EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For carbon disulphide, CAS No 75-15-0 (EC No 200-843-6)

Addressees: Registrants[1] of carbon disulphide (hereafter also referred to as CS_2)

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by Anses on behalf of the French Competent Authority, the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 29 April 2014 , i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of France has initiated substance evaluation for carbon disulphide, CAS No 75-15-0 (EC No 200-843-6) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to CMR (reproductive toxicity) potential properties, suspected endocrine disruptor, exposure of workers and environment, high aggregated tonnage, carbon disulphide was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. Anses, on behalf of the French Competent Authority, was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA noted additional concerns regarding substance identity (benzene as potential impurity).

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 19 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant commenting phase

By 5 June 2014, ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s).

On basis of this information, the request 1 of Section II was amended. This request was updated by including a request from an additional draft decision that no longer exists. The route of exposure of request 5 was made dependent on the results of a preliminary study and an additional request regarding risk of flammability was deleted. The Statement of Reasons (Section III) was changed accordingly. For the requests 2 and 3, the information contained therein is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 23 July 2015 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification. Subsequently, Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 28 August 2015, ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

Referral to Member State Committee

On 7 September 2015 ECHA referred the draft decision to the Member State Committee.

On 28 September 2015, in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant(s) on the proposals for amendment into account.

After discussion in the Member State Committee meeting on 27 – 29 October 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 29 October 2015 and ECHA took the decision pursuant to Article 52(2) and 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) and 10 (ii) as well as Annex VI, Section 2 and 3 of REACH Regulation and the guidance for identification and naming of substances under REACH and CLP,

1. Unless already provided, in his respective registration dossier, each Registrant shall provide information enabling the verification of the composition and the confirmation of the structure of the substance. In particular, each Registrant has to:

    - specify the maximum concentration for the impurity benzene;
    - provide the typical composition of the substance with 100% disclosure and identify all CMR impurities or provide a statement indicating that no relevant impurities is present in the substance as further specified in Section III;
    - provide spectral data (UV, IR, NMR) and
    - Confirm the composition of the substance with high pressure liquid chromatogram or gas chromatogram.

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) shall also submit the following information on the registered substance in a revised version of their chemical safety report:

2. Complete the environmental exposure scenarios regarding the use of carbon disulphide in manufacturing of regenerated cellulose;
3. Provide the environmental exposure assessment for uses as further specified in Section III and
4. Detail further information on worker exposure as further specified in Section III.

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) shall also submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) on the registered substance subject to the present decision:

5. Tiered approach: Extended One Generation Reproductive toxicity study in rats according to test method OECD TG 443 including cohort 2A and 2B (DNT). Pre-mating

exposure duration of 10-weeks should be included. The route of exposure (oral or inhalation) shall be determined on the basis of a pre-study ("Tier 1") investigating the comparative Toxicokinetics *via* these routes.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **6 September 2018** an update of the registration(s) containing the information required by this decision2, including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

Based on the evaluation of the registration dossiers submitted on carbon disulphide, on other relevant and available information and taking into account the comments of the Registrant(s), proposals for amendment submitted by Member State Competent Authorities/ECHA and the deliberations of the Member State Committee, ECHA concludes that further information is required in order to enable the evaluating MSCA to complete the evaluation of whether the substance constitutes a risk to human health or the environment

1. Information of the composition and the structure of the substance

The typical composition of the substance should reach 100% disclosure. Normally, impurities present in a concentration > 1% should be specified. However impurities that are relevant for classification and/or PBT assessment, as CMR substances shall always be clearly identified and specified. Indeed, based on the manufacturing process and the starting materials, it is considered that presence of benzene, which can be relevant for the classification and the risk assessment, is possible. Benzene is i.a. classified as Carc. 1A and Muta. 1B (Annex VI of CLP, Index number 601-020-00-8); consequently any substance that contains >0.1% of benzene is also to be classified as Carc. 1A and Muta. 1B. The Registrant(s) in their comments agreed "that benzene could be a side product of the carbon disulphide synthesis if the synthesis starts with coal or natural gas and therefore benzene would be an impurity considered relevant for the classification and labelling of the substance".

