Regulatory Management Option Analysis (RMOA)

**Authority: France**

**Date: September 2022**

**Substance name: Carbon disulfide**

**General structure: CS2**



**Revision history**

|  |  |  |
| --- | --- | --- |
| *Version* | *Date* | *Description* |
| 1 | September 2022 | This RMOA is used to determine whether there is a risk to workers and if further risk management measures are necessary. |

General comments and additional relevant information are invited on this RMOA by xxx.

**Specific questions:**

- Do you have information to complete the knowledge on uses and more specifically on laboratory use of the substance?

- Do you have exposure data (e.g. exposure measurements) to refine the worker risk assessment?

- What is your view on the approach followed for the DNEL to be used for worker risk assessment (namely current IOELV still appropriate)?

- Do you have information on potential alternatives to carbon disulfide?

**Substances within this RMOA:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| EC/List number | CAS number | Substance name[and Substance name acronyms (\*)] | Chemical structures  | Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) |
| 200-843-6 | 75-15-0 | Carbon disulfide, (carbon disulphide, methandithione) | CS2 | Full> 100,000 – 1,000,000 |

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The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage. Assessment of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

# Foreword

The purpose of the assessment of regulatory needs of a group of substances is to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. the combination of the regulatory risk management instruments to be used and any intermediate steps, such as data generation, needed to initiate and introduce these regulatory measures.

An assessment of regulatory needs can conclude that regulatory risk management at EU level is required for a (group of) substance(s) (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. While the assessment is done for a group of substances, the (no) need for regulatory action can be identified for the whole group, a subgroup or for single substance(s).

The assessment of regulatory needs is an important step under ECHA’s Integrated Regulatory Strategy. However, it is voluntary, i.e., it is not part of the processes defined in the legislation but aims to support them.

The assessment of regulatory needs can be applied to any group of substances or single substance, i.e., any type of hazards or uses and regardless of the previous regulatory history or lack of such. It can be done based on different level of information. A Member State or ECHA can carry out this case-by-case analysis. The starting point is available information in the REACh registrations and any other REACh and CLP information. However, more extensive set of information can be available, e.g. assessment done under REACh/CLP or other EU legislation, or can be generated in some cases (e.g. further hazard information under dossier evaluation). Uncertainties associated to the level of information used should be reflected in the documentation. It will be revisited when necessary. For example, after further information is generated and the hazard has been clarified or when new insights on uses are available. It can be revisited by the same or another authority.

The responsibility for the content of this assessment rests with the authority that developed it. It is possible that other authorities do not have the same view and may develop further assessment of regulatory needs. The assessment of regulatory needs does not yet initiate any regulatory process but any authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

For more information on Assessment of regulatory needs please consult ECHA website[[1]](#footnote-2).

# Glossary

|  |  |
| --- | --- |
| ANSES | *Agence Nationale de Sécurité Sanitaire de l’alimentation, de l’environnement et du travail* [French Agency for Food, Environmental and Occupational Health & Safety] |
| ART | Advanced REACh tool |
| BLV | Biological limit value |
| BOEL | Binding occupation exposure level |
| CCH | Compliance Check |
| CLH | Harmonised classification and labelling |
| CAD | Chemical agent directive |
| CMR | Carcinogenic, mutagenic and/or toxic to reproduction |
| CNS | Central nervous system |
| CoRAP | Community rolling action plan |
| CSR | Chemical safety report |
| DEv | Dossier evaluation |
| DNEL | Derived no effect level |
| ECETOC TRA | European centre for chemical safety assessment - targeted risk assessment |
| ECHA | European Chemical Agency |
| ED | Endocrine disruptor |
| HCNL | Health council of Netherland |
| IOELV | Indicative occupational exposure level value |
| OC | Operational condition |
| OEL | Occupational exposure limit |
| ECG | Electrocardiogram |
| EOGRTS | Extended one-generation reproductive toxicity study |
| ES | Exposure scenario |
| LEV | Local exhaust ventilation |
| LOAEL/LOAEC | Lowest observed adverse level/concentration |
| MCV | Motor Nerve Conduction |
| MSCA | Member state competent authority |
| NOAEL/NOAEC | No observed adverse level/concentration |
| OSII or TII | On-site isolated intermediate or transported isolated intermediate |
| PC | Product category |
| PND | post-natal day |
| PNS | Peripheral nervous system |
| PPE | Personal protective equipment |
| PROC | Process category |
| RCR | Risk characterisation ratio |
| REACh | Regulation (EC) No 1907/206 of 18/12/06 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACh) |
| RMOA | Regulatory management options analysis |
| RMM | Risk Mitigation Measure |
| RRM | Regulatory risk management |
| SCOEL | Scientific Committee on Occupational Exposure Limits |
| SCV | Sensory nerve Conduction Velocity |
| SEv | Substance evaluation |
| STOT RE | Specific target organ toxicity, repeated exposure |
| STOT SE | Specific target organ toxicity, single exposure |
| SU | Sector of end-use |
| SVHC | Substance of very high concern |
| TTCA | thiazolidine-2-thione-4-carboxylic acid |
| TWA | Time Weight Average |

# Overview of the substance

Carbon disulfide was included in the list of substances in the CoRAP (community Rollin Action Plan) in 2013 on the grounds of suspected endocrine disruptor (ED), suspected CMR (Reproductive toxicity), high aggregated tonnage, high release to the environment and high worker exposure. The evaluation was taken in charge by France.

