Helsinki, 13 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114356486-40-01/F
Substance name: disodium molybdate
EC number: 231-551-7
CAS number: 7631-95-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22 December 2015
Registered tonnage band: 100-1000T

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. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance.**

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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **20 March 2018**. You shall also 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. Advice and further observations are provided in Appendix 3.

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, shall 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a pre-natal developmental toxicity study in rats ([redacted] 2013). According to the information provided in your dossier you consider that *"Although no clear toxic effects were observed in either the dams or on the embryos/fetuses, the top dose is equivalent to approximately 20,000 times the average human daily intake of molybdenum from food and water of about 2 µg/kg bw/day"*. However, this study does not provide the information required by Annex IX, Section 8.7.2., because the current pre-natal developmental toxicity study, seemingly otherwise following OECD TG 414 ([redacted] 2013), is conducted using too low dose levels to induce some maternal toxicity or developmental toxicity. According to OECD TG 414 *"Unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering."* ECHA notes that, based on the information provided in your dossier, there seem to be no physical/chemical or biological reason why the study could not have been conducted with higher doses or potentially up to the limit dose of 1000 mg/kg bw/day.

In addition, the reasoning for the acceptability of the low doses used is not supported by the REACH Regulation and by the registration dossier. First, the REACH Regulation requires information on the hazard potential and does not provide for the adaptation of a study's dose levels based on exposure considerations. Second, the justification ("*average human daily intake of molybdenum from food and water of about 2 µg/kg bw/day*") is not substantiated; as there is no information available (e.g., no exposure assessment has been provided in the Chemical Safety Report) to which concentrations the workers and the consumers are exposed to, safety cannot be demonstrated.

For these reasons, the existing pre-natal developmental toxicity study in rats ([redacted], 2013) does not meet the specifications of OECD TG 414. Due to this deficiency, this study does not meet the requirements of Article 13(3) of REACH and it is not sufficient to address the information required by Annex IX, Section 8.7.2.

For the same reasons, this study is not adequate for the purpose of classification and labelling and/or risk assessment and does not provide adequate and reliable coverage of the key parameters of the OECD TG 414. Thus, the study does not meet the conditions of Annex XI, Section 1.1.2 of the REACH Regulation.

In addition, the dossier contains several studies that were disregarded by you, raising a concern for developmental toxicity which are the following:

- *The study from [redacted] 1965 shows that high doses of sodium molybdate (1000 mg/kg bw/day and above) fed to the weanling rats causes bone deformities [and reduced body weight](no NOAEL).*
- *Arrington 1965: weanlings and adults: 500 ppm Mo in the diet or drinking water did not reduce the body weight with a LOAEL of 1000 ppm in the rats. The dietary NOAEL for the rabbits were 1000 ppm with a LOAEL of 2000 ppm for the body weight gain.*
- *Bandyopadhyay 1981: young rats, 500 mg/kg bw/day liver, kidney, hormonal etc alterations.*
- *Miller 1956: young rats: dietary administration of 75 and 300 ppm Mo suppressed growth and caused chondrodystrophy of the epiphyseal cartilage.*
- *Wide 1984: mouse dev tox study, iv injection on pregnancy day 8 caused reduction in fetal weight and interfered with fetal skeletal ossification.*
- *Valli 1969: young rabbits: Intracartilaginous epiphyseal fractures occurred in the humeri and the femoral epiphyseal plates were increased in width. In addition degeneration of the myocardium and degeneration of skeletal muscle.*
- *Cong-Ming Bi et al 2013: in vitro development of mouse preimplantation embryos and results from embryo transfer study: various effects at and above concentration of 40 ug/ml.*

ECHA acknowledges that the deficiencies in the study design or in the level of information reported in those studies mentioned above, affect the reliability of the individual line of evidence and is therefore not sufficient to fulfil the information requirement. However, taken together, this suggests that the sustance subject to this decision may have the potential to cause developmental toxicity at doses exceeding those used in the existing pre-natal developmental toxicity study [redacted], 2013).

Thus, ECHA considers that the existing pre-natal developmental toxicity study in rats [redacted], 2013) does not address the concern stemming from the available data and that the registered substance may affect the embryo-foetal development above the dose levels used in pre-natal developmental toxicity study in rats ([redacted], 2013) (above 40 mg/kg bw/day of molybdenium and approximately 100 mg/kg bw/day of the registered substance) up to the limit dose of 1000 mg/kg bw/day of registered substance. Therefore, there is a data gap.

Because of the low dose levels used in the OECD TG 414 study, and supported by the concern for developmental toxicity from available studies with limitations, there is a data gap which needs to be fulfilled with a new pre-natal developmental toxicity study conducted up to the dose levels determined in accordance with the OECD TG 414, i.e. aiming to induce some maternal and/or developmental toxicity or up to the limit dose.

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.

In your comments to the draft decision you addressed the issues listed above.

ECHA considered these and points out the following:

i. Low dose levels used in the [redacted], 2013 pre-natal developmental toxicity study (OECD TG 414): Based on the existing data you considered that it was anticipated that at the high dose used in the OECD TG 414 study, i.e. 40 mg/kg bw/day of molybdenum, toxicity would have been noted. You also further argued on the appropriateness of the dose selection based on the fact that the serum levels noted in the [redacted], 2013 study were 15 000 times higher when compared to normal serum levels in humans (EFSA, 2006).

