baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

dapsone

EC No 201-248-4

CAS No 80-08-0

Evaluating Member State: Germany

Dated: 14 June 2017

Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Safety and Health
Division 5 - Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

Year of evaluation in CoRAP: 2016

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 registrants 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 registrants 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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Dapsone (4,4'-diaminodiphenylsulfone, CAS No. 80-08-0, EC No. 201-248-4) was selected for substance evaluation in order to clarify concerns about its potential to act as an endocrine disruptor in the environment.

The concern was raised as there exists preliminary evidence from *in vitro* studies and structure activity considerations, which indicates the potential of an estrogen like endocrine activity of dapsone. The eMSCA considered a substance evaluation necessary to clarify whether the substance has endocrine disrupting properties for the environment. The available data on human health endpoints provided by the registrants within the CSR was screened for potential endocrine related evidences but not analysed and assessed in detail.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A compliance check according to Article 41 of REACH is ongoing.

According to Maran et al. (2004), dapsone is used as an antibiotic in aquaculture. Its use is restricted in Italy following the regulation (CE) no. 2377/90 with respect to residue limits of veterinary medical products in food stuff of animal origin. Dapsone is included in Annex IV of this regulation.

Dapsone is classified as Acute Toxic 4 H302 according to the CLP regulation with respect to human health, self classifications as Acute Toxic 3 are available. With respect to the environment the registrants provide a self classification as Aquatic Chronic 2.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusion with respect to the environment.

Table 1

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

4. FOLLOW-UP AT EU LEVEL

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

On the basis of the available information, there is currently no need for follow-up regulatory actions at EU level (see section 5).

4.1.1. Harmonised Classification and Labelling

Based on the available data there is currently no need to revise classification and labelling for the environment.

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

On the basis of the available information, there is currently no need for an identification of the substance as SVHC (see section 5).

4.1.3. Restriction

On the basis of the available information, there is currently no need for a proposal for a restriction of the substance or certain uses with respect to the environment (see section 5).

4.1.4. Other EU-wide regulatory risk management measures

On the basis of the available information, there is currently no need for a proposal for other regulatory risk management measures with respect to the environment (see section 5).

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Currently, no follow-up is foreseen at EU-level.

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	x
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

There is currently no need for follow-up action at EU level with respect to the environment and the evaluated concern. This is due to to the low probability of environmental releases from the currently registered uses and the resulting predicted environmental exposures. The concern on potential endocrine properties of dapsone is low, but cannot be completely removed by the available data. Therefore a certain

uncertainty about the potential of dapsone to act as an endocrine disruptor in the environment still remains. Generally, the data availability for dapsone (also from public literature) is low with respect to both exposure as well as hazard aspects. If any further information on the potential mode of action and a possible endocrine activity on receptors or hormone synthesis from *in vitro* studies, long-term and endocrine-related *in vivo* effects, releases to the environment or other relevant uses becomes available, this is to be considered in the CSA. In such case, if considered necessary, the substance could be included in the CoRAP again and a new substance evaluation could be initiated. The particular reasoning is as follows:

There are indications for potential estrogen like endocrine modes of action of dapsone from *in silico* data. Additionally, dapsone shows a structural similarity and comparable interaction potentials (similar 3D structure, phenol-like H-bond donor potential, sulfone moiety) to bisphenol S, a suspected ED currently under substance evaluation. In contrast to bisphenol S, the aromatic ring systems of dapsone carry an amino group (aniline group) in para position providing a H-bond donor potential, which is essential for binding to the estrogen receptor proteins. In BPS this H-bond donor potential is provided by hydroxyl groups (phenolic OH groups) in para position of the aromatic ring systems. Although anilines are known to have a weaker binding affinity to the estrogen receptor proteins than phenols, they show significant binding to the estrogen receptor *in vitro* (Hamblen et al. 2003). Therefore, binding to the estrogen receptor proteins or influence of steroidogenesis via other pathways in wildlife species seems possible for dapsone. The available *in vitro* screening data from ToxCast assays provided by the US EPA show a low but concentration dependent binding affinity of dapsone to the estrogen receptor. However effects here were only observed below the cut-off value of the respective assays. Furthermore, these screening assays are not very sensitive and specific. Hence, reliable and conclusive data from *in vitro* tests are missing to be able to conclude on the endocrine properties of Dapsone. The environmental hazard assessment conducted by the registrants results in a high ecotoxicity of dapsone towards invertebrates and algae. Despite of the low acute toxicity to fish, a potential long-term toxicity including endocrine-mediated effects to fish cannot be excluded at the moment as no long-term fish study is available. No *in vivo* data for effects related to an endocrine mode of action is available from open literature. Hence, the data availability regarding potential endocrine effects in general is extremely poor and a conclusion on possible endocrine properties and *in vitro* and *in vivo* effects can currently not be reached. If uses of Dapsone lead to environmental emissions and exposure in the future, the remaining uncertainty about the potential of an endocrine activity of dapsone should be considered by the registrants and a re-initiation of a substance evaluation would be needed.

With respect to ecotoxicity, it is important to note that there is some indication (Kawabata et al. 2013), that - although STP micro-organisms were not affected by dapsone - other micro-organisms seem to be much more sensitive. Moreover, there is some indication (Kawabata et al. 2013) that metabolites of dapsone, occurring under UV radiation, might have a 5-fold higher toxicity to micro-organisms and toxicity might thus be increased under UV radiation. Hence, also the metabolites of dapsone should be considered.

There are no measured data provided by the registrants on environmental releases. Processes with potential releases were indicated by the registrants, but formulation and industrial end uses seems to proceed under controlled conditions and often via automated processes, according to the registrants, and waste is incinerated. According to the registrants, dapsone polymerises into very strong networks, and a release of monomeric dapsone is very unlikely. This is supported by available monitoring studies (n=5) from open scientific literature where dapsone was measured, and only detected at concentrations below LOQ and only once in groundwater at > 10 ng/L (Sacher et al. 2001).

EFSA conducted a leaching study with respect to the use of dapsone in food contact materials, which was also referred to by the registrants. However, the study cannot be assessed as no details on the test conditions and results are available and no further

information could be retrieved. Furthermore, the registrants confirmed that dapsone is not used in food contact materials. Thus, the study is seen as not relevant for the assessment of environmental exposure.

For any other uses that might be registered at a later point in time, conclusions might differ and environmental exposure as well as the hazards need to be assessed again. In summary, based on the available data the concern for endocrine properties is low and exposure to the environment from the currently registered uses within the scope of REACH seems to be negligible at the moment. It is to be mentioned however, that data availability (also from the open literature) for both exposure and endocrine properties is very poor. Still, concerns are weak and there is not enough evidence to justify a request for more specific *in vitro* and also *in vivo* data to be able to conclude on the initial concern. Therefore, no further data is requested on the endocrine properties at the moment. However, the registrants should include information in the CSR, when further data becomes available e.g. from *in vitro* or *in vivo* studies as well as on environmental releases. If the assessment will result in a relevant environmental exposure, at least tests clarifying the concern with respect to endocrine disrupting properties (i.e. an estrogen agonistic mode of action) should be considered by the registrant and a re-initiation of a substance evaluation might be needed. More specific evidence regarding the endocrine activity of dapsone could for example be provided by *in vitro* assays that include cell metabolism and growth and also consider other pathways than receptor binding (*e.g.* steroidogenesis).

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

Not applicable, see section 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Dapsone was originally selected for substance evaluation in order to clarify concerns about potential endocrine disruption.The concern was raised as there exists some evidence from *in vitro* studies and structure activity relation, which indicate the potential of an endocrine activity. eMSCA considered a substance evaluation necessary to clarify whether the substance has endocrine disrupting properties for the environment.