Based on the evaluation of the available data, the evaluating MSCA concluded that there was a need to request further information to clarify the concerns related to substance identity, worker and environmental exposure, ED, reproductive and neurodevelopmental toxicity potential. Therefore, eMSCA prepared a draft decision to request further information, including an extended one-generation reproductive toxicity study (EOGRTS). The decision was submitted to ECHA and was agreed by the member state Committee in October 2015.

The substance evaluation conclusion was prepared based on the updated lead registration dossier containing this additional study from December 2019.

At its 20th meeting (October 2021), the Endocrine Disruptor Expert Group (ED EG) supported the outcome of this evaluation that, based on the data presented in the conclusion report, including the new EOGRTS requested under SEv (Unpublished report, 2019a), the substance does not meet the criteria to be identified as an endocrine disruptor.

The substance evaluation conclusion report was published in April 2022 (ANSES, 2022). It was concluded that it should be clarified whether carbon disulfide poses a realistic risk to workers, and whether further risk management measures are necessary in order to protect workers. Therefore, it was concluded that follow-up regulatory action at EU level needed to be discussed in a RMOA.

## Substance identifiers

Table 1 Substance identity

|  |
| --- |
| SUBSTANCE IDENTITY |
| **Public name:** | Carbon disulfide |
| **EC number:** | 200-843-6 |
| **CAS number:** | 75-15-0 |
| **Index number in Annex VI of the CLP Regulation:** | 006-003-00-3 |
| **Molecular formula:** | CS2 |
| **Molecular weight range:** | 76.141 |
| **Synonyms:** | Methanedithione |

Type of substance: Mono-constituent

**Structural formula:**



## Completed or ongoing process

Table 2 Completed or ongoing processes

|  |  |  |
| --- | --- | --- |
| RMOA |  | ☐ Risk Management Option Analysis (RMOA) other than this RMOA |
| REACh Processes | Evaluation | x Compliance check, Final decision |
| ☐ Testing proposal |
| x CoRAP and Substance Evaluation: starting in March 2013 by FranceConcluded in 2022 (conclusion: need for follow-up regulatory action at EU level to be discussed in a RMOA) |
| Authorisation | ☐ Candidate List |
| ☐ Annex XIV  |
| Restri-ction | ☐ Annex XVII |
| Harmonised C&L  |  | x Annex VI (CLP) (see Annex I) |
| Processes under other EU legislation |  | ☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009  |
|  | ☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments  |
| Previous legislation |  | ☐ Dangerous substances Directive ; Directive 67/548/EEC (NONS) |
|  | ☐ Existing Substances Regulation; Regulation 793/93/EEC (RAR/RRS)  |
| (UNEP) Stockholm convention (POPs Protocol) |  | ☐ Assessment  |
|  | ☐ In relevant Annex  |
| Other processes/ EU legislation |  | x Other (see further details below) |

## Regulatory process

*a. CLP regulation*

Carbon disulfide has an harmonised classification under regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixture at European level (CLP regulation). As detailed in Annex 1, carbon disulfide is classified as Flam. Liq. 2, H225, Repr. 2, H361fd; Skin Irrit. 2, H315; Eye Irrit. 2; H319 and STOT RE 1\*\*, H372 with specific concentration limit for STOT RE and reproductive toxicity (CLP00).

In the lead registration dossier the following self-classifications are proposed in addition to the current harmonised classification: Acute Tox. 4, H332 and STOT RE 1, H372 (cardiovascular system, eye, nervous system).

Manufacturers and importers are obliged to notify the classification and labelling of their substances which are placed on the market. There is a high number of notifications in the ECHA inventory with 955 notified classification and labelling according to the CLP criteria (ECHA inventory database, consulted in June 28, 2022). No additional human health hazards are notified.

