ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114366603-48-01/F
Substance name: Dapsone
EC number: 201-248-4
CAS number: 80-08-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 02/02/2017
Registered tonnage band: 100-1000 tonnes per year

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

2. **Revise the hazard assessment for pre-natal developmental toxicity using the available study / studies, which give rise to the highest concern as well as provide a robust study summary for that study / robust study summaries for these studies.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **26 July 2019**. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

The scope of this decision is limited to the standard information requirements of Annex I, Sections 3.0.4 and 3.3, and Annex IX 8.7.3. of the REACH Regulation.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

1. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, December 2016).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity have been noted. More specifically, in the technical dossier you provided two fertility studies on male and female rats ([redacted], 2005) showing adverse effects after treating the animals with the registered substance. The effects in male rats include reduction in sperm number and sperm motility and in female rats decrease in implantation sites and increased number of early resorptions and derived effects. According to ECHA's Guidance document[2], the effects observed in these studies, which include effects on litter size and effects on sperm parameters analysis can be considered as triggers to conduct an extended one-generation reproductive toxicity study at REACH Annex IX level. Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

b) Information provided

In the registration dossier, you have provided the following studies:

1. Effect on the fertility of male rats, oral (gavage) (no test guideline followed; GLP) with the registered substance, [redacted], 2005 (publication). Rel. 1.
2. Effect on the fertility of female rats, oral (gavage) (no test guideline followed; GLP) with the registered substance, [redacted], 2005 (publication). Rel. 1.

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

[2] ECHA's Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 5.0 December 2016 (p.464-465).

You have not provided an explanation or justification on how the sources of information/studies, which you have provided enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to the reproductive toxicity endpoint. ECHA understands that you conclude that the registered substance does not have a dangerous (hazardous) property with respect to fertility.

To support your weight of evidence adaptation you have provided the two fertility studies specified above.

Under the '*Toxicity to reproduction'* endpoint (IUCLID Section 7.8.1.), you also provide the following justification for not classifying the registered substance: *"The effect observed happens at doses which likely provoke methemoglobinaemia. Clinical signs in the test animal support this assumption." "There is a clear evidence that the fertility effects occur at doses which provoke clear signs of toxicity. The effect is therefore considered secondary to parental toxicity. There are Human data (see e. g. the review by Wolf et al (2002) from pregnant leprosy patients exposed to high doses of dapsone. The effects on the foetus were not teratogenic, but sometimes embryotoxic/lethal (likely by low availability of oxygen during development)."*

c) ECHA's evaluation and conclusion of the information provided

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation.

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect endocrine disruptive properties. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.

ECHA observes that both studies are GLP studies, but they do not follow any test guidelines. Some relevant elements of reproductive toxicity have not been evaluated in the studies provided. More specifically, in the male fertility study only males were treated and were dosed for 63 days prior to cohabitation with untreated females whilst in the female rat study the registered substance was only administered 15 days prior mating. Exposure in the female rats lasted for only 17 days after mating. The premating exposure duration for the parental generation did not last for 10 weeks in both male and female rats. Furthermore, for the F1 generation only the male fertility was examined, hence the extensive investigations on post-natal development of the F1 generation have not been conducted and F1 generation

was not separately exposed. Therefore, both fertility studies together do not provide information on relevant elements, which would be evaluated in an extended one-generation reproductive toxicity study and needed to conclude on reproductive toxicity.

The two fertility studies do not address the missing elements as indicated above. In this respect, ECHA also notes that you have not provided any justification why this information together addresses the questions whether the registered substance has or has not a dangerous (hazardous) property for this information requirement.

In addition, ECHA notes that the available information indicates that effects on male fertility (sperm motility) in rats seems to be the most sensitive effects, being statistically significant at even 0.3 mg/kg bw/day. The effects on the litter size (reduced number of implantations and increased early resorptions), observed at 30 mg/kg bw/day, were evaluated as being secondary to the effect of the substance on sperms. Based on the provided information, impairment of male fertility could also be expected as being the most sensitive effect for the F1 offspring generation, which might even occur at lower doses. ECHA notes that your weight of evidence approach does not address this concern (no justification provided). Therefore, an extended one-generation reproductive toxicity study is required to provide further information, in particular for classification purposes.

Hence, the sources of information you provided do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.7.3. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required.

In your comments provided to the draft decision you agreed to conduct the study.

The following refers to the specifications of the required study.

d) The specifications for the required study

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, December 2016), the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, December 2016).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

e) Outcome

Based on the available information, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, December 2016). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

2. Hazard assessment for pre-natal developmental toxicity (Annex IX, 8.7.2.) and submission of robust study summary/ies (RSS) for Annex IX, 8.7.2.