The evaluation was focused on environmental aspects, human health was not evaluated. The available data on human health in the CSR was only screened for potential endocrine-related evidences but not analysed in detail.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Ecotoxicity short-term	Acute tests with fish are reliable, no effects ≥ 100 mg/L. The data is sufficient for PNEC derivation. No effects on micro-organisms (STP) were observed at concentrations of 1000 mg/L. However, one study showed an increased photo-induced toxicity to bacteria (fast degradation, but 5-fold higher toxicity (EC_{50} of 31.4 instead of 172.0 mg/L) after 6h UV radiation, possibly due to metabolites).
Ecotoxicity long-term	Chronic tests are available for daphnids and algae, which also were most sensitive (NOEC 0.22 mg/L, EC_{50} 0.52 mg/L). Data is appropriate for ecotoxicological assessment and PNEC derivation. Dapsone is very toxic to daphnids and algae. No data available from literature to conclude on long-term effects for fish or other organisms. It cannot be concluded whether fish might be more sensitive than daphnids. For the sediment and terrestrial compartment no data is available.
Endocrine disrupting properties in silico	Structural similarity to bisphenols such as BPS: similar 3D structure, sulfone moiety and a phenol-like H-bond donor potential. The only difference are the primary aromatic amine groups of Dapsone instead of a phenol goup. BPS binds to the estrogen receptor and there are indications from scientific studies that it excerts endocrine effects *in vitro* and *in* vivo (substance evaluation ongoing). Also aromatic amines (*i.e.* anilines, such as 4-methylendianilin MDA) are able to bind to the estrogen

	receptor (Hamblen et al. 2003), although with a weaker binding affinity than phenols. Moreover, a relative binding of Dapsone to the estrogen receptor (RBA 0.0010) was estimated by a QSAR study (Maran et al. 2004). Hence, there is some indication for an ER binding potential of Dapsone due the structural similarity to the two substances and a QSAR study.
Endocrine disrupting properties *in vitro* (including read-across)	There is some indication for a binding affinity to the estrogen receptor in 2 *in vitro* tests from the US EPA EDSP21 programme, although effects were observed below the cut-off and were not significant (relative binding affinity compared to E2:0.00158). No details on test conditions and results are available, and the tests did not integrate intrinsic metabolic activity. Results can only be taken as weak evidence for a possible binding to the ER. More specific tests would be needed to clarify the binding ability. No indications for androgen or thyroid related activities are available. Some evidence for a possible *in vitro* binding of dapsone to the estrogen receptor is given by a read-across to 4-methylendianilin (MDA) and Bisphenol S (see also previous box). There are several studies indicating a binding of the structural similar BPS to the estrogen receptor and a weak estrogen agonist acitivity *in vitro*. The aromatic amine MDA, which shows a high structural similarity to dapsone, binds to the ER receptor in a recombinant yeast assay (estrogenic activity EC50 $2*10^{-4}$; 17ßEstradiol: 10^{-10}, Hamblen et al. 2003). Hence, this gives supporting evidence that aromatic amines are potential ER binders (although weaker than phenols).
Endocrine disrupting properties *in vivo*	No data available from CSR or further literature. Thus, currently no drawing of a conclusion is possible. Data for human health indicate effects on an impaired fertility, the number of motile sperm and a reduced uterine weight in rats, but were not analysed in detail. Endocrine-mediated effects cannot be excluded or rejected in light of the structural similarity to bisphenols, such as BPS. For BPS there are scientific studies showing effects in fish (altered hormone levels, impaired reproduction and offspring production, offspring malformations), that might be endocrine mediated (substance evaluation ongoing).
Exposure of environment and related risks for the individual environmental compartments	According to the information available from registrants/CSR the calculated risks are below 1 for all compartments. Production mainly takes place in closed and controlled systems. Dapsone polymerizes with high cross-link densitiy to very stable networks. The corresponding polymers are mainly used in extremely stable and lightweight materials for aerospace. Waste is

	incinerated. Possible leaching is unprobable according to the registrants. The cited leaching study of EFSA with respect to use in food contact materials cannot be assessed as no details were retrievable. Study seen as not relevant as an use in food contact materials (FCM) is not registered and use conditions deviate from that for registered uses. Two ECHA Roadmap 2020 exposure relevance trigger are met (wide dispersive[1] and wide spread use[2]). However, based on information from registrants, probability of an exposure to environment for the registered uses seems to be unlikely due to substance properties (polymerisation to dense networks), strictly controlled conditions, incineration of waste and the specific uses.
Monitoring Studies	Only few monitoring studies are available (5). No indications for occurrence in environment as measurements below LOD/Q in most studies, only one study reported concentrations >10 ng/L).

[1] indicated by sum of use tonnage significantly exceeds 10 t AND 2 formulation uses and 5 uses at industrial sites (> 3).

[2] indicated by more than 10 locations for several uses.

7.2. Procedure

The registration data was evaluated on the basis of the CSR of the Lead registrant (latest update 30.1.2015) and the aggregated registration dossier (updated latest on 17.03.2016). The evaluation covered all endpoints (physico-chemical data, ecotoxicity data, exposure, fate and behavior). Data on human health was only screened with respect to relevant results for endocrine disruting properties and the environment.

The Lead registrant was contacted via email and phone to clarify questions and was asked for further information on endocrine-related effects, read-across, possible metabolites, uses, fate or leaching of the substance to the environment and planned activities (latest on 8th of August 2016).

The eMSCA conducted a comprehensive and structured literature research to gather literature on the ecotoxicity to different organism groups, endocrine modes of action, endocrine effects, exposure, fate and monitoring studies for Dapsone using defined keywords and synonymes. However, data availability with relevance for the SEV was very scarce and restricted to medical relevance and the use of dapsone as an antibiotic in most cases (overall 586 hints).

The concern with respect to the endocrine disrupting porperties for the environment was evaluated considering the available *in silico* and *in vitro* data, relevant information from human health data, and a read across to 4-Methylendianilin (CAS 101-77-9). *In vivo* data on endocrine effects was not available.

The exposure relevance was evaluated on the basis of the information from the registrants provided in the CSR and via personal communication with the registrants.

The Endocrine Disruptors Expert Group was consulted in September 2016. The received comments have been taken into account for the evaluation.

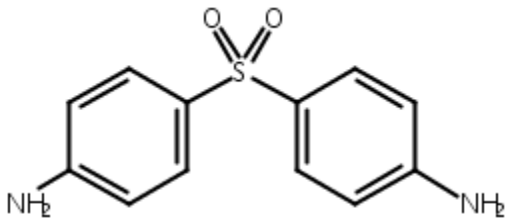
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Dapsone 4,4'-sulfonyldianiline
EC number:	201-248-4
CAS number:	80-08-0
Index number in Annex VI of the CLP Regulation:	612-084-00-1
Molecular formula:	$C_{12}H_{12}N_2O_2S$
Molecular weight range:	248,3 g/mol
Synonyms:	4,4'-DDS 4,4'-DDS Dapsone 4,4'-Diamino diphenyl sulfone 4,4'-Diaminodiphenylsulfone 4-(4-aminophenyl)sulfonylaniline 4-Aminophenyl sulphone 4-[(4-aminobenzene)sulfonyl]aniline Bis(4-aminophenyl) Sulfone Dapson dapsone P,P'-DIAMINODIPHENYL SULFONE Benzenamine, 4,4'-sulfonylbis-

Type of substance Mono-constituent

Structural formula:



Multiconstituent/UVCB substance/others

Not applicable. Metabolites are not known.

Read across

A read-across to 4-Methylendianilin (MDA) (CAS 101-77-9, EC 202-974-4) and 4,4'-sulphonyldiphenol (BPS) (CAS 80-09-1, EC 201-250-5) was performed.

Table 5

SUBSTANCE IDENTITY	
Public name:	4-Methylendianilin
EC number:	202-974-4
CAS number:	101-77-9
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	$C_{13}H_{14}N_2$
Molecular weight range:	198.27 g/mol
Synonyms:	Bis(4-aminophenyl)methane 4,4'-Diaminodiphenylmethane 4,4'-Methylenebisbenzenamine MDA para, para'-Diaminodiphenyl-methane Dianilinomethane 4,4'-Diphenylmethanediamine

Table 6

SUBSTANCE IDENTITY	
Public name:	4,4’-sulphonyldiphenol (BPS)
EC number:	201-250-5
CAS number:	80-09-1
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	$C_{12}H_{10}O_4S$
Molecular weight range:	250.27
Synonyms:	Phenol, 4,4'-sulfonylbis- (9CI) Phenol, 4,4'-sulfonyldi- (6CI, 8CI) 1,1'-Sulfonylbis[4-hydroxybenzene] 4,4'-Bisphenol S 4,4'-Dihydroxydiphenyl sulfone 4,4'-Sulfonylbisphenol 4-Hydroxyphenyl sulfone Bis(4-hydroxyphenyl) sulfone Bis(p-hydroxyphenyl) sulfone Bisphenol S BPS 1 Diphone C p,p'-Dihydroxydiphenyl sulfone