Spectral data are necessary to confirm the structure of the substance and should be provided. High pressure liquid chromatogram or gas chromatogram are necessary to confirm the composition of the substance and should be provided.

Therefore, as no additional data were given in the Registrant(s) comments, each Registrant is required to provide the following data using the registered substance subject to this decision:

- a maximum concentration for the impurity benzene in the composition of each substance of the different registrants;
  The typical composition of the substance with 100% disclosure with the identification of all CMR impurities (with name and CAS number) and percentage of each impurities or a statement indicating that no relevant impurities is present in the substance. Manufacturer will provide a description of the manufacturing/ technological process of the substance. When not available, a statement of each supplier will be provided instead in order to confirm that benzene and other CMR

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

substances are below 0.1% together with the description of the analytical methods used;
- Spectral data (UV, IR, NMR) and
- High pressure liquid chromatogram or gas chromatogram.

The requested information is necessary to verify whether there remains an uncontrolled risk with the substance that should be subject to further risk management measures. Comments provided by the Registrant(s) have been taken into account and request adapted depending on the status of each registrant.

2. Complete the environmental exposure scenarios regarding the use of CS_2 in manufacturing of regenerated cellulose

Exposure of the environment is one of the initial concerns. The available data do not allow to conclude on this concern, therefore further information is needed. Where not already provided, environmental exposure scenarios and estimation of emissions in all the relevant environmental compartments are required from Registrant(s) using carbon disulphide in manufacturing of regenerated cellulose in accordance with the Guidance on information requirements and chemical safety assessment Chapter R.16: Environmental Exposure Estimation. Registrant(s) provided an estimation of carbon disulphide concentrations in the atmosphere and surface water only. The atmosphere was considered by Registrant(s) as the only relevant compartment for direct emission. In fact, concentrations in surface water were based on the equilibrium partitioning between air and water, considering the atmosphere contamination as the only way of water exposure. The absence of scenarios covering direct and indirect (through the STP) emissions to the aquatic and terrestrial compartments were not justified. Then, the assessment is not in accordance with the guidance R.16. for the exposure assessment.

Therefore, pursuant to Article 46(1) of the REACH Regulation, for the manufacturing of regenerated cellulose, the Registrant(s) are required to provide exposure scenarios with related release estimation and risk assessment for all the environmental relevant compartments considering the different routes of exposure (*via* the atmosphere as already available, but also *via* the direct releases to the aquatic and terrestrial compartments and/or *via* the indirect releases through the STP). Sufficient information to demonstrate the control of risks regarding the use of carbon disulphide in manufacturing of regenerated cellulose must be provided. If risk management measures or specific processes are proposed, they have to be properly described and their efficiency in limiting the emissions has to be proven for example with emission data (if available). All the parameters have to be explained and justified in accordance with the guidance in order to allow the eMSCA to evaluate the appropriatness of the descriptions and calculations. Based on Registrant(s) comments, this request has been amended.

3. Provide the environmental exposure assessment for uses as specified below

Exposure of the environment is one of the initial concerns. The available data do not allow to conclude on this concern for the reasons detailed below.

ECHA notes that no environmental risk assessment is available for the following uses:

- manufacture phase of carbon disulphide,
- use as pH-regulators, flocculants, precipitants, and neutralization agents,
- use as an intermediate in the manufacturing of biocidal and plant protection products,
- use as a laboratory chemical,

- use in the manufacturing of polymer preparations and compounds.

ECHA further notes that it has been reasoned by the Registrant(s) that the exposure scenarios were not submitted due to the fact that carbon disulphide is mainly processed in closed systems, in strictly controlled conditions. This is however not a reason for not submitting exposure scenarios. To the contrary, exposure scenarios shall specifically reflect on all operational conditions and risk management measures, including closed systems and strictly controlled conditions. Furthermore, the scope of the exposure assessment is triggered by the hazards identified during the hazard assessment (see Annex I 5.0 of REACH). This includes not only classified but also non classified hazards. This means that even if a substance is not classified for the environment it could still be hazardous to the ecosystems. For carbon disulphide the concern is based on the adverse effects seen in aquatic organisms(fish at 1 mg/L and Daphnia at 2.1 mg/L).
The scope of the exposure assessment is addressed further in ECHA guidance document B.8. (Guidance on information requirements and chemical safety assessment Part B: Hazard assessment, Version 2.1, December 2011, Reference: ECHA-11-G-16-EN, see chapter B8.1, page 43 http://echa.europa.eu/documents/10162/13643/information_requirements_part_b_en.pdf)