Pursuant to Article 12(1) the technical dossier shall include all toxicological information that is relevant and available to the registrant. Pursuant to Articles 10(a)(vii) and 12(1)(d) as well as Section 1.1.4 of Annex I of the REACH Regulation, a registration for a substance produced in quantities of 100 tonnes or more per year shall contain robust study summaries of the information derived from the application of Annexes VII to IX and XI if required under Annex I. According to Annex I, 1.1.4., robust study summaries are required for all key data used in the hazard assessment. If there are several studies addressing the same effect, normally the study or studies giving rise to the highest concern shall be used in the hazard assessment. Pursuant to the same provision, if the study or studies giving rise to the highest concern are not used then this shall be fully justified and included as part of the technical dossier and robust study summaries shall be included for all studies demonstrating a higher concern than the study being used. Pursuant to Articles 10(a)(vii) and 111, the technical dossier containing robust study summaries shall be provided in the IUCLID format.

In the present registration dossier for the information requirement on developmental toxicity/teratogenicity one key study (Anonymous, 2004) and two supporting studies (Wolf *et al.*, 2002; Anonymous, 2001) are available. The key study represents a prenatal developmental toxicity study in mice. The two supporting studies represent review data from human observations.

ECHA however observes that in the technical dossier you used a reference ([redacted] U.S. FDA, 2005) to cover information requirements under toxicity to reproduction and repeated dose toxicity. It notes that this reference also makes information for developmental toxicity in rats and rabbits available:

i. Dapsone and diethylene glycol monoethyl ether: combined oral (gavage) fertility and developmental toxicity study in female rats, ATLS-120, cited in [redacted], U.S. FDA, 2005.
ii. Dapsone and diethylene glycol monoethyl ether: oral (stomach tube) developmental toxicity study in rabbits, ATLS-121, cited in [redacted], U.S. FDA, 2005.
iii. Dapsone and diethylene glycol monoethyl ether: oral (gavage) developmental and perinatal/postnatal reproduction toxicity study in rats, including a postnatal reproduction toxicity study in rats, including a postnatal behavioral/functional evaluation, ATLS-137, cited in [redacted], U.S. FDA, 2005.

These studies give rise to a higher concern than the study you used for the hazard assessment for prenatal developmental toxicity.

In the technical dossier you failed to justify why in the hazard assessment for pre-natal developmental toxicity you did not use the study/ies giving rise to the highest concern. Furthermore, ECHA notes that in the endpoint study record the key study in mouse is not accompanied by an explanation of why this species has been selected to fulfill the information requirements for prenatal developmental toxicity. This is of importance because in the OECD test guideline 414 for prenatal developmental toxicity for the selection of the

test animal species "*It is recommended that testing be performed in the most relevant species, and that laboratory species and strains which are commonly used in prenatal developmental toxicity testing be employed. The preferred rodent species is the rat and the preferred non-rodent species is the rabbit. Justification should be provided if another species is used.*" ECHA notes that in accordance with Annex I, Section 1.1.4., the relevance of the test species is a criterion to be taken into account when choosing the study or studies to be used. Therefore it is also relevant that the studies showing a higher concern than the mouse study are carried out in preferred rodent and non-rodent species.

In your comments to the draft decision you argue that the study in mice is the most suitable study to be used for the hazard assessment of the registered substance, since: (i) the study gives rise to higher concern than the other three studies where "*all developmental effects noted ...were clearly secondary to maternal toxicity*"; and (ii) the mouse is the most sensitive species as "*the higher tolerance of the mouse*" to the registered substance "*can increase the chances of identifying fetal effects in the absence of maternal effects*". However, ECHA notes that similar toxic effects were observed with the registered substance in both humans and rats but not with mice. Hence, the rats can be considered to be similar to humans. ECHA notes that further justification is required on the choice of study for providing the basis of the hazard assessment for this endpoint.

Therefore, you are requested to revise the hazard assessment and you also shall provide a robust study summary for the study (or robust study summaries for the studies) giving rise to the highest concern.

In your comments, you already agree to provide a robust study summary of the missing studies in the technical dossier.

Notes for your consideration

Under Article 3(28), the robust study summary shall include a "*detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report.*" You are advised to refer to 'ECHA Practical Guide 3 How to report robust study summaries' (Version 2.0, November 2012) for detailed advice.

You retain the right to make use of the possibility to use the study in mice for the hazard assessment, but would need to fulfil the conditions set out in Annex I, 1.1.4., i.e. you would need to provide a full justification as well as the robust study summary of any study demonstrating a higher concern. ECHA would in the follow-up procedure pursuant to Article 42 of the REACH Regulation assess the justification in light of the robust study summaries and would in case of non-compliance with REACH notify the Enforcement Authorities of the Member States.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 08 November 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the request(s).

You updated your registration on 2 February 2017. ECHA took the information in the updated registration into account, and amended the draft decision. The updated information is reflected in the Reasons (Appendix 1).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is listed in the Community rolling action plan (CoRAP) and the substance evaluation started in 2016.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.