	Phenol, sulfonylbis- Bis(hydroxyphenyl)sulphone Dihydroxydiphenyl sulphone Phenol, sulphonyldi- Sulfonyldiphenol-

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	*crystalline white to off-white powder with no detectable odor*
Vapour pressure	*0.0000000271 mmHg at 25°C ($3,61*10^{-6}$ Pa)* *(Estimated using US EPA 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.10)*
Water solubility	*380 mg/L at 37°C (publication)*
Partition coefficient n-octanol/water (Log K_{ow})	*0.97 at 25 °C (QSAR estimation)*
Flammability	*idem*
Explosive properties	*idem*
Oxidising properties	*idem*
Granulometry	*The diameter of 4,4'-DDS particles is from 0,31 µm to 301.68 µm with the following particles size distribution : D(v,0.1) = 22.46µm, D(v,0.5) = 126.24 µm, D(v, 0.9) = 224.19µm.* *The mean diameters are D[4, 3] = 126.85 µm and D[3, 2] = 33.57 µm.*
Stability in organic solvents and identity of relevant degradation products	*stability of the substance, it is not considered to be critical. (waiver based on Column 1 of REACH, Annex IX)*
Dissociation constant	*pK_b = 13.0 (publication)*

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

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

The number of production sites is >10.

7.5.2. Overview of uses

Dapsone is only registered for industrial uses, e.g. as adhesives and sealants and for polymer preparation and their compounds.
According to the registrants, the main use is the production of plastic products. These plastic products are mainly used for production of high performance composite materials. An important area of application of dapsone is the aerospace industry. There are seven active registrations under REACH. Dapsone is solely imported, therefore, the manufacturing process of dapsone is considered out of scope of the evaluation. The uses are listed in Table 9.

Table 9

USES	Use(s)
Uses as intermediate	
Formulation	- Industrial formulation powder phase - Industrial formulation liquid/viscous phase
Uses at industrial sites	- Industrial use as intermediate - Industrial application of adhesives (cartridge, rolling, brushing) - Industrial prepreg manufacturing via automated impregnation - Industrial prepreg processing (shaping, mould lay-up, cure in autoclave or compression moulding) - Industrial production of preparations or articles by tabletting, compression, extrusion, pelletisation
Uses by professional workers	Not indicated in the CSR (professional uses were taken out in an update 2015)
Consumer Uses	Not indicated in the CSR. (listed in SPIN database: occupational use index 3-4)
Article service life	Not indicated in the CSR (SPIN database: probable to be used in articles)

After the industrial formulation (liquid or powder phase) dapsone is used either in the industrial application of adhesives or in the preimpregnated fibres (Prepreg) manufacturing via automated impregnation. Manufacturing via automated impregnation

results in prepreg processing and finally the production of preparations of articles by tableting, compression, extrusion, pelletisation.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 10

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
612-084-00-1	dapsone 4,4'-diamino diphenyl sulfone	201-248-4	80-08-0	Acute Tox. 4 *	H302		

7.6.2. Self-classification

- In the registrations (derivations from Annex VI entry):

  STOT SE 2 H371 (Blood)

  STOT RE 2 H373 (Blood, spleen)

  Aquatic Chronic 2 H411 M(chronic) = 1

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

  STOT SE 1 H370

  STOT RE 1 H372

7.7. Environmental fate properties

The eMSCA supports the conclusions of the registrants that dapsone is not bioaccumulative and not biodegradable.

7.7.1. Degradation

The substance ist not biodegradable. An OECD 301 D Ready Biodegradability test showed no degradation after 28 days (<1%). Hence, dapsone is not readily biodegradable. Further studies are not provided by the registrants.

7.7.2. Environmental distribution

The substance has a low adsorption potential with a K_{oc} of 57 (experimental result).

7.7.3. Bioaccumulation

No potential for bioaccumulation is indicated, as the log K_{ow} is 0.97.

7.8. Environmental hazard assessment

The eMSCA concludes that the ecotoxicological tests provided by the registrants for the aquatic compartment are sufficient for the environmental hazard assessment of the aquatic compartment.

Dapsone has a high toxicity to algae and aquatic invertebrates (both NOEC 72h algae, 21d daphnids: 0.22 mg/L). Long-term toxicity to fish was waived by the registrants as acute toxicity was >100 mg/L (LC_{50} 96h *C. caprius*). Possible long-term effects on fish and in particular possible endocrine mediated effects at lower concentrations cannot be estimated due to the lack in data also from the open literature.

Toxicity towards STP microorganisms is very low (LC_{50} >100 mg/L). However, toxicity for other microorganisms might be much higher. Kawabata et al. (2013) reported a considerable higher (5-fold) toxicity (EC_{50} 31 mg/L with radiation, 172 mg/L without) to the *Photobacterium phosforeum* (ISO 11348) when test solutions with Dapsone were exposed 6h to UV-B, which could probably be triggered by metabolites of dapsone.

All conducted tests are reliable and valid. For aquatic sediments no data are available.

There is very limited ecotoxicological data available in the literature. A comprehensive literature research was conducted and approx. 500 citations found, but mainly on microorganisms and only studies with a medical background. The reason for this might be that dapsone is used as antibiotic for leprosy and malaria treatment (nowadays extremely low production volumes < 1 tpa), and in fish aquaculture. Hence, only the ecotoxicological studies provided by the registrants are available.

No further data on ecotoxicity was found during the literature search providing further insights.

Table 11

ECOTOXICITY DATA			
Method	**Species**	**Effect conc.**	**Reference**
Fish short term	*Cyprinus carpio* (OECD 203)	**>100 mg/L** meas init. (96h LC_{50})	Study report 2011
Fish long-term	data waived		
Aquatic invertebrates acute	data waived		
Aquatic invertebrates chronic	*Daphnia magna* (OECD 211)	**0.22 mg/L** nom. (NOEC 21d reproduction) **0.46 mg/L** nom. (NOEC 21d mort.)	Study report 2012a
Algae	*Pseudokirchnerella subcapitata* (OECD 201)	**0.52 mg/L** meas. geomean (72h EC_{10} cell number)	Study report 2004
Microorganisms (STP)	activated sludge (OECD 209)	**> 1000 mg/L** nom. (3h EC_{50})	Study report 2012b

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

One acute study (96 h) for fish (*Cyprinus* carpio) is provided by the registrants (Study report, 2011). The study is accurately described and in accordance with the OECD Guideline 203. All validity criteria are met.
The LC_{50} concentration is above 100 mg/L, no mortality or abnormal responses have been observed at 100 mg/L.

7.8.1.2. Aquatic invertebrates

One chronic semi-static study (21 d) on aquatic invertebrates (*Daphnia magna*) is provided by the registrants (Study report, 2012a). The study is accurately described and in accordance with the OECD Guideline 211. All validity criteria are met.

The lowest NOEC is based on reproduction and stated as 0.22 mg/L.

7.8.1.3. Algae and aquatic plants

One study (72 h) on algae (*Selenastrum capricornutum*) is provided by the registrants (Study report, 2004). The study is accurately described and in accordance with OECD Guideline 201. The validity criteria of the Guideline are met.

The NOEC is 0.52 mg/L based on cell number.

7.8.1.4. Sediment organisms

No toxicity test is available. The toxicity to sediment organisms is determined with the equilibrium partitioning method (see section 7.8.4.).

7.8.1.5. Other aquatic organisms

Kawabata et al. (2013, JToxicolSci) reported that dapsone degrades rapidly under sunlight and UV-A/B/C (6 h), but exerted a 5-6 fold higher toxicity after 6 h UV-B radiation to *Photobacterium phosforeum* (ISO 11348) (Method: 6 h UV-B irridation, concentration of solution, measurements after 15 min in counter). An EC_{50} of 31.35 ± 0.80 mg/L with UV-B radiation was optained compared to an EC_{50} of 172.01 ± 31.74 mg/L without UV-B radiation. It remains unknown which metabolites are formed and may be more toxic.

7.8.2. Terrestrial compartment

Data is waived by the registrants as direct and indirect exposures of the soil compartment are unlikely. However, the substance is assumed to be persistent in soil. Therefore, it must be categorized in soil hazard category 3 (Guidance R.7c).

