EUROPEAN CHEMICALS AGENCY

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

For carbon tetrachloride, CAS No 56-23-5 (EC No 200-262-8)

Addressees: Registrants of carbon tetrachloride (concerned registrants)

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 meeting the following criteria are *not* addressees of this decision: i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants 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 French Agency for Food, Environmental and Occupational Health Safety (ANSES)on behalf of the French Competent Authority (evaluating MSCA), 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 does not take into account any updates of the registrations of the concerned registrants after 1 August 2013, the date upon which the draft decision was circulated to the other Competent Authorities of the MemberStates and ECHA pursuant to Article 52(1) of the REACH Regulation.

This decision does not imply that the information provided by the concerned registrants in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the concerned registrants 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 tetrachloride, CAS No 56-23-5 (EC No 200-262-8) based on registration dossiers submitted by the addressees (concerned registrants) and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/CMR, Exposure/High exposure for workers, and high aggregated tonnage, carbon tetrachloride was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. The CoRAP was published on the ECHA website on 29 February 2012. The Competent Authority of France was appointed to carry out the evaluation.

Further information is required to clarify the abovementioned concerns. Therefore, a draft decision was prepared pursuant to Article 46(1) of the REACH Regulation to request further information. This draft decision was submitted to ECHA on 28 February 2013.

Further information requirements related to evaluation of carbon tetrachloride have been addressed to the relevant registrant in a separate confidential draft decision.

On 4 April 2013 ECHA sent the draft decision to the Registrants 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. The Registrants provided comments on the draft decision by the given timeline. Having taken the comments into account, the Competent Authority of France modified the draft decision.

In accordance with Article 52(1) of the REACH Regulation, on 1 August 2013 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.

Subsequently, MSCAs submitted proposals for amendment to the draft decision.

On 6 September 2013 ECHA notified the concerned registrant of the proposals for amendment to the draft decision and invited it pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA has reviewed the MSCAs' proposals for amendment and amended the draft decision.

On 16 September 2013 ECHA referred the draft decision to the Member State Committee.

On 6 October 2013 the Registrants provided comments on the proposed amendments.

After discussion in the Member State Committee meeting on 4 to 8 November 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 7 November 2013. Having taken proposals for amendments and the registrant comments thereon into account, section II of the decision was changed to request an Extended One Generation Reproductive Toxicity Study (OECD 443) by inhalation route. Section III was amended accordingly. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information using the indicated test method and the registered substance subject to the present decision:

- Extended One Generation Reproduction Toxicity Study by inhalation route (test method: OECD443).

Pursuant to Article 46(2) of the REACH Regulation, the concerned registrants shall submit to ECHA by 26 May 2016 an update of the registration dossiers containing the information required by this decision.

At any time, the concerned registrants shall take into account that there may be an

obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

Based on the evaluation of all relevant information submitted on carbon tetrachloride and other relevant and available information, 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.

Information of section II is required in order to enable the evaluating MSCA to assess properties on reproduction.
Without the requested information it will not be possible to verify whether there remains an uncontrolled risk with the substance that should be subject to further risk management measures.

On the basis of available data, provided by registrants and found in the literature, no clear conclusions about the reproductive toxicity potential of the registered substance, carbon tetrachloride, can be made. Further the first draft decision and following the PfA period, Registrants refuted the original draft decision and proposals for amendment made by three MSCAs by providing more detailed information about the existing data (translation of results tables of the Nagano study and justifications of the Alumot study).

In their registration dossier, the registrant(s) provided a non-guideline study[1].

In this study[2], the potential of carbon tetrachloride to adversely affect the health and the fertility of rats was analysed in a chronic 2 year feeding study with fumigated food concentrations of 80 and 200 ppm. Females were mated with untreated males, 6 weeks after the start of the treatment, to test their basic reproductive capacity. At intervals of 2 months, 9 of the 18 males of each dose group were mated with 2 treated females each, the other 9 males mating with 18 sterile untreated females. The only observations for mated females included percentage of females that got pregnant and percentage of mated females with litters. The offspring was only examined for litter size, viability, body weight and body weight gain. After study termination the parental animals were only examined for biochemical parameters of liver toxicity, feed consumption and body weight gain.