Based on its classification, carbon disulfide may be concerned by other regulations due to its presence in the Annex VI of the CLP regulation (ECHA disseminated database, consulted in July 26, 2022):

* Directive Chemical Agent Directive “CAD” (directive 98/24/EC on the protection of the health and safety of workers from the risk related to chemical agents at work),
* Active implantable medical device directive,
* Aerosol dispensers directive,
* Construction product regulation,
* Food contact material: not allowed for use,
* End of life vehicle directive,
* EU ecolabel regulation,
* General product safety directive, medical device,
* Marine environmental policy framework directive,
* Protection of Pregnant and Breastfeeding Workers Directive,
* Pressure Equipment Directive,
* Protection of Young People Directive,
* Safety and Health of Workers at Work Directive,
* Safety and/or Health Signs at Work Directive,
* Waste Framework Directive.

*b. Chemical Agents Directive (CAD) and carcinogens, mutagens or reprotoxic substance directive (CMRD)*

Occupational exposure limit (OEL) values are adopted under two legal frameworks for protecting the health of workers: the chemical agent directive (Directive 98/24 EC, CAD) and the carcinogen, mutagen or reprotoxic directive (Directive 2004/37/EC, CMRD).

Directive 2004/37/EC (CMRD)[[2]](#footnote-3) on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work and in subsequent amendments applies to a substance or mixture that meets the criteria for classification as a Category 1A or 1B carcinogen, germ cell mutagen or reprotoxic substance set out in Annex I to the CLP Regulation (Article 2). In addition, it applies to carcinogenic substances, mixtures or processes referred to in Annex I to the Directive, as well as a substances or mixtures released by a process in that annex.

Thus, carbon disulfide is not eligible to directive CMRD as the substance is not classified in category 1A or 1B for carcinogenicity, mutagenicity or reproductive toxicity and is not referred in Annex I of this directive.

It may be noted that in ECHA disseminated database carbon disulfide is stated to be listed in Annex I & Art. 2, of CMRD, as amended by Dir (EU) 2022/431, 16 March 2022. However, as the substance is classified in category 2 for reproductive toxicity, it is not our understanding that the substance falls within the scope of this directive as defined in article 2. The substance was also not found in Annex I of this directive.

However, an indicative occupational exposure limit value (IOELV) has been set for carbon disulfide at European Union level, in directive 2009/161/EU establishing a third list of IOELVs in implementation of directive 98/24/EC (CAD)[[3]](#footnote-4) on the protection of health and safety of workers from the risks related to chemical agents at work. IOELVs are health-based, non-binding values derived from the most recent scientific data available and the availability of measurement techniques. For carbon disulfide, a long-term exposure limit (8 hour time-weighted average (8-h TWA)) was set at 15 mg/m3 (equivalent to 5 ppm). A skin notation[[4]](#footnote-5) was also proposed. “Indicative” means that Member States are free to follow or not the proposed value when transposing it into national laws.

The table below gives an overview of the OELs set at national levels available in the Gestis database in EU (consulted in May 2022). In the database, there is no information on the basis of the OEL derivation.

Table 3 Overview of OEL derivation in the European Union (reported in Gestis database[[5]](#footnote-6), consulted in May 2022)

|  |  |  |
| --- | --- | --- |
|  | 8h-TWA (mg/m3) | Short-term |
| Austria | 15 | 60 |
| Belgium, Italy | 3.16 |  |
| Denmark | 15 | 30 |
| Finland, Ireland, Latvia, Spain, The Netherlands, Norway | 15 |  |
| France | 15\* |  |
| Germany (AGS) | 30 | 60 |
| Germany (DFG) | 16 | 32 |
| Poland | 12.5 |  |
| Sweden | 16 | 25 |
| Hungary | 30 | 120 |

\*Restrictive statutory value in France

Directive 98/24/EC sets also binding occupational exposure limit (BOEL) values as well as biological limit values (BLVs) at European Union level. In addition to the factors considered when establishing IOELVs, BOELs take into account socio-economic and technical feasibility factors. For any chemical agent for which a BOEL is established at EU level, Member States must establish a corresponding national BOEL which can be more stringent, but cannot exceed the European Union limit value. No binding value or BLVs were set for carbon disulfide.

*c. Other chemical legislations*

According to ECHA website, the substance is also included in:

* Cosmetic directive: annex II – Prohibited substance (ban),
* Inland transport of dangerous goods directive, Annex I, II, III (ban),
* MRL pesticide regulation: 0.01 mg/kg.

## Information on tonnage and uses

**Overview of tonnage**

Carbon disulfide is registered under REACh regulation with both full and intermediate submissions. There are seven active registrants for carbon disulfide (disseminated ECHA database, consulted in June 2022) with a full registration dossier (joint submission) in accordance with art. 10 of REACh regulation with a total tonnage range ≥ 100 000 tons per year. Carbon disulfide is also registered by three registrants for intermediate use only (joint submission).