7.8.3. Microbiological activity in sewage treatment systems

The activated sludge toxicity test on microorganisms is in accordance with the OECD Guideline 209 (Study report 2012b). Validity criteria are met.

The EC_{50} is > 1000 mg/L.

7.8.4. PNEC derivation and other hazard conclusions

Table 12

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.0044 mg/L	Assessment factor: 50 Extrapolation method: assessment factor
Marine water	PNEC aqua (marine water): 0.00044 mg/L	Assessment factor: 500 Extrapolation method: assessment factor
Intermittent releases to water	PNEC aqua (intermittent releases): 0.01 mg/L	Assessment factor: 100 Extrapolation method: assessment factor
Sediments (freshwater)	PNEC sediment (freshwater): 0.041 mg/kg sediment dw	Extrapolation method: partition coefficient
Sediments (marine water)	PNEC sediment (marine water): 0.0041 mg/kg sediment dw	Extrapolation method: partition coefficient
Sewage treatment plant	PNEC STP: 10 mg/L	Assessment factor: 100 Extrapolation method: assessment factor
Soil	PNEC soil: 0.0056 mg/kg soil dw	Extrapolation method: partition coefficient
Marine water	PNEC aqua (marine water): 0.00044 mg/L	Assessment factor: 500 Extrapolation method: assessment factor
Intermittent releases to water	PNEC aqua (intermittent releases): 0.01 mg/L	Assessment factor: 100 Extrapolation method: assessment factor

Conclusions on ecotoxicity

Dapsone has a high toxicity to algae and aquatic invertebrates (NOEC 0.22 mg/L).

Overall, very few information on ecotoxicity from the CSR and the open literature is available. This is in particular true for chronic effects. A long-term terrestrial test is not available. Furthermore, Kawabata et al. (2013) reported a considerable (5-fold) higher phototoxicity on microorganisms (EC50 31.4 mg/l after UV-B radiation, 172.0 mg/L before UV-B radiation) probably triggered by metabolites of dapsone. Hence, metabolites could be more toxic than the mother substance dapsone. And, although no effects on sewage treatment plant (STP) micro-organisms were observed, other micro-organisms in the aquatic or terrestrial environment could be affected at lower concentrations.

7.8.5. Conclusions for classification and labelling

With respect to the environment, the current self-classification (aquatic chronic 2) seems to be appropriate based on the available data. A harmonised classification and labelling with respect to aquatic toxicity has not been done yet.

7.9. Human Health hazard assessment

Not applicable for the current assessment as out of scope for the concern of the substance evaluation. Human health data with relevance for the environmental assessment are provided below in the section on the assessment of endocrine properties.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

For the assessment of the available data we followed the structure of the conceptual framework in the OECD Guidance Document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption (OECD, 2012b), covering non-testing information (level 1), in vitro data (level 2) as well as information from in vivo studies (level 3-5).

Non-test information (OECD conceptual framework level 1)

There are structural alerts indicating a potential binding affinity to ER:

General SAR
Dapsone has two primary aromatic amine groups indicating a potential binding, via the phenol-like H-bond donor potential, ability to the estrogen receptor (ER). This structural alert is indicated by the OECD QSAR Toolbox as well as an internal scanning tool for EDs at the eMSCA (unpublished).
In general, dapsone is structurally quite similar to Bisphenol S with respect to its main 3D structure and the molecular interaction potential (sulfone moiety and a phenol-like H-bond donor potential). Dapsone is the respective anilin derivate of BPS. The only difference are the primary aromatic amine groups of Dapsone instead of a phenol group. Scientific studies show that BPS is able to bind to the estrogen receptor *in vitro* and may also exert estrogenic effects *in vivo* (substance evaluation ongoing), as will be refered to later below (read-across).

It is known that also aromatic amines (i.e. anilines, such as 4-methylendianilin MDA) are able to bind to the estrogen receptor (Hamblen et al. 2003), although with a weaker binding affinity than phenols. Hence, there is some indication for an ER binding potential of Dapsone due the structural similarity to the two substances.

In silico/QSAR

Maran et al. (2004) estimated the relative binding activity (RBA) of Dapsone to the estrogen receptor (log RBA) on the basis of 132 QSAR screening substances already suspected as ED to be 0.0010 (Category C) with a reliability coefficient of 0.38 (<0.5 low). Hence, there is some indication for an ER binding potential of Dapsone due the structural similarity to the two substances and a QSAR study. According to Maran et al. (2004) dapsone was analysed because it was suspected to act as endocrine disrupting compound (EDs) in the Endocrine Disrupter Knowledge Base (EDKB) of US EPA (https://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/ucm135074.htm#2000).

In vitro assays providing data on selected endocrine mechanisms (OECD conceptual framework level 2)

The US EPA EDSP21 Programme analyzed dapsone in different *in vitro* tests for an estrogenic, androgenic or thyroid action. The test specifications are available under https://actor.epa.gov/edsp21/ and summarized in the following. Two assays were indicated in the EPA report and database with a positive response, i.e demonstrating a moderate binding affinity of dapsone to the estrogen receptor. However, these two assays are not reliable when having a look at the concentration-response curves (via https://actor.epa.gov/dashboard/) as will be described below. Observed effects were just below the cut-off values of the respective assays or effects were above the cytotoxicity level. No detailed test results were available. Hence, these *in vitro* assays, even though a concentration dependency could be observed, do not provide reliable evidence for an ER activity of dapsone.

In general, the ToxCast data and Tox21 assays are high-troughput data made for a first screening and are not very sensitive. Moreover, as most *in vitro* data they cannot provide information on the potential effects in living cells as they do not integrate cell metabolism. Also, a potential estrogenic action via effects on steroidogenesis, responsible for the production of estradiol (and testosterone) that is catalysed by enzymes, may be overlooked as this is not covered by the conducted tests.

To be able to clarify the remaining concern that dapsone has a potential for an estrogen receptor binding and an estrogenic activity, more specific *in vitro* assays are needed that cover different possible mechanisms of action, for example also include the intrinsic metabolic activity (via pre-incubation with a S9 mix), or may be able to prove a estrogen receptor binding (as for example the YES assay) or indicate effects on steroidogenesis (as the steroidogenesis assay).

The ToxCast assays for androgenic and thyroid-related activity were all negative. However, as the assays are not very sensitive the results have to be taken with care in general.

Summary of ToxCast assays for Estrogenic action

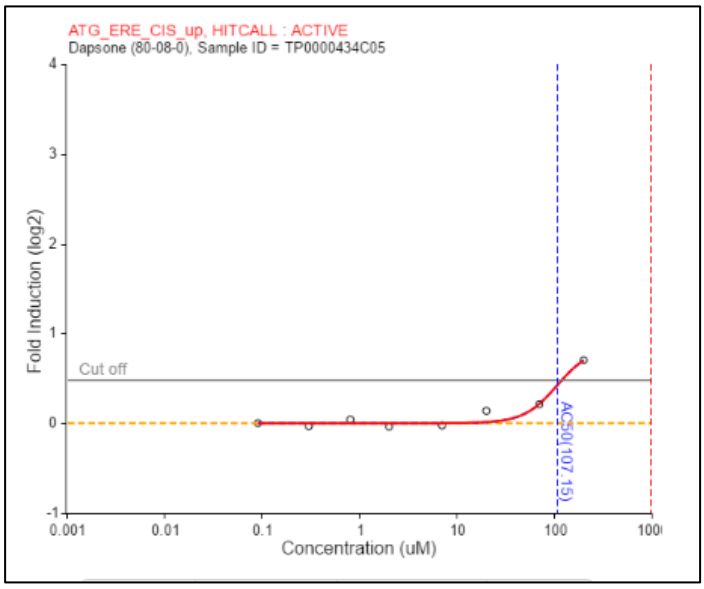
The USEPA EDSP21 programme included *in vitro* testing on dapsone. 16 assays for estrogen receptor (ER)-related effects were conducted. 14 demonstrated no activity of dapsone, but 2 were indicated as positive (ATG_CIS and Tox21_Era_LUC_BG1_Agonist, marked in bold in Table 13), although one having an activity only identified at concentrations above the cytotoxicity limit of 161.93 µM dapsone. According to the ToxicityForecaster (ToxCast) of US EPA dapsone demonstrates a moderate binding affinity to the estrogen receptor of 0.00158 compared to ethinylestradiol (E2) in an ER binding assay (for Comparison BPA: 0.45, BPS: 0.263) (USEPA. 2016. ToxCast & Tox21 Summary Files from invitrodb_v2. Retrieved from http://www2.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data on October 28, 2015. Data released October 2015). No antagonist activity was shown. As the agonistic receptor binding of 0.00158 was below the EPA cut-off of 0.05 for further prioritization (EPA, 2014), dapsone was not prioritized for further assessment by US EPA based on the EDSP21 results on dapsone and the EPA white paper conclusions (2014).