The treatment groups did not differ in any of the parameters from the control, except for the number of parturitions in the high dose group in the fourth mating. But this rate recovered to normal in the fifth mating.

This study was judged with a Klimisch score of 4 due to extensive deviations from any available recognised guidelines/protocols for reproductive endpoints (neither OECD guidelines n°416/443 nor RACB (Reproductive Assessment by Continuous Breeding) protocol). The comparison of the protocol study with recognised protocols showed some deviations on the choice of tested doses, exposure design and data collected.

Indeed, only two concentrations were tested instead of three as recommended in the protocol and at the highest dose no toxicity was observed. An expected difference in body weight of 10% compared to the controls should be observed, however it was not the case. Although the exposure seems (as the schedule of treatment is unclear) continuous, major differences from the RACB protocol were found, notably the cross mating (task 3 of protocol) and second generation (task 4) were not performed.

[1]E. Alumot, E. Nachtomi, E. mandel, P. Holstein, 1976.Tolerance and acceptable daily intake of chlorinatedfumigantsin the rat diet.Food CosmetToxicol., vol. 14, no. 2, p. 105-10.

The parameters that were evaluated in the study are not sufficient to assess the capability of the animals to reproduce themselves and to check the fertility endpoint. Several fertility parameters were not analysed such as: day of delivery, sex ratio, development of pups until weaning and second generation. Furthermore, gross and microscopic observations of all organs and body cavities, reproductive organs weights (ovary, testis, epididymis, seminal vesicle and prostate), oestrous cycle, testicular spermatid head and cauda epididymal sperm counts of the parents and pups should be observed and reported as recommended in the protocol but that is not the case in this study.

In the Registrants' comments on the Proposals for amendment, the Registrants argued that there was no need for the study due to the absence of effects on reproductive organs or tissues in the repeated-dose toxicity studies of Nagano[2,3].

However, gross and/or microscopic findings were observed but they were either not dose-related or not reported as statistically significant.The functional activities of the reproductive organs, notably spermatogenesis were not investigated.

Further data, not submitted by the registrants, were found in the literature. In these publications (Chatterjee, 1966[4]; Chatterjee 1968[5]; Kalla and Bansal 1975[6]), testicular atrophy, abnormality in the process of spermatogenesis, inhibition of oestrous rhythm and weight and vascularization decreases of ovary and uterus, were observed.

Carbon tetrachloride was also used in several studies published in 2013[7] as an inductor of sperm damages (including abnormal sperm rate and decreased sperm concentration and motility) and testicular apoptosis in male rats treated weekly with 0.25 ml/kg of CCl4 in olive oil by gavage for 10 weeks. An oxidative stress mechanism is suspected by formation of free oxygen radicals which have high affinity to cell membrane lipids leading to tissue damage of testis and effects on sperm during maturation.

In conclusion, considering the contradictory data and the low relevance of the available studies, concern raised in the literature about reproductive toxicity could not be dismissed and must be clarified.

Moreover, male rats produce a number of spermatozoids that greatly exceed the minimum requirements for fertility, particularly as evaluated in reproductive studies that allow multiple matings[8]. In some strains of rats and mice, sperm production can be drastically reduced (by up to 90% or more) without affecting fertility[9]. Human sperm production appears to be much closer to the infertility threshold; therefore, less severe sperm count reductions may cause human infertility. It is therefore important to assess the sperm quality of the animals instead of assessing only female fertility index or gestation index. Negative results in rodent studies that are limited to only fertility and pregnancy outcomes provide insufficient information to conclude that the test substance has no reproductive hazard in