No information about how and to what extent applied operational conditions and risk management measures limit or prevent environmental releases of carbon disulphide for these uses. Exposure scenarios for each uses should be submitted and their refinements have to be justified to explain the levels of release and to demonstrate the control of risks. Recent emissions data demonstrating the efficiency of those systems claimed in the registration dossiers and leading to negligible releases may be provided as supportive data in the exposure scenarios. Beyond the specifications indicated above, the exposure scenarios shall comply with Annex I, Section 5 of the REACH Regulation governing exposure assessment.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide exposure scenarios with sufficient information on operational conditions and risk management measures under which the risks associated to the identified uses of carbon disulphide can be controlled. If available, recent monitoring data demonstrating efficiency of those systems and conditions, and justifying prevention of carbon disulphide environmental releases, may be provided as supportive information. If these uses are not under SCCs, appropriate risk assessments should be carried out for each step of the life cycle of the substance and for each use. All the parameters have to be explained and justified based on the guidance documents in order to allow the evaluating MSCA to evaluate the appropriatness of the descritptions and calculations.

Based on the Registrant(s) comments, it is acknowledged that the lead Registrant is neither proprietary nor responsible for downstream users data. However, it is emphasized that those data are necessary for a relevant/ realistic evaluation of the safe use of the substance.

4. Further detailed information on worker exposure

Occupational exposure assessment was based on tier 1 tool ECETOC TRA v2 only. Some of the Risk characterization ratio (RCR), with the Registrant's proposed DNEL, were close to 1 ([redacted]). Using the currently latest version of ECETOC TRA (v3), PROC 8a, PROC 5, PROC 9, PROC 14 (industrial) and PROC 15 (professional) lead to RCR >1. Moreover, as detailed in point 5, new experimental toxicological study is requested, that may affect the evaluation of the DNEL. A refined risk assesment for this scenario is thus required using appropriate RMMs, and, if necessary, higher Tier exposure assessment and/or available monitoring data

area also warranted.

In this context, the Registrant(s) are requested to provide:

An update of tier 1 modelling, preferably by using ECETOC TRA v3. When modeled estimates of exposure are provided the choice of model should be justified.

Information on RMM should be sufficiently described to justify refinements proposed in the exposure scenarios (e.g. ventilation/extraction). In fact, it is considered that CSR is not sufficiently detailed and an updated CSR should be provided in order to demonstrate that the risk for workers is adequately controlled.

All input values, assumptions used to generate the exposure estimates and output data, model report, including choice of percentile of the output distribution if applicable, should be reported and the deviation from standard parameters should be justified.

It is reminded to the Registrant(s) that the exposure scenarios have to be extensively and properly described. A brief description of the sequence of the activities/tasks, operating conditions/RMMs, estimation of the number of workers involved in these uses should be provided if available to enable a better understanding of the practices.
If available, recent monitoring data demonstrating efficiency of the operating conditions/RMM should be provided as supportive information. If available, monitoring data should be provided together with details of the protocols used to generate them. This should include the analytical methods, the operational conditions, a description of the task being undertaken, the personal protective equipment worn during the measurements. In addition, all raw measurements should be provided.

Based on the Registrant(s) comments, ECHA agrees that only available data need to be provided.

5. **Tiered approach: Extended One generation Reproductive toxicity study in rats, according to test method OECD TG 443 including cohort 2A and 2B (DNT) . Premating exposure duration of 10-week should be included. The route of exposure (oral or inhalation) shall be determined on the basis of a pre-study ("Tier 1") investigating the comparative toxicokinetics *via* these routes.**.

In addition to the reproductive concern and ED potential, a concern on postnatal development related to potential neurodevelopmental toxicity was identified during the evaluation of all available toxicological information from the registration dossiers and literature.