Table 13

DETAILS ON THE ASSAYS WITH REGARD TO ESTROGEN ACTIVITY CONDUCTED DURING THE US EPA EDSP21 PROGAMME (16 ASSAYS, 2 POSITIVE), "POSITIVE " BUT NOT RELIABLE RESULTS REFERED TO IN THE TEXT ARE MARKED IN BOLD				
Assay	**Cell line**	**Test details**	**Exposure**	**Activity**
ACEA_T47D	T47D, estrogen-sensitive human breast	Real-time cell growth kinetics, label-free	80h	No activity
ATG_CIS	**Human liver HepG2**	**mRNA induction, regulation of TF activity through human ERE (estrogen response element)**	**24h**	**Agonist Activity AC 107,0012**
ATG-TRANS	Human liver HepG2	Multiplexed mRNA induction , changes to regulation of TF activity through ESR1 TF	24h	No activity
NVS_NR_mERa	mouse Esr1 protein	Biochemical assay, radioligand binding	18h	No binding
OT_ER_ERaERa_0480	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR1 homodimer	8h	No activity
OT_ER_ERaERa_1440	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR1 homodimer	24	No activity
OT_ER_ERaERb_0480	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR1 and ESR2 heterodimer	8h	No activity
OT_ER_ERaERb_1440	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR1 and ESR2 heterodimer	24h	No activity
OT_ER_ERbERb_0480	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR2 homodimer	8h	No activity
OT_ER_ERbERb_1440	HEK293T human kidney	Protein fragment complementation assay, changes to protein dimerization and response pathways through human ESR2 homodimer	24h	No activity
OT_Era_EREGFP_0120	Human cervix HeLa	Protein induction, changes in gene expression through human ESR1 and ERE	2h	No activity
OT_Era_EREGFP_0480	Human cervix HeLa	Protein induction, changes in gene expression through human ESR1 and ERE	8h	No activity
TOX21_ERaBLA_Agonist_ratio	HEK293T human kidney	Lactamase induction, induction, regulation of gene expression through human ESR1 and ERE	24h	Not agonistic

TOX21_ERaBLA_Antagonist_ratio	HEK293T human kidney	Lactamase induction, induction, regulation of gene expression through human ESR1 and ERE	24h	Not antagonistic
Tox21_Era_LUC_BG1_Agonist	**Human ovary BG1**	**Luciferase induction, regulation of gene expression through human ESR1 and ERE**	**48h exposed**	**Agonist Activity AC 56,1064**
Tox_21ERaLUC_BG1_Antagonist	Human ovary cellline BG1	Luciferase induction, regulation of gene expression through human ESR1 and ERE	48h	Not antagonistic

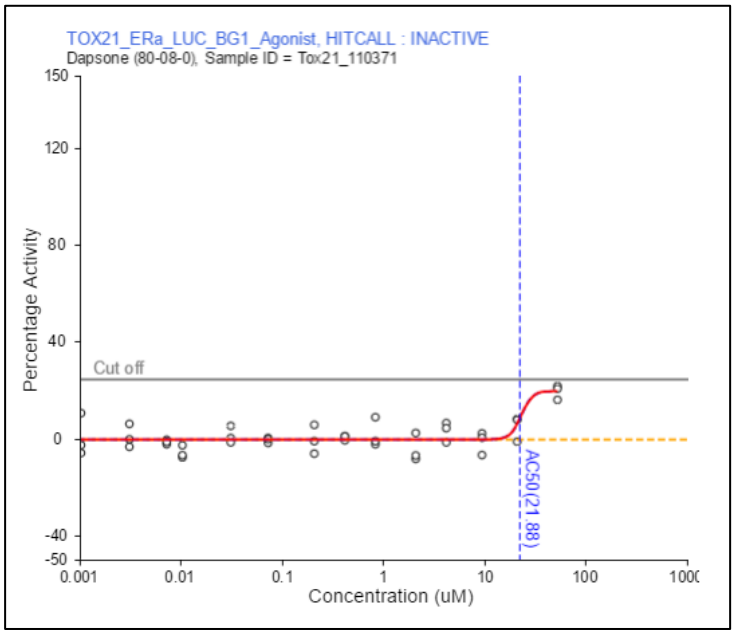
When looking at the concentration response-curve of the ATG_CIS assay, marked as positive in the report, it is clear that there is only an effect at the highest test concentration which is more than 100 µM (assumed to be 200 µM, around/above cytotoxicity), and this response is only just above the cut-off limit and hence not reliable (see Figure 1).



Model	AIC	RMSE	Top	AC50	Slope
Constant	-0.3	0.26	-	-	-
Gain-Loss	-14.42	0.05	0.84	107.15	2.53
Hill	-18.42	0.05	0.84	107.15	2.53

Figure 1: Concentration response curve for dapsone activity in the ATG_CIS assay from the EPA iCSS Dashboard

Also, when having a look at the concentration response-curve of the Tox21_Era_LUC_BG1_Agonist assay, marked as positive in the report, it becomes clear, that effects are below the cut-off (see Figure 2).



Model	AIC	RMSE	Top	AC50	Slope
Constant	298.63	7.03	-	-	-
Gain-Loss	278.33	4.63	20.02	21.88	8
Hill	274.33	4.63	20.02	21.88	8

Figure 2: Concentration response curve for dapsone activity in the Tox21_Era_LUC_BG1_Agonist assay from the EPA iCSS Dashboard

Summary of ToxCast assays for Androgenic action

The USEPA EDSP21 programme also included *in vitro* testing on dapsone with 8 assays conducted to measure androgen receptor (AR)-related effects. Here 8 assays were conducted and demonstrated no activity with dapsone in all assays. Thus the summary shows AR AUC for agonist and antagonist as zero (0).

Table 14

Details on the assays with regard to androgen activity conducted during the US EPA EDSP21 progamme (8 tests conducted, all inactive)				
Assay	**Cell line**	**Test details**	**Exposure**	**Activity**
ATG-TRANS	HepG2, human liver	mRNA induction changes to the regulation of TF activity through AR TF	24 h	No activity
OT-AR_AR OT-AR_ARELUC_AG0480	chinese hamster ovary CHO-K1	Luciferase induction, regulation of gene expression through human AR and androgen response element ARE	24h	Not AR agonistic
OT_AR_ARSRC1_0480	HEK293T human kidney	Protein fragment complementation assay, protein dimerization through human AR and coupling protein SRC1	8 h	No activity

OT_AR_ARSRC1_0960	HEK293T human kidney	Protein fragment complementation assay, protein dimerization through human AR and coupling protein SRC1	16h	No activity
Tox 21_AR_BLA_ agonist_ratio	HEK293T human kidney	Beta lactamase induction, regulation of gene expression through human AR and estrogen response element ERE	24h	Not antagonistic
Tox 21_AR_BLA_ antagonist_ratio	HEK293T human kidney	Beta lactamase induction, regulation of gene expression through human AR and estrogen response element ERE	24h	Not antagonistic
TOX21_AR_LUC_MDAKB2_agonist	MDA-kb2 human breast	Luciferase induction, regulation of gene expression through human AR and androgen response element ERE	24h	Not agonistic
TOX21_AR_LUC_MDAKB2_antagonist	MDA-kb2 human breast	Luciferase induction, regulation of gene expression through human AR and androgen response element ERE	24h	Not antagonistic

Summary of ToxCast assays for Thyroid-related activity

Limited *in vitro* information was identified on dapsone and its potential for interaction with the thyroid hormone system. In particular, the USEPA EDSP21 website (http://actor.epa.gov/edsp21/) includes results from three reporter gene binding assays conducted on dapsone, with all assays demonstrating no activity (THRA/B and TRE regulation). These *in vitro* data did not demonstrate any relevant thyroid-related binding activity. The conclusion is that dapsone is not active with key thyroid system elements.

