given below (Table 19).

Table 19

Exposure values	AC 10	AC 13
Oral, mg/kg/d	0.1	0.02
Dermal, mg/kg/d	0.35	1.46
Inhalation, mg/kg/d	0.00176	0.00176
Inhalation, mg/m³	0.00962	0.00962

At a later stage of the process all registrants updated their registration dossiers. The update includes a change of the identified uses. The supported use of the substance is now restricted to a stabilizing agent in polymers for manufacture of plastic products (Status: 25. October 2018). In consequence exposure due to the use of rubber products by consumers is no longer considered in the refined exposure assessment performed by the eMSCA. It also takes into account the substance´s maximum concentrations indicated in the operational conditions for the remaining Article Service Life. The exposure values obtained for the refined exposure assessment by the eMSCA are given in the confidential annex.

7.12.2. Environment

Not assessed during this substance evaluation.

7.13. Risk characterisation

7.13.1. Human Health

7.13.1.1. Workers

Dermal exposure

Based on the physico-chemical properties, e.g. molecular weight < 500 g/mol and a moderate Log K_{OW} (cf. section 7.3 and 7.4), dermal absorption cannot be excluded. Therefore, and due to the identified skin sensitising properties, the registrant specifies that the handling of $Ca(acac)_2$ should be strictly controlled to avoid dermal contact. The eMSCA agrees with the conclusions of the registrant.

Inhalation exposure

As described in the chapter “exposure assessment”, the eMSCA carried out an exposure assessment for the inhalation exposure pathway with ECETOC TRA v3. The assessment was based on the parameters given in the CSR and the most conservative assumptions (full 8 hour shift, substance as such (100 %), indoors with basic general ventilation, no local exhaust ventilation (LEV), no respiratory protection (RPE)) were made during calculation.

The model estimation yielded the highest inhalation exposure value for PROC 8a. For this PROC, the estimate exceeds the DNEL, derived by the eMSCA (10 mg/m^3). However, these values were obtained with a combination of very conservative assumptions and therefore most likely overestimate the actual situation at the workplace. The registrant stipulated a combination of several OCs and RMMs, including e.g. high level of containment, effective exhaust ventilation, for the use of $Ca(acac)_2$.The combination of PROC 8a with LEV would already yield an inhalation exposure, which is about half the DNEL.

Therefore, the RCR is < 1, even without adapting the other conservative parameters used for the estimation to the “real” situation at the workplace (shorter periods, lower concentration of the substance, use of RPE …).

To conclude, the OCs and RMMs described by the registrant (for dermal exposure) ensure that the risks related to the inhalation exposure to $Ca(acac)_2$ are adequately controlled as well. As the eMSCA could demonstrate no risk, the eMSCA waives the request for a quantitative exposure assessment for the inhalation exposure pathway.

7.13.1.2. Consumers

The lead registrant did not perform any specific risk characterisation for consumers. The eMSCA performed own calculations of DNELs and consumer exposure.

$Ca(acac)_2$ is a skin sensitising chemical, a property which is generally regarded as a threshold effect. However, based on the available experimental data it was not possible to derive an appropriate DNEL to compare it with exposure levels resulting from the use of the compound in consumer products. Hence, no risk characterisation ratio could be determined and the level of risk for skin sensitisation and/or allergic skin reactions for consumers could not be estimated. With a potency as a strong sensitising agent, $Ca(acac)_2$ would qualify for the high hazard band. Exposure to such potent substances should be strictly contained and dermal contact avoided (Guidance on information requirements and chemical safety assessment. Part 3: Risk Characterisation, Version 2.0, November 2012).

Since the exposure values were confidential the full tables for risk characterisation are available in the confidential annex.

Risk characterisation of inhalation exposure

The eMSCA concludes that the inhalation exposure scenario did not yield a RCR > 1.

Risk characterisation of oral exposure

The eMSCA concludes that the oral exposure scenario did not yield a RCR > 1.

Risk characterisation of dermal exposure

The eMSCA concludes that all dermal exposure scenarios did not yield a RCR > 1.

Conclusion on risk characterisation for consumers

Every exposure scenario yielded in RCR < 1 indicating controlled risks for consumers.

7.13.2. Overall risk characterisation

Human health (combined for all exposure routes)

Every exposure scenario yielded in RCR < 1 indicating controlled risks for consumers.

7.14. References

AgBB (2012): Bewertungsschema für VOC aus Bauprodukten Bewertungsschema für VOC aus Bauprodukten. https://www.umweltbundesamt.de/sites/default/files/medien/355/dokumente/agbb-bewertungsschema_2012.pdf (last accessed 2019-07-16)

AGS (2015): Technische Regel für Gefahrstoffe 900 "Arbeitsplatzgrenzwerte".