Carbon disulphide has not been subject to standard regulatory toxicity tests for reproductive endpoint. However, extensive literature data on experimental animals are available for this endpoint. Furthermore, some epidemiological studies have evaluated the effect of carbon disulphide exposure on reproductive parameters.

In the animal experimental studies, most of the studies were performed via whole body inhalation as it is the most likely route of exposure. Nevertheless, some developmental toxicity studies were also performed using oral or intraperitoneal routes.

With regard to reproductive toxicity of carbon disulphide, none of the studies were performed according to guidelines and available studies showed limited reliability (e.g. study protocol). Carbon disulphide may affect male fertility in rats through changes in

sperm count and mating behavior. The NOAEC in laboratory animals for these effects was found above 300 ppm (Zennick *et al.*, 1984[3], Chen *et al.*, 2005[4]). There is some evidence that this toxicity is caused by a toxic effect on the testicles or by indirect effects on the ejaculation process.

A few studies have evaluated the effects of carbon disulfphide on female reproduction. According to a GLP compliant but non-regulatory study report[5], no effects were observed on the reproductive function and reproductive performance (estrous cycling, mating index or fertility index) of female rats at 500 ppm, exposed via inhalation route (6 h/d, during gestation). In none of these studies, behavioral assessments were performed. Based on the Registrant(s) comments, it was clarified that no behavioral assessment on offsprings were performed.

With regard to developmental toxicity of carbon disulphide, well-conducted studies are available in rat and rabbit either by inhalation or via oral route. Carbon disulphide exerts embryotoxic effects at high doses without maternal toxicity (Jones-Price *et al.*, 1984)[6] [7]. Teratogenic effects were described exclusively at maternally toxic doses. The NOAEC for embryotoxic effects for rabbits were approximately 300 ppm and was higher for teratogenic effects. Initial neurotoxic effects already occurred at these concentrations in the 90-day tests. Finally, there is an evidence that carbon disulphide can cross the placenta and is distributed to the fetal brain, blood, liver, and eyes (Danielsson *et al.*, 1984)[8].

Studies in which neurobehavioral effects were tested in pups have the lowest LOAEC. Developmental delays and neurobehavioral effects in rats have been reported in the offspring of exposed dams at 3.2 ppm and above after exposure *in utero* over one or two generations (Tabacova *et al.* 1978, reported also in 1980, 1983; Tabacova and Balabaeva, 1980; Lehotzky *et al.* 1985[9]). These studies were not performed according to standard regulatory toxicity test guidelines and show some deficiencies. In general, lack of maternal observation, no positive controls, statistical significance of behavioral effects and chemical purity were not stated, exposure method was not explained and no historical controls were available. Despite the questionable quality of these studies and the inconsistency of some of the results, the studies indicate that carbon disulphide exposure *in utero*, or perinatally can affect motor coordination, auditory and visual development, and other behaviors in rat pups at doses as low as 3.2 ppm. In conclusion, the biological significance of the neurobehavioral effects in the Tabacova *et al.* and lehotzky *et al.* studies cannot be elucidated with the available information. Despite the questionable quality of these studies, these data were considered suitable for identifying potential adverse effect and justifying further testing.

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[3] Zenick H et al. (1984). An evaluation of the copulatory, endocrinologic, and spermatotoxic effects of carbon disulfide in the rat

[4] Chen G, et al; Study on the Reproductive Effects of Carbon Disulfide in Male Rats and Their Subgeneration. Chinese Journal (not specified), 2005, 34:6, 658-660.

[6] Holson JF (1992). An assessment of reproduction in female rats exposed to CS2 via inhalation. Testing laboratory: WIL Research Laboratories, Inc. Report no.: WIL-186001.

[6] Jones-Price C, Wolkowski-Tyl R, Marr MC, et al. 1984a. Teratologic evaluation of carbon disulfide (CAS No. 75-15-0) administered to CD rats on gestational days 6 through 15. Research Triangle Park, NC: National Center for Toxicological Research, Division of Teratogenesis Research. NCTR 222-80-2031(C); NTIS PB84-0192343.