Table 15

Details on the assays with regard to thyroid activity conducted during the US EPA EDSP21 progamme (3 assays, all inactive)				
Assay	**Cell line**	**Test details**	**Exposure**	**Activity**
ATG_THRa1_TRANS	HepG2, human liver	Multiplexed mRNA induction, changes to regulation of TF activity through THRA TF	24h	No activity
Tox21_TR_LUC_GH3_agonist	GH3 rat pituitary gland	Luciferase induction, regulation of catalytic activity through human THRA and thyroid response element (TRE)	48h	Not agonistic
Tox21_TR_LUC_GH3_Antagonist	GH3 rat pituitary gland	Luciferase induction, regulation of catalytic activity through human THRA and THRB and thyroid response element (TRE)	48h	Not antagonistic

In vivo assays providing data on selected endocrine mechanisms or relevant endocrine endpoints (OECD conceptual framework level 3, 4 and 5)

For dapsone, there is a lack of data. No *in vivo* test data is available from the open scientific literature or the CSR that addresses potential endocrine properties or chronic effects in fish. Thus, currently it is not possible to draw a conclusion.

Data for human health indicate effects on an impaired fertility, the number of motile sperm and a reduced uterine weight in rats, but were not analysed in detail.

There is only information on *in vivo* effects for the structurally related bisphenols, such as BPS (see section on SAR, QSAR, read-across). For BPS there are scientific studies showing effects in fish (altered hormone levels, impaired reproduction and offspring production, offspring malformations), that might be endocrine mediated (substance evaluation ongoing).

Hence, potential endocrine-mediated effects of dapsone cannot be excluded or rejected.

Human Health data

The CSR was screened for indications in the human health hazard assessment section for possible estrogenic or endocrine-related effects and the following data were found:

Table 16

Overview on HH data			
Organism	**Dose**	**Effect**	**Reference**
Male rat	> 75 mg/kg bw/day	Impaired fertility at high doses, reduction of sperm number and motility at toxic doses (methemoglobinaemia)	Study report (2005)
Female rat	>= 12 <= 75 mg/kg bw/day	Reduced number of implantations, increased number of early resorption rate, reduced mean litter size probably secondary to maternal toxicity	Study report (2005)
Female mouse	200 mg/kg bw/day	Reduced maternal body weight, maternal body weight change and gravid uterine weight	Anonymous (2004)

Read across to anilines/amines

4,4'-Methylenedianiline (CAS 101-77-9) has a relative ER binding affinity of 0.00885 compared to 17β ethinylestradiol. 4,4'-Methylenedianiline (CAS 101-77-9) is identified as SVHC due to its cancerogenic properties (57a) and has a relatively high chronic toxicity to aquatic invertebrates (5-18 µg/L), whereas fish are far less sensitive. It is on the SIN list due to its classification as CMR (Class I & II) according to Annex 1 of Directive 67/548/EEC.

4,4'-Methylenedianilin is structuraly very similar to dapsone (backbone and anilin groups) and demonstrates a moderate binding affinity to the ER receptor with an EC_{50} of $1{,}85*10^{-4}$ in the YES Assay (Hamblen et al. 2003*).* Also other anilines have been shown to bind to the estrogen receptor in vitro (Hamblen et al. 2003). US EPA EDSP reports 4 tests with an agonistic estrogen receptor binding (AC50 34-66), but does not report androgen- and thyroid-related binding affinities. Hence, *in vitro* tests indicate a moderate binding of 4,4'-methylenedianiline to ER. (Please also refer to the sections on SAR/QSAR).

Read-across/endocrine activity of Bisphenol S

The structural similarity of dapsone to BPS (4,4'-sulfonyldiphenol, CAS No. 80-09-1) and also other bisphenols with respect to its main 3-D structure and the molecular interaction potential (sulfone moiety and a phenol-like H-bond donor potential (primary aromatic amine groups instead of phenol groups) of dapsone) was already described above (SAR/QSAR section).

BPS has been subjected to substance evaluation under REACH by the Belgian competent authority in 2014[2] (still ongoing). It is known to bind to the estrogen receptor, with a weak to strong binding affinity depending on the model. *In vitro* data for BPS points towards a weak estrogen agonist activity, and also a possible weak androgenic activity and effects on steroidogenesis by decreasing testosterone levels and increasing progesterone levels without effects on the estradiol levels.

Moreover, scientific studies indicate that BPS exerts estrogenic effects *in vivo*, i.e. estrogen agonistic and antagonistic effects in rodents depending on exposure dose, as well as a disturbed balance of sex steroid hormones and disturbed reproduction, offspring-production and offspring malformations in fish. There are also indications that BPS interferes with the HPG axis and influences hypothalamic development.

Conclusions on ED

With respect to OCED conceptual framework level 1, non-testing methods, the structural similarity to an aniline (MDA) and bisphenol (BPS), the structural alert of two primary aromatic amine groups which indicates a potential to bind to the estrogen receptor, the binding ability of anilines (Hamblen et al. 2003) to the ER in general, and a relative binding to ER of Dapsone estimated by a QSAR study (Maran et al. 2004) are provided. Hence, there are indications for a possible (although weak, RBA 0.001) binding affinity of dapsone to the ER.

With respect to level 2, *in vitro* assays, the binding affinity to estrogen receptor was indicated by 2 out of 16 *in vitro* tests from US EPA EDSP21 programme (0.00158 compared to E2). However, these data proved to be not reliable when having a look on the test details and assays had only the purpose of a screening and were not very sensitive and specific. There is a lack of sound *in vitro* data. Furthermore, no tests were available which integrate intrinsic metabolic activity or cell growth or check other possible pathways as e.g. steroidogenesis. The studies of US EPA are not reliable as effects were only observed below the defined cut-off values of the respective assays or at cytotoxicity levels and thus not significant/reliable. Furthermore, the applied test systems are not very specific and do not integrate cell metabolism or growth for more specific information on the mode of action. From the screening assays there are no indications for an anti-estrogenic, androgen or thyroid related activities. A read-across to 4,4'-methylenedianiline (binding affinity to ER receptor, high chronic toxicity, binding to ER in the more specific YES-assay) supports a possible binding and *in vitro* activity of aromatic amines. Hence, there are weak *in vitro* indications for a possible binding affinity as estrogen agonist, but also other pathways could be possible. More specific *in vitro* assays, including metabolism and cell growth and considering other pathways than receptor binding, such as for example effects on steroidogenesis, would be needed to completely reject the concern for endocrine disrupting properties.

With respect to level 3, *in vivo* studies with data regarding MoA, no data or indications were available in CSR or the open literature. Therefore, based on the currently available data, a conclusion on endocrine properties of dapsone for the environment is not possible.

Also with respect to level 4, *in vivo* studies with data regarding adverse effects, no data or indications in studies are available to be able to draw a conclusion.

However, in light of the structural similarity to MDA and bisphenols, such as BPS, the concern of a potential endocrine action via ER binding cannot be neglected, as scientific

[2] https://echa.europa.eu/documents/10162/776a7a2e-1526-430a-8630-70163473dfc0 Decision on Substance Evaluation pursuant to Article 46(1) of Regulation (EC) No 1907/ 2006 for 4,4'-sulfonyldiphenol, CAS No 80-09-1 (EC No 201-250-5)

studies indicate *in vitro* and *in vivo* effects that seem to be endocrine-mediated for bisphenols such as BPS.

Hence, there are moderate (Q)SAR and very weak *in vitro* indications for a binding affinity to the estrogen receptor. The concern of a potential endocrine disruption cannot be rejected. But the available data is not sufficient to conclude in more detail on ED properties and possible adverse effects *in vivo* as we do not have any relevant data. To be able to conclude on the ED properties and clarify the raised concern, more specific *in vitro* data integrating cell metabolism and cell growth (such as e.g. YES assay or E-screen) as well as *in vivo* tests (e.g. fish sexual development test), that are able to detect estrogen-related long-term effects, would be required.

7.10.2. Endocrine disruption - Human health

Not evaluated.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

The initial ED concern cannot be rejected. There is weak evidence from SAR/QSAR and read across that dapsone binds to the ER and might excert endocrine effects. Data availability is very limited in general, also with respect to *in vivo* data. Further *in vitro* and *in vivo* data would be needed to clarify the concern. Data on BPS from the ongoing substance evaluation could also provide relevant information.