ECHA notes that in three of the studies referred by you in your comments from which only study by Su-Ling et al. (2007) is present in the dossier, toxicity were reported at low doses of molybdenum. In the developmental toxicity study by Fungwe et al. (1990) sodium molybdate was administered to rats via drinking water at concentration ranges of 5 to 100 mg/L of molybdenum from weaning for six weeks including mating and treatment until day 21 of gestation. Prolonged length of oestrous cycle, increased number of resorptions per dam, fetal death and decreased body weight gain were reported from 10 mg/L upwards (actual doses could not be verified as water consumption has not been reported). In the fertility study by Panday and Singh (2002) male rats were exposed via oral route (cannula) five days per week for 60 days with 10, 30 or 50 mg/kg bw of sodium molybdate. Significant decrease of testis and secondary sex organ weights, reduction of sperm count and mobility were reported at 30 and 50 mg/kg bw. In addition males treated with 30 mg/kg bw were mated with untreated females and reduced fertility, increased pre- and post-implantation loss and decreased fetal weights were noted. In the study by Su-Ling et al. (2007) pregnant rats were dosed with 0 to 40 mg/mg kg with molybdenum acid ammonium salt via oral route from gestation day 7 to 15 and sacrificed on gestation day 20. Increased fetal death and malformations were reported for doses 20 and 40 mg/kg bw. ECHA observes that in two of the studies (Fungwe et al., 1990; Panday and Singh, 2002) the exposure duration was much longer than in the prenatal developmental toxicity study and the studies further suggest that the developmental toxicity (lethality) was male mediated and required longer exposure duration. ECHA points out that in the OECD TG 414 male mediated effects are not examined, as only females are exposed with restricted exposure duration i.e. during pregnancy. In the third study (Su-Ling et al., 2007), the exposure duration was short and the results suggest that toxicity could be observed at 20 and 40 mg/kg bw/day of molybdenum acid ammonium salt; it is, however, not clear how the presence of ammonium may have influenced the observed toxicity level.

Concerning the 28-day range finding study, no effects in females were noted; only in males effects were observed where 20 mg/kg molybdenum caused reduction of body weight of 19%. In the 90-day study at 60 mg/kg of molybdenum, female body weight was decreased at the end of the treatment by 5.6% when compared to the control group, which reversed during the recovery period. In addition, slight diffuse hyperplasia of the proximal tubules of the kidney were noted in 2/10 female rats, which normalised during the recovery period.

Based on the information provided, ECHA does not agree that 60 mg/kg of molybdenum would be a too high dose to be used in the OECD TG 414 even though the 90-day study showed mild effects in the kidney. On the contrary, ECHA considers that based on the 90-day study results the registrant should have chosen even a higher dose than 60 mg/kg due to the shorter exposure period in the OECD TG 414 compared to the 90-day study and therefore the selected 40 mg/kg dose of molybdenum in the current pre-natal developmental toxicity study is regarded as too low to satisfy the specification of the OECD TG 414. It should be verified in a dose range finding study how much higher than 60 mg/kg bw/day of molybdenum the dose should be. Therefore, ECHA considers that the registrant has not provided scientifically sound reasoning why the OECD TG 414 cannot be conducted at higher dose levels than 40 mg/kg molybdenum. Moreover, it is important to note that the results obtained are not only relevant for risk assessment (NOAEL and DNEL derivation) but also for hazard identification which may result in classification and labelling of the substance.

ii. Disregarded studies: You have re-evaluated the seven studies listed above and have provided further considerations why those studies are not relevant for prenatal developmental toxicity. In your comments, you have also included two additional studies (Fungwe at al., 1990; Panday and Singh 2002) that were not included in the dossier evaluated under compliance check. Based on this information you still believe that the information presented in those publications lack relevance and reliability and therefore the only meaningful information on prenatal developmental toxicity is the recent study by [redacted], 2013. ECHA agrees that all of the studies have their limitations, and that alone or together they are not sufficient to address developmental toxicity. However, ECHA still considers that those studies disregarded by you indicate that molybdemun may disturb the development under certain conditions. As the prenatal developmental toxicity study [redacted] 2013) was performed with too low concentrations, the potential impact of the registered substance to development (skeletal effects and any lethality) cannot be excluded without performing a prenatal developmental toxicity study with appropriate dosing.

iii. Worker and consumer exposure: In your comments, you have provided further information on exposures. Based on the exposure estimates you consider that the estimated maximum systemic dose is 130 to 400-fold lower than the NOAEL obtained from the prenatal developmental toxicity study. ECHA acknowledges the additional information provided on exposures. However, ECHA notes that the exposure assessment provided lacks any detail on the operational conditions and risk management measures and therefore the values cannot be verified.
For dust exposure, some argumentation on the fraction that may be inhaled and absorbed have been provided, however this cannot be verified based on the data provided.

The exposure estimations provided for aqueous solution are outside of the boundary of the reliable application of the model used. Based on this, the exposure assessment is flawed in many ways, however it is clear that worker exposure will occur (dusty solids and concentrated aqueous solutions), but it is impossible to verify the amount of potential exposure levels (PROCS 7, 8a, 11 and 13 are normally associated with high exposure depending on the conditions). In addition, you compared the NOAEL from the pre-natal developmental study directly to the estimated exposure without deriving a DNEL, hence the proposed safety margins are not calculated according to the REACH provisions. Therefore, based on the information provided you, it is clear that exposure will occur to workers and consumers which further supports that concerns and uncertainties related to developmental toxicity needs to be addressed by a guideline compliant study.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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 4.1, October 2015) 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.

Therefore, 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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

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 27 June 2016.

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the agreed commenting period, and they are 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.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.