[7] Jones-Price C, Wolkowski-Tyl R, Marr MC, et al. 1984b. Teratologic evaluation of carbon disulfide (CAS No. 75-15-0) administered to New Zealand white rabbits on gestational days 6 through 19. 189
Research Triangle Park, NC: National Center for Toxicological Research, Division of Teratogenesis Research. NCTR 222-80-2031(C), NTIS PB84-0192350

[8] Danielsson BR, Bergman K, D'Argy R. 1984. Tissue disposition of carbon disulfide: 2. Whole-body autoradiography ^{35}S- and ^{14}C-labelled carbon disulfide in pregnant mice. Acta Pharmacol Toxicol 54:233-240.

[9] Tabacova S, Hinkova L, Balabaeva L. 1978. Carbon disulfide teratogenicity and postnatal effects in rat. Toxicol Lett 2:129-133.
Tabacova S, Balabaeva L. 1980a. Carbon disulfide intra uterine sensitization [Abstract]. Toxicol Lett (Amst) 0:256.
Tabacova S, Balabaeva L. 1980b. Subtle consequences of prenatal exposure to low carbon disulphide levels. Arch Toxicol Suppl 4:252-254.
Tabacova S, Nikiforov B, Balabaeva L. 1983. Carbon disulfide intrauterine sensitization. J Appl Toxicol 3:223-229.
Lehotzky K, Szeberenyl JM, Ungvary G, et al, 1985. Behavioural effects of prenatal exposure to carbon disulphide and to aromatol in rats. Arch Toxicol Suppl 8:442-446.

Moreover, it is noteworthy that the substance has an EU harmonized classification as toxic to reproduction, category 2, H361fd "Suspected of damaging fertility. Suspected of damaging the unborn child.". Moreover, carbon disulphide is classified for specific target organ systemic toxicity (STOT) after repeated exposure, category 1 –H372 "causes damage to nervous system through prolonged or repeated exposure".

The classification to STOT RE 1 for neurotoxicity together with the indication of higher sensitivity of developing organisms to neurotoxic effects than adults as suggested by the studies of Tabacova and coworkers (1978, 1980, 1983) and Lehotzky and coworkers (1985), support the need to clarify the potential effect of carbon disulphide on neurodevelopmental toxicity. Due to the expected higher sensitivity this may lead to a more severe classification for developmental effects and potentially the need to set a lower OEL and DNEL.

In humans, occupational exposure investigations suggest that carbon disulphide exposure might be associated with menstrual cycle disturbance below 10 ppm (Bao *et al.*, 1981[10]; Zhou *et al.*, 1988[11]) and disturbed pregnancy outcome (Zielhuis, 1984[12]) but the database is very limited. In addition, adverse effects on pregnancy might occur at exposure below 10 ppm. Other investigation did not show adverse effect on pregnancy with an exposure to carbon disulphide around 3.3 ppm. Male workers often complain about reduced libido and sexual potency when exposed to high doses (above 10 ppm). However, inconsistent results, lack of valid information on actual exposure levels, lack of dose-response curve and potential co-exposure with other chemicals (e.g. H_2S) raise uncertainties about these studies. It is still unclear if these effects can occur at lower exposure level than those leading to neurological and cardiotoxic effects.

With regard to occupational exposure assessment, an 8-hour TWA of 5 ppm has been established by the SCOEL (2008) based on the observed occupational neurotoxicity and cardiotoxicity in human. However, this value has not taken into account potential developmental or neurodevelopmental effects of carbon disulphide. Although, it is claimed that workers in the viscose industry, in Western Europe, are exclusively males (Gelbke *et al.*, 2009[13]), women may be exposed through other occupational uses to carbon disulphide (e.g. laboratory reagent). Moreover, general population may also be exposed to very low doses (EC, WRc-NSF-November 2002). Finally, other international agencies have raised the need for further investigation of behavioral effects of low concentrations of carbon disulphide (OEHHA, 1999; DECOS, 2011). With regard to the ED potential, disturbance of the oestrus cycle was found (Akecadzhanova, 1978) in a rat study with limitations. Results of investigations with rats on fertility are contradictory; due to poor reporting, these experiments are difficult to compare and do not allow definitive conclusions. The Registrant(s) agree that "the studies reporting potential ED properties of CS2 were not reliable as the effects were not related to estimated exposure (Bao et al. 1991, WHO 2002) and none of these effects were observed in three other Chinese studies, where reporting was limited on a similar level (He et al. 1996, Q. Wang et al. 1999, Zhang et al. 1999). Thus, potential effects on female reproduction have not been adequately investigated and study results regarding the frequency of abnormal menstrual duration or pain/bleeding in populations of female Chinese viscose rayon worker are contradictory and inconsistent (Cai & Bao, 1981; Zhou et al., 1988; He et al. 1996; Q. Wang et al. 1999; Zhang et al. 1999)."