However, evidence for a probable exposure is not sufficient. Dapsone is not detected in the environment (few monitoring studies) and the current uses are all industrial and closed systems, predicted emissions are stated to be extremely low. Also here data availability was limited.

In total, the evidences for both ED and exposure are too weak to justify data requests. This was discussed in the ED EG and considered that requests to clarify an ED concern would not be justified if there is no indication for a relevant exposure. In particular as only *in silico* evidence on CF level 1 support an ED concern.

7.11. PBT and vPvB assessment

1) Persistence

Dapsone does not contain any hydrolysable bond and therefore hydrolysis is not possible. Also dapsone is not biodegradable within 28 days according to a screening test for biodegradation in water (closed bottle test according to OECD 301). On this basis dapsone is expected to fulfill the P/vP criteria. It can however not be finally concluded whether dapsone would fulfill the criteria for very persistent. Further data would be needed for confirmation, but is not required within the scope of this evaluation.

Table 16

Screening test for biodegradation in water with dapsone			
Method	**Result**	**Remarks**	**Reference**
Test type: ready biodegradability Activated sludge (adaption not specified) OECD Guideline 302 D (Ready Biodegradability: Closed Bottle Test)	Under the conditions no biodegradation was observed % Degradation of test substance: > 0 - < 1 after 11 d (O_2 consumption) > 0 - < 1 after 28 d (O_2 consumption)	1 (reliable without restriction) experimental result	Study report (2005)

2) Bioaccumulation

Due to the low log K_{ow} (0.77) dapsone has a low potential for bioaccumulation and is not expected to fulfill the screening criteria for bioaccumulation with regards to the environment. No studies have been conducted.

3) Toxicity

Dapsone is not expected to fulfill the T criteria. The lowest long-term NOEC is above 0.01 mg/L (0.22 mg/L, Daphnia). Kawabata et al. (2013) examined a 5-times higher toxicity of dapsone under UVB irradiation to microorganisms. However even under UVB irradiation the T criteria is not expected to be fulfilled with regards to the environment.

4) Overall conclusion

Dapsone is not expected to have PBT or vPvB properties.

7.12. Exposure assessment

7.12.1. Human health

Not evaluated.

7.12.2. Environment

The initial concern for performing a substance evaluation of dapsone was the endocrine disrupting potential in the environment. Thus, all available exposure information has been evaluated to clarify the environmental relevance of dapsone with respect to the hazard concern mentioned above.

The literature search did not reveal any insights of environmental releases of dapsone. The examined monitoring studies (5) from literature did not show a relevant exposure of the environment (see below).

Information from the registration dossier and direct information from the registrants has been evaluated. Taking into account the available data on the uses, it is concluded that within the scope of current active registrations, dapsone is not likely to enter the environment in relevant quantities (see also chapter 7.5.2).

Dapsone has solely industrial uses and is mainly used to produce preimpregnated fibers various articles (mainly aerospace). In those products, dapsone is bound due to a strong polymerisation.

7.12.2.1. Aquatic compartment (incl. sediment)

Exposure estimates of the registrants:

The range of predicted environmental concentrations (PECs) based on worst case assumptions of the lead registrant for the different uses are as follows:

- STP: 0 - 11.79 µg/L
- Freshwater: 0.00174 – 1.181 µg/L
- Marine water: 0.000175 – 0.118 µg/L
- Frehwater sediment 0.016 – 11.044 µg/kg dw
- Marine sediment: 0.00164 – 1.104 µg/kg dw
- Agricultural Soil: 0.00171 – 0.893 µg/kg dw
- Grassland: 0.00166 – 0.182 µg/kg dw

The overall exposure (combined for all relevant emission/releases including regional exposure) was estimated by the lead registrant as follows:

- Soil: 0.000395 to/year
- Air: 0.02529 to/year
- Water: 0.043495 to/year

Occurrence in environment: Monitoring Studies

In the literature, only few studies were found analysing Dapsone in environmetal samples. Concentrations were below the limit of detection, except in one study were it was detected once in concentrations above 10 ng/L (see below).

Table 17

Monitoring data			
Location	**LOQ/D**	**Measured concentration**	**Reference**
Wastewater hospital		< LOQ	Ort et al. (2010)
groundwater DE, BW	7.9 ng/L / 2.1 ng/L	Detected once >10 ng/L	Sacher et al. (2001, JChromatA)
Rivers in Brazil		< MDL	Monteiro et al. (2016)
Monitoring programm Netherlands		Reports not available	Dersken et al. (2004)
Surface waters (use as antibiotic)		< 0.1 µg/L	FKZ 371264419

Ort et al. (2010) analyzed exposure residues in wastewater from a hospital and their contribution to the sewage treatment plant; dapsone concentrations were < LOQ. Sacher et al. (2001) analyzed dapsone during method validation in Baden-Württemberg

(Germany) and measured concentrations in groundwater. The limit of quantification (LOQ) was 7.9 ng/L, the limit of detection (LOD) 2.1 ng/L, the recovery in surface waters was 6.1%, in tap waters 19%. It was at least detected once above 10 ng/L. Alves Monteiro et al. (2016) analysed dapsone in Brasilian rivers during a method validation and found concentrations < MDL (Method detection limit). Dapsone was measured in a monitoring programm in the Netherlands according to Dersken et al. (2004), but reports were not available.

In a R&D project of the eMSCA on antibiotics in surface waters (FKZ 371264419, FKZ 36014013) concentrations < 0.1 µg/L were cited. According to Maran et al. (2004) dapsone is used as fish antibiotic in aquaculture. Moreover, dapsone is used as pharamaceutical. These uses most probably contribute to potential releases to the environment.

Fick et al. (2010) estimated a predicted critical surface water concentration of 1.0 x 10^6 ng/L dapsone that would elevate plasma concentrations in fish equal to known human plasma concentrations. The aim was to priortise chemicals. This concentration would be expected to cause pharmacological effect in fish, based on literature on human potencies and predicted bioconcentration factors for fish based on lipophilicity. The underlying assumptions are that fish share drug target with humans and there is a fish plasma model concentration ratio between human therpeutic plasma concentration and measured/predicted fish steady state plasma concentrations.

7.12.2.2. Terrestrial compartment

Exposure estimates of the registrants:

The range of predicted environmental concentrations (PECs) based on worst case assumptions of the lead registrant for the different uses and the overall exposure (combined for all relevant emission/releases including region exposre) are listed in Annex 1.

We do not have information from monitoring studies on measurements in soil. However, the substance is potentially persistent as it does not degrade readily. The registrants stated that since there is no release of dapsone to the outside air and sludge, there is no exposure of the soil compartment.

7.12.2.3. Atmospheric compartment

According the the registrants there is no atmospheric emission. Information on measurements in air is not available.

7.12.2.4. Relevance of exposure to environment

Relevance criteria

The substance fullfills the criteria for inclusion in CoRAP list of substances with regard to exposure (Annex 1).

Dapsone is listed in the SPIN-database of Nordic countries and is noted to have an use index between 1 and 2 for most uses indicating a potential or probable exposure (www.spin2000.net). For occupational uses the index is between 3 and 4, which indicates a very propable exposure. The range of use is very narrow (indicated by an index of 1), but it is very propable to be used in articles. An industrial use is not listed in the SPIN database, but use category UC62 for adhesive materials and construction materials or building construction materials. There is no hint on a use as building construction material. Registrants confirmed that dapsone is solely used for airospace.

Uses, manufacturing processes and potential releases

Dapsone is only registered for industrial uses (professional uses were taken out in an update 2015). The main part is used for the manufacture of prepregs and production of articles. Only a small amount is used as intermediate and industrial formulation as powder.

According to the registrants dapsone imparts properties to materials making them similar to steel in terms of robustness and stability of, except being lightweight. Therefore, the materials are mainly used in aviation or astronautics such as for the construction of planes. Due to the high economic costs, dapsone is mainly used in high performance composite materials. Dapsone is used as a low dust powder (0.5% < 1µm) with high melting temperature, i.e. 180 °C.