Dodd D.E., Garman R.H., Pritts I.M., Troup C.M., Snellings W.M., and Ballantyne B. (1986): 2,4-Pentanedione - 9-Day and 14-Week Vapor Inhalation Studies in Fischer-344 Rats. Fundamental and Applied Toxicology 7 (2), 329-339. DOI: Doi 10.1016/0272-0590(86)90163-6

EC (2014): Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work, last amended by Directive 2014/27/EU.

EC (2015): Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, last amended by Regulation (EU) No 2015/1221.

ECETOC (2012): Technical Report No. 114 - ECETOC TRA version 3: Background and Rationale for the Improvements. http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-114-ECETOC-TRA-v3-Background-rationale-for-the-improvements.pdf (last accessed 2019-07-16)

ECHA (2012): Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.8: Characterisation of dose [concentration]-response for human health; Version: 2. https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258 (last accessed 2019-07-16)

ECHA (2012): Practical Guide 15: How to undertake a qualitative human health assessment and document it in a chemical safety report. https://echa.europa.eu/documents/10162/13655/pg_15_qualitative-human_health_assessment_documenting_en.pdf (last accessed 2019-07-16)

Gay, M. and Henrio, F. (2002): Coated calcium or magnesium acetylacetonate, and their use as stabilizer for halogenated polymers. United States patent US6482887B1.

Hansen E., Nilsson N., and Ravnholt Vium K.S. (2014): Hazardous substances in plastics. Survey of chemical substances in consumer products No. 132. Danish Environmental Protection Agency, Copenhagen, DK. http://www2.mst.dk/Udgiv/publications/2014/12/978-87-93283-31-2.pdf (last accessed 2015-07-02)

Heris C. and Uysal T.: Patent: Zinnfreie Stabilisatorzusammensetzung, 2011. DE201010020263. https://patents.google.com/patent/DE102010020263A1/de (last accessed 2015-12-09)

MAK (2006): Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten (MAK-Begründung) Acetylaceton, 2006 WILEY-VCH Verlag GmbH & Co. KGaA.

OECD, Organisation for Economic Co-operation and Development (2004): Emission Scenario Document on Additives in Rubber Industry. Document Number: ENV/JM/MONO(2004)11, date: 2004-06-24. OECD Environment Directorate, Paris, FR. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2004)11&doclanguage=en (last accessed 2018-10-30)

OECD, Organisation for Economic Co-operation and Development (2009): Emission Scenario Document on Plastic Additives. Document Number: ENV/JM/MONO(2004)8/REV1, date: 2009-07-09. OECD Environment Directorate, Paris, FR. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2004)8/rev1&doclanguage=en (last accessed 2018-10-30)

South East Europe PVC Forum: Stabiliser Fact Tables. http://www.seepvcforum.com/en/content/23-stabiliser-fact-tables (last accessed 2018-10-30)

Study report (1999): safety assessmen screen comprising: Acute oral toxicity, acute skin irritation/corrosion acute eye irritation, delayed dermal sensitisation and genotoxicity (Ames test). Research Toxicology Centre S.p.A., Via Tito Speri, 12, 00040 Pomezia (Roma), Italy

SPIN database (2015): Substances in Products in Nordic Countries - Exposure Toolbox. http://195.215.202.233/DotNetNuke/default.aspx

Tyl R.W., Ballantyne B., Pritts I.M., Garman R.H., Fisher L.C., France K.A., and Mcneil D.J. (1990): An Evaluation of the Developmental Toxicity of 2,4-Pentanedione in the Fischer 344 Rat by Vapor Exposure. Toxicology and Industrial Health 6 (3-4), 461-474. DOI: Doi 10.1177/074823379000600308

7.15. Abbreviations

AC	Article Category
AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (German Committee for Health-Related Evaluation of Building Products)
AGS	Ausschuss für Gefahrstoffe (Committee on Hazardous Substances)
AGW	Arbeitsplatzgrenzwert (Occupational Exposure Limit)
APF	Assigned Protection Factor
CSR	Chemical Safety Report
DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals – Targeted Risk Assessment Tool
ERC	Environmental Release Category
ESD	Emission Scenario Document
LEV	Local Exhaust Ventilation
MAK	Maximale Arbeitsplatzkonzentration (Maximum Workplace Concentration); MAK Commission: German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
OC	Operational conditions
OEL	Occupational Exposure Limit
NOAEC	No Observed Adverse Effect Concentration
NOEL	No Observed Effect Level
PNEC	Predicted No Effect Concentration
POD	Point of Departure
PPE	Personal Protective Equipment
PROC	Process Categories
PVC	Polyvinyl chloride
RCR	Risk Characterisation Ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Management Measures
RPE	Respiratory Protection
STOT RE	Specific Target Organ Toxicity Repeated Exposure