[10] Bao Y, Cai S, Zhao SF, et al. 1991. Birth defects in the offspring of female workers occupationally exposed to carbon disulfide in China [Abstract]. Teratology 43(5): 451-452.
[11] Zhou SY, Liang YX, Chen ZQ, et al. 1988. Effects of occupational exposure to low-level carbon disulfide (CS2) on menstruation and pregnancy. Ind Health 26:203-214.
[12] Zielhuis RL, Stijkel A, Verberk MM, et al. 1984. Carbon disulfide. In: Health risks to female workers in occupational exposure to chemical agents. Berlin, FRG: Springer-Verlag, 15-21.
[13] Gelbke HP, Göen T, Mäurer M, Sulsky SI. A review of health effects of carbon disulfide in viscose industry and a proposal for an occupational exposure limit. Crit Rev Toxicol. Oct; 39 Suppl 2: 1-126

According to the Registrant(s) comment, a developmental neurotoxicity study might be considered sufficient to fully evaluate the potential neurobehavioral effects. ECHA is of the opinion that in this case there is a need for a well-conducted reproductive toxicity study to clarify fertility, neurobehavioural concern and ED properties in a single study.

Therefore, the requested extended one-generation reproductive toxicity study (OECD 443 EOGRTS) is regarded as necessary to clarify the abovementioned issues. It should be noted that this new study may impact the setting of the actual DNELs and potentially lead to a more severe classification and labelling (reprotoxicity categorisation both for development and fertility) and a stricter OEL.

Route of exposure

Carbon disulphide should preferably be administered *via* inhalation route to rats as it is the most relevant route to potential human exposure. Indeed, carbon disulphide is highly volatile with a vapor pressure of 27400 Pa (at 25°C). The Registrant(s) comment that performing an EOGRTS by inhalation with DNT cohort is currently technically very challenging (stressful exposure, no historical control data, technical equipment, time issue). Based on Registrant(s) comments, it is agreed to modify the request: the Registrant(s) need to prove ahead that performing this study by oral route is appropriate, based on relevant kinetics data for route-to-route extrapolation. Therefore, a tiered approach for this study is requested:

- **Tier 1:**

Both human and animal data indicate that the target organs for carbon disulphide are similar across species *via* inhalation. Existing ADME data by inhalation in humans are supported by animal data by this route. However, there are very few animal and human data regarding the pharmacokinetics of carbon disulphide following oral exposure (ATSDR 1996).

For an adequate route-to-route extrapolation, the potential differences between carbon disulphide kinetics after inhalation or after oral routes should be investigated in rat. As proposed by the Registrant(s), gavage is considered an acceptable oral route of exposure. Based on a PfA it is agreed that the comparative toxicokinetic assessment should include whole body exposure as this is considered the most common route of administration for inhalation exposure in reproductive toxicity studies and because due to the dermal absorption of this substance the nose-only kinetics may be different from kinetics after whole body exposure. Indeed, it is the commonly used route in reproductive toxicity study by inhalation. Moreover, whole body exposure is the most realistic route regarding the expected exposure of workers because dermal absorption of carbon disulphide can occur. The following toxicokinetics measurements should be assessed after single exposure/administration at the same dose range level and in the same rat strain as for the requested EOGRTS:

- Calculation of area under the plasma concentration-time curve, Cmax and Tmax for plasma concentration versus time profiles, clearance rates, data on bioavailability (F, absorption rate) of carbon disulphide,
- Calculation of area under the plasma concentration-time curve, Cmax and Tmax for plasma concentration versus time profiles of TTCA,
- Differences in first pass metabolism as metabolic parameters following oral exposures could differ from those following inhalation exposure,
- Rate and extent of excretion from urine, faeces and air (TTCA, CS2).