Release or waste occur in the following situations according to the registrants:

- Release to the air. Limited air release upon formulation, i.e. physical incorporation into a liquid epoxy resin. At room temperature dapsone does not dissolve (only physical dispersion) and does not react with the host resin. This property is fundamental for the use as latent polymerization hardener. A few solid particles may be emitted upon charging the mixer. However this occurs with full containment at highly automated industry set-up. Scarce emitted particles are collected on filters and incinerated.
- Cleaning of the mixers with solvents. Cleaning solvents are collected by contracting companies for incineration.
- Wastes: The resulting paste material is used mainly for prepreg impregnation in automated processes or in lower amount as industrial hot curing adhesive (< 10 t). In the former process prepregs are fully covered/lined with thin plastic films. Going down the value chain, the next step consists of fitting several layers of prepregs into a mold before cure at high temperature in fully contained conditions. Cut down pieces are incinerated. There is virtually no release when processing and using adhesive materials.

According to the registrants, manufacture proceeds under controlled conditions and mostly via automated processes. The powder is mixed in an automated process with epoxy resins in a closed mixing reactor. A release to air is not probable. The resulting paste/pulp contains maximum of 28% w/w dapsone, is highly viscous and is applied on fiber materials which are then imbedded between two plastic films. These are the so-called „prepregs", which are stored and transported refigerated/frozen. At this stage, dapsone is disperged as a powder and not yet polymerised. Nevertheless, emissions are not probable due to the high viscosity according to the registrants. During further processing these prepregs are folded, arranged in piles in the forms and cut appropriately. The cut left-overs of the material are waste and are incinerated. The formed materials are cured at high temperatures (>180 °C) and dapsone polymerises fully to tightly cross-linked 3-dimensional structures.

Leaching

According to the registrants, leaching from these materials is excluded. Dapsone is a relatively big molecule with 4 reactive sites. This substance creates upon cure 3-dimensional densely crosslinked polymer networks with very high glass transition temperatures (T_g > 150 °C). During service-life time no depolymerisation is probable – if the material degrades other substances than dapsone would result.

In an EFSA opinion (EFSA/AFC/FCM/291-Rev.IA/15267 of May 2005) the leaching potential of dapsone was assessed for a use in food contact materials and concluded to be acceptable or not present.
Details on the leaching study: Migration of 4,4'-diaminodiphenyl sulphone was determined in 10% ethanol and 3% acetic acid applying test conditions of 2 h at 121 °C followed by 10 days at 40 °C. In oil the migration was determined after 1 h at 200 °C followed by 10 days at 40 °C. The monomer was determined by HPLC and UV detection. The method was

properly validated for precision and recovery of the monomer. The monomer was not detectable at the level of 0.008 mg/6 dm².

No further details on the test method and information on e.g. "surface to solvent ratio" were retrievable, thus the reliability and value of the study was not assessed during the evaluation.

Further possible uses in FCM
The EFSA Opinion (EFSA/AFC/FCM/291-Rev.IA/15267 of May 2005) states that "according to the petitioner 4,4'-diaminodiphenyl sulphone is used as monomer in the plastics production of polyetherimide. The final polymer is intended to be used in contact with all types of food and at any time/temperature condition."
According to the registrants (pers. com. 2016) there is neither a use in Food Contact Materials (FCM), nor was this ever considered by the registrants. The eMSCA does not have further information on this use.

More accurate quantifications of emissions or relases
The registrants requested further information from downstream users on potential emissions during manufacturing and the treatment of waste. The aim is to quantify emissions to the environment more acurately and update the CSR accordingly. However, details where measurements are to be done are not yet available.
Effluent data from production sites and details on fate of waste are recommended to be included in CSR.

Conclusions

Release to environment seems not to be very probable based on the information available.

7.13. Risk characterisation

The eMSCA reviewed the risk characterisation of the registrants and concluded the risk characterisation as reasonable. All RCRs are below 1 and the used exposure scenarios are reliable in the eMSCA's opinion.

7.14. References

FKZ 36014013 (2010). Compilation of monitoring data on environmental concentrations of pharmaceutical products. IWW Rheinisch-Westfälisches Institut für Wasser Beratungs- und Entwicklungsgesellschaft mbH.

FKZ 3712 64 419, Coors, A. (2016). Combination effects of pharmaceuticals and industrial chemicals from wastewater treatment plant processes - testing concepts for risk assessment using experimental scenarios. ECT Oekotoxikologie GmbH.

Anonymous (2004). Developmental Toxicity Evaluation of 3'-Azido-3'-deoxythymidine (AZT; CAS no. 30516-87-1) and Dapsone (CAS no. 80-08-0) Administered by Gavage to Swiss Albino (CD-1) mice in gestational Days 6-15. https://ntp.niehs.nih.gov/testing/types/repro/abstracts/racb98001/index.html

Study report (2011). 96-hour acute toxicity study in carp with 4,4'-DDS.

Study report (2012a). Daphnia magna, 21-day reproduction study with 4,4'-DDS.

Derksen (2004). "Diffuse pollution of surface water by pharmaceutical products." Water Science and Technology 49 (3): 213–221.

Study report (2012b). Activated sludge respiration inhibition test (carbon and ammonium oxidation) with 4,4'-DDS.

Elizabeth L. Hamblen a, Mark T.D. Cronin b, T. Wayne Schultz (2003): Estrogenicity and acute toxicity of selected anilines using a recombinant yeast assay. Chemosphere (52): 1173-1181.

Fick, J., R. H. Lindberg, M. Tysklind and D. J. Larsson (2010). "Predicted critical environmental concentrations for 500 pharmaceuticals." Regulatory Toxicology and Pharmacology 58(3): 516-523.

Kawabata, K., K. Sugihara, S. Sanoh, S. Kitamura and S. Ohta (2013). "Photodegradation of pharmaceuticals in the aquatic environment by sunlight and UV-A,-B and-C irradiation." The Journal of toxicological sciences 38(2): 215-223.

Maran, E., M. Novič, P. Barbieri and J. Zupan (2004). "Application of counterpropagation artificial neural network for modelling properties of fish antibiotics." SAR and QSAR in Environmental Research 15(5-6): 469-480.

Monteiro, M. A., B. F. Spisso, J. R. M. P. dos Santos, R. P. da Costa, R. G. Ferreira, M. U. Pereira, T. da Silva Miranda, B. R. G. de Andrade and L. A. d'Avila (2016). "Occurrence of antimicrobials in river water samples from rural region of the State of Rio de Janeiro, Brazil." Journal of Environmental Protection 7(02): 230.

Study report (2005).

Ort, C., M. G. Lawrence, J. Reungoat, G. Eaglesham, S. Carter and J. Keller (2010). "Determining the fraction of pharmaceutical residues in wastewater originating from a hospital." Water Res. 44(2): 605-615.

Sacher, F., S. Gabriel, M. Metzinger, A. Stretz, M. Wenz, F. T. Lange, H.-J. Brauch and I. Blankenhorn (2002). "Occurrence of drugs in groundwaters. Results of a monitoring program in Baden-Wuerttemberg." Vom Wasser 99: 183-195.

Study report (2004). 4,4'-Diaminodiphenyl sulfone growth and reproduction toxicity test with the freshwater algae Selenastrum capricornutum.

Study report (2005). Biodegradability of 4-aminophenyl sulfone (CAS no. 80-08-0) using the closed bottle test.

7.15. Abbreviations

AC	Activity Concentration
AR	Androgen Receptor
BPA	Bisphenol A
BPS	Bisphenol S
CLP	Classification, Labelling and Packaging
CoRAP	Community Rolling Action Plan
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
EC	Effect Concentration
ED	Endocrine Disruptors
EDKB	Endocrine Disrupter Knowledge Base
EFSA	European Food Safety Authority
eMSCA	evaluating Member State Competent Authority
EPA	Environmental Protection Agency
ER	Estrogen Receptor
FCM	Food Contact Material
HPG axis	Hypothalamic–Pituitary–Gonadal axis
HPLC	High-Performance Liquid Chromatography
ISO	International Organization for Standardization
Koc	Soil Organic Carbon-Water Partitioning Coefficient
Kow	Octanol-Water Partion Coefficient
LC	Lethal Concentration
LOD	Limit Of Detection
LOQ	Limit Of Quantification
MDA	4-Methylendianilin
MDL	Method Detection Limit
MO	Microorganism
MoA	Mode of Action
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
QSAR	Quantitative Structure–Activity Relationship
R&D	Research and Development
RBA	Relative Binding Activity
STP	Sewage Treatment Plant
SVHC	Substance of Very High Concern
THR	Thyroid Hormone Receptor
TRE	Thyroid hormone Response Element
UBA	German Environment Agency
UV	Ultraviolet
YES	Yeast Estrogen Screen