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[2] Nagano K (2007). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. J Occup Health 2007; 49: 249-259
[3] Nagano K (2007). Inhalation Carcinogenicity and Chronic Toxicity of Carbon Tetrachloride in Rats and Mice. Inhalation Toxicology, vol. 19, no. 13, p. 1089-1103
[4]Chatterjee A (1966) Testicular degeneration in rats by carbon tetrachloride intoxication.Experientia(Basel), 226: 395-396
[5]Chatterjee A (1968) Effect of CCl_4 on gonadal physiology in female rats. ActaAnat, 71: 82-86.
[6]Kalla NR &Bansal MP (1975) Effect of carbon tetrachloride on gonadal physiology in male rats. ActaAnat, 91: 380-385.
[7]Türk G. et al. ; Ameliorating effect of pomegranate juice consumption on carbon tetrachloride-induced sperm damages, lipid peroxidation, and testicular apoptosis. ToxicoInd Health. 2013 sep 30
Sönmez M. et al. ;Quercetinattenutescabon tetrachloride-induced testicular damage in rats. Andrologia. 2013 sept 10
Yüce A. et al. ; Effectiveness of cinnamon bark oil in the prevention of carbon tetrachloride-induced damages on the male reproductive system Andrologia. 2013 Feb 15
[8]Amann R.P. ; A critical review of methods for evaluation of spermatogenesis from seminal characteristics, J. Androl., 2, 37, 1981
Working P.K. ; Male reproductive toxicity : comparison of the human to animal models. Environ. Health, 77, 37, 1988
[9]Aafjes, J.H., et al.., Fertility of rats with artificial oligozoospermia, J. reprod. Fertil., 58, 345, 1980.
Meistrich, M.L., Quantitative correlation between testicular stem cell survival, sperm production, and fertility in the mouse after treatment with different cytotoxic agents, J. Androl. 3, 58, 1982.
Robaire, B., et al., Supression of spermatogenesis by testosterone in adult male rats : effect on fertility, pregnancy, outcome and progeny, Biol. Reprod., 31, 221, 1984

humans.

In order to evaluate
- the integrity and performance of the male and female reproductive systems,
- the effect on neonatal and postnatal developmental toxicity.

it is requested to carry out the EOGRTS (OECD 443).

DIT/ DNT cohorts are considered to be included in the OECD 443 but can be omitted by the registrants by providing sufficient scientific justification. Considering the very high vapour pressure of CCl4, the inhalation route appears to be the most appropriate.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the registrant(s) are required to carry out the following study: An Extended One Generation **Reproduction Toxicity Study (test method : OECD443) using the registered substance subject to this decision** by inhalation route.

In the absence of complete information on reproduction toxicity, **no consolidated DNEL could be derived**. The results of the Extended One Generation reproduction toxicity study even without the second generation would allow deriving the consolidated DNEL.

Indeed, the data provided lately by the registrant impacted the original concern. Still, the effects of Carbon Tetrachloride on several parameters such as sperm quality or oestrous cycle need to be assessed. Based on these considerations on this specific case, Extended One Reproductive Toxicity Study is finally requested.

As some RCR with the proposed DNEL by registrants are close to 1, the use of a lower (FR-CA) DNEL would result to RCR superior to 1. In this context refinement of exposure scenarios are necessary.

IV. Adequate identification of the composition of the tested material

The substance identity information submitted in the registration dossiers has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation

In relation to the required test, the sample of substance used for the new study shall have a composition identical to the composition of the substance specified by one of the two registrants which performed a full registration. It is the responsibility of all the concerned registrants to agree on the tested materials to be subjected to the test 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 study must be shared by the concerned registrants.

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

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants. Since several registrants of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other concerned registrants and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

If ECHA is not informed of such agreement within 90 days, it shall designate one of the concerned registrants to perform the tests on behalf of all of them. If a registrant performs a test on behalf of other registrants, they shall share the cost of that study equally and the registrant performing the test shall provide each of the others concerned with copies of the full study reports.

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.aspxFurther advice can be found at http://echa.europa.eu/datasharing_en.asp.

VI. General requirements regarding Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

VII. 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.

[redacted]

Jukka Malm
Deputy Executive Director

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