Differences in the distribution (volume, Tissues or Organs to plasma partition coefficients) in major organs and tissues (blood, plasma, liver, kidney, lung, brain, heart, ovaries, uterus, testes, prostate) was included in the initial draft decision but based on the Registrant(s) comment, this information is not required anymore. In fact, if the internal dose of carbon disulphide is comparable between the two routes, no differences are expected in the distribution of carbon disulphide within the body and on its accumulation in fat-rich tissues, specifically the brain.

- **Tier 2:**

In case the following criteria are not met (based on IGHRC, 2006), a reliable route-to-route extrapolation is not considered possible and the requested EOGRTS shall be performed via inhalation route:

- Hepatic first pass effects are minimal;
- There is no significant metabolism of the chemical by oral, gut or skin enzymes or in pulmonary macrophages, or transformation by other processes in the gut or lung;
- Absorption is the same between routes, or the difference is known and can be quantified.

In case these criteria are met, a route-to-route extrapolation will be considered possible based on the Toxicokinetics data provided in Tier I and the requested EOGRTS study could be performed by oral route.

EOGRTS Study design

DNT

With regard to the strong neurotoxicity potential in adult animals and in human of carbon disulphide, and alerts on neurodevelopmental toxicity, as detailed above, the DNT cohort is justified and inclusion of Cohort 2A and 2B is therefore requested.

Conclusion

Therefore, the Registrant(s) is requested to submit an extended one-generation reproductive toxicity study with the following study-design specifications:

- Depending on the preliminary toxicokinetic study "Tier I", oral or inhalation route of exposure;
- Ten weeks premating exposure duration; Pre-mating scenario for males need to be adapted as effects on sperm integrity has been identified following an exposure to carbon disulphide. A pre-mating period of 10-week for males is required in order not to miss functional effects;
- This study should cover a wide range of doses, with at least 3 dose levels in order to established dose-response relationships properly, especially at low dose. The higher dose has to be one that produces a slight toxicity and effect on the nervous system (e.g. 300 ppm or equivalent oral dose level) and the lowest dose 3 ppm (The lowest LOAEC established in the Tabacova/Lehotsky studies or equivalent oral dose level);
- Cohort 1A (Reproductive);
- Cohort 1B (Reproductive);
- Cohorts 2A and 2B (Developmental neurotoxicity (DNT)).

Note for consideration:

Proposals for amendment of a Member State were submitted proposing the inclusion of cohort DIT and an extension of Cohort 1B to produce F2. The justification with the reference to column 2 of section 8.7.3 of Annex X and specifically referring to the significant exposure and potential ED properties triggering F2 and alerts for potential immunotoxic effects for DIT was provided[14]. The justification did not include the elements considered specifically important for this substance evaluation in terms of technical challenges in case it is conducted by inhalation. Because of the expected higher sensitivity of developmental neurotoxicity endpoint, the inclusion of additional cohorts was considered of no added value for risk management. Therefore, in view of proportionality, ECHA decided not to request additional cohorts F2/DIT.

The Registrant(s) may expand the study by including the extension of cohort 1B to include the F2 generation and by conducting cohort 3 (DIT) if information indicating a concern that needs to be adressed justifies such an inclusion. Such information may already be available or stem from the conduct of the extended one-generation reproductive toxicity study amd/or from additional scientific information. The justification of such an extension must be documented.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test(s) must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/regulations/reach/registration/data-sharing.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the stud(y/ies) on behalf of all of them.

[14] Dimitrova N, Kopcheva H. (2013). Non specific immune reactivity of workers exposed to carbon disulfide. Bulgarian Journal of Public Health 2013 Vol. 5 No. 1 pp. 15-24
European commission, study on the scientific evaluation of 12 substances ni the context of endocrine disrupter priority list of actions, 2002

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals.
The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[16] by Leena Ylä-Mononen, Director of Evaluation

Annex I: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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