Helsinki, 3 February 2020

Addressee
Registrant of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
14 December 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Zinc bis(dibutyldithiocarbamate)
EC number: 205-232-8
CAS number: 136-23-2

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***10 February 2022***.

A. Requirements applicable to all the Registrants subject to Annex X of REACH

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, with the Substance, specified as follows:

- **Ten weeks premating exposure duration for the parental (P0) generation;**
- **Dose level setting shall aim to induce systemic 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;**
- **Cohorts 2A and 2B (Developmental neurotoxicity); and**
- **Cohort 3 (Developmental immunotoxicity).**

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Conditions to comply with the requests

You are bound by the request for information corresponding to the REACH Annex applicable to your own registered tonnage of the Substance at the time of evaluation.

You have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Appendix A states the reasons for the request for information to fulfil the requirements set out in Annex X of REACH.

The testing material used to perform the required studies must be selected and reported in accordance with the specifications prescribed in the Appendix entitled Observations and technical guidance.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons for the request to comply with Annex X of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier at tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII-X to the REACH Regulation.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided a reference to an earlier decision requesting an EOGRT study on the Substance, but no information that would fulfil the information requirement of Annex X, 8.7.3. Therefore, an EOGRT study is required.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must 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 to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration[2].

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

In your comments you agree that the extension of Cohort 1B is not required.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

[2] ECHA Guidance R.7a, Section R.7.6.

Existing information on the Substance itself derived from the available OECD TG 408 study (Triskelion, 2018) shows evidence of neurotoxicity:

- increased body temperature was observed in high dose males
- hindlimb grip strenth was decreased in males of the mid and high dose groups

In your comments, you acknowledge that the mean body temperature of the high dose male group was statistically significantly increased (mean 38.41) when compared to the control group (mean 38.11), and that this value was outside the range of historical control data (mean 37.98, range 37.77 -38.35), i.e. it is an effect of the treatment. However, you consider that this is only a minor increase which is not biologically relevant. ECHA considers that although the increase seems to be only slight (by 0.3°C), it is statistically significant and outside the range of historical controls. The body temperature is monitored and regulated by the nervous system (reviewed e.g. in Tan & Knight 2018[3]). Elevated body temperature is a sign of dysfunction of the nervous system, and therefore it is a relevant finding when considering a particular concern for (developmental) neurotoxicity.

Furthermore, you acknowledge that the mean hindlimb grip strength in males of the mid- and high dose groups were statistically significantly decreased when compared to the control group, and that the values of the mid- and high dose groups were outside the range of the historical control data. You consider that as there were no changes in other parameters of the same functional domain, this effect is not a reflection of neurotoxicity but related to the general state of discomfort.

However, you do not elaborate the statement on the general state of discomfort nor explain why a general state of discomfort would only affect hindlimb grip strength, but not have any impact on other parameters. ECHA considers that the decrease in hindlimb grip strength in males at the mid and high dose level is a biologically relevant change: it's magnitude is up to 17%, it is statistically significant, dose-dependent, and furthermore the values are clearly outside the range of historical controls (746 and 728 vs. historical range of means 781-1271). Therefore, it is a relevant finding when considering a particular concern for (developmental) neurotoxicity.

The OECD TG 408 study also reported occasional hypoactivity in high dose animals. In your comments, you explained that the occurrence was very low, i.e. this observation was made once in week 5 and once in week 10. Based on the data provided, ECHA agrees that it was only incidental, and has removed the occasional hypoactivity from the justification for the DNT cohorts.

ECHA considers that taken together there is sufficient evidence for a particular concern for (developmental) neurotoxicity based on the information on increased body temperature and reduced hindlimb grip strength both in male rats.

Therefore, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

[3] Tan CL and Knight ZA (2018): Regulation of Body Temperature by the Nervous System. *Neuron.* 98(1): 31-48.

Existing information on the Substance itself derived from the available OECD TG 408 study (Triskelion, 2018) shows evidence of immunotoxicity:

- Dose-related decreases in thymus weights in females attaining statistical significance at the high dose (relative -29%, absolute -33%), and a non-significant decrease in high dose males (relative -18%, absolute -7%).
- Increased spleen weights in females at all doses with statistical significance only in high dose (relative +24%, absolute +17%). Relative spleen weights were increased in mid and high dose males (+6% and +12%, respectively).
- the Substance has a harmonised classification for skin sensitisation (Skin Sens. 1)

In your comments, you refer to two criteria: that a particular concern should be specific to (developmental) immunotoxicity, and that the concern needs to reach a certain level of severity. You refer to the text in REACH Annex VIII, 8.6.1. and interpret that a particular concern is indicated by serious or severe effects which have regulatory consequences, i.e leads to NOAEL values and/or contribute to hazard classification. You argue that effects were seen only at the high dose, which does not influence the NOAEL values or any specific hazard classification, therefore not contributing to any regulatory consequences.

The ECHA Guidance, with respect to concern for developmental immunotoxicity (Appendix R.7.6-2, Point 4 'Inclusion of Cohort 3') explains that a particular concern is an expectation that the substance has (developmental) immunotoxicity properties contributing to the regulatory decision making. The particular concern itself does not need to lead to change of NOAEL or hazard classification. The inclusion of the DIT cohort is expected to clarify the concern.

The effects listed above, i.e. dose-related decreases in thymus weights in females and increased spleen weights in females at all doses, were not observed only at the highest dose although reached the statistical significance only there. These effects, supported by the harmonised classification for skin sensitisation, form a particular concern for developmental immunotoxicity which needs to be investigated further.

Therefore, the developmental immunotoxicity Cohort 3 needs to be conducted.

Species and route selection

The study must be performed in rats with oral[4] administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. However, you may expand the study by including the extension of Cohort 1B if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[3].

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

On 17 November 2017 ECHA issued decision CCH-D-2114375518-38-01/F[5].

On 23 November 2018 and 14 December 2018 the registrant updated the dossier and provided the results of the 90-day sub-chronic toxicity study (OECD TG 408).

On 14 January 2019 ECHA informed the registrant that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

The compliance check was initiated on 7 March 2019.

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.

You submitted comments one working day after the indicated draft decision commenting period. ECHA's ICT system was not functioning during part of the draft decision commenting period. Against this consideration, ECHA decided to take into account your comments but did not amend the request(s).

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

[5] https://echa.europa.eu/documents/10162/0dd1d5f7-1cfb-9bde-39e6-0867897c7cca

Appendix C: Observations and technical guidance

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

2. 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 the Member States.

3. Test guidelines, GLP requirements and reporting
Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries[6]'.

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[3].

[6] https://echa.europa.eu/practical-guides

5. List of references of the ECHA Guidance documents[7]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[9]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]