Table 4 Tonnage and registration status

|  |
| --- |
| ECHA disseminated database |
| Registrations | [x]  Full registration(s)(Art. 10)[x]  Intermediate registration(s)(Art. 17 and/or 18) |
| Total Tonnage band  | 100,000-1,000,000 tpa |

**Overview of uses**

Carbon disulfide is an organic solvent. Technical function reported for carbon disulfide in the registration dossiers are ‘intermediate (precursor)’, ‘pH regulating agent’, ‘solvent’ or ‘laboratory chemical’.

The following uses are reported in the registration dossiers: manufacturing of carbon disulfide, manufacturing of regenerative cellulose (viscose rayon, cellophane, and sponge), use as an intermediate in the manufacture of rubber chemicals, pharmaceuticals, fine chemicals, flotation chemicals, plant protection products and biocides, use as a solvent in the manufacture of polymer preparations and compounds and use as a laboratory chemical.

In addition, to viscose rayon, cellophane and sponge reported in the dossier, manufacturing of viscose casings is also reported in the literature to be an important use of carbon disulfide. In Rubber industry, carbon disulfide is reported to be used to make the specialty accelerator chemicals that replaced carbon disulfide in its pure form.

Carbon disulfide is used by professional workers (widespread use as a laboratory chemical or in research and development) or at industrial sites. There is no consumer use relevant for the use of carbon disulfide. The exact number of industrial sites or workers in the EU is unknown.

Confidential information on uses and tonnages available in the registration dossiers are presented in a separate Annex. Uses as available in the ECHA disseminated database are reported in the table below. Descriptors (PROC, SU, PC) used in the table below are explained in Annex 2.

Table 5 Uses registered according to Art. 10 of the REACh regulation, full registration (ECHA dissemination site, consulted on 16 June 2022)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Exposure Scenario (ES) name** | **Process category (PROC)** | **Product category (PC) and Sector of use (SU) covered** |
|  | No identified uses |  | This substance is imported into the EU in a polymer.  |
| M | Manufacture of Carbon disulfide | 1 | / |
| F | Formulation  | 1, 2, 3, 4, 5, 8a, 8b, 9 | / |
| F | Formulation as a laboratory chemical | 1, 5, 8b, 9, 15 | PC21: Laboratory chemical |
| I | Industrial use as a laboratory chemical | 15 | PC21: Laboratory chemicalSU9: Manufacture of fine chemicalsSU0: Other: SU 3: Uses of substances as such or in preparations at industrial sites |
| P | Professional use as a laboratory chemical | 15 | PC21: Laboratory chemicalSU0: Other: SU 22: Professional uses: Public domain (administration, education, entertainment, services, craftsmen) |
| I | Industrial use of products such as pH-regulators, flocculants, precipitants, neutralization agents, other unspecific | 1, 2, 8a | PC19: Intermediate1PC20: Products such as pH-regulators, flocculants, precipitants, neutralisation agentsSU0: Other: SU 3: Uses of substances as such or in preparations at industrial sites |
| I | Industrial use as a solvent | 1, 2, 3, 4, 8b, 14, 15 | PC32: Polymer preparations and compoundsSU8: Manufacture of bulk, large scale chemicalsSU24: Scientific research and development |
| I | Industrial use as intermediate | 1, 2, 3, 4, 8b, 15 | PC8: Biocidal products (e.g. disinfectants, pest control)PC19: Intermediate1PC20: Products such as pH-regulators, flocculants, precipitants, neutralisation agentsPC27: Plant protection productsPC32: Polymer preparations and compoundsSU8: Manufacture of bulk, large scale chemicalsSU9: Manufacture of fine chemicalsSU24: Scientific research and developmentSU0: Other: SU 3: Uses of substances as such or in preparations at industrial sites |
| I | Manufacture of polymer preparations and compounds | 14 | PC 32: Polymer preparations and compoundsSU0: Other: SU 3: Uses of substances as such or in preparations at industrial sites |
| I | Industrial use in the manufacturing of regenerated cellulose | 1, 2, 4, 8a, 8b, 15, 19, 20, 28 | PC0: Other: textilePC19: Intermediate1PC20: Products such as pH-regulators, flocculants, precipitants, neutralisation agentsPC32: Polymer preparations and compoundsSU0: Other: SU 3: Industrial uses: uses of substances as such or in preparations at industrial sitesSU5: Manufacture of textiles, leather, furSU24: Research and developmentTechnical function: Intermediate (precursor); solvent |
| I/P | Industrial use/Professional use in scientific research and development | 1, 2, 3, 4, 5, 8a, 8b, 9, 15 | PC20: Products such as pH-regulators, flocculants, precipitants, neutralisation agentsPC21: Laboratory chemicalsSU20: Health servicesSU24: Scientific research and development |

M: Manufacture; F: Formulation, I: Industrial use, P: Professional workers;

1: Removed from PC list and relocated in the technical function list in the latest version of REACh guidance, chapter R12 on the description of uses

Table 6 Intermediate uses only registered according to REACh Article 17/18 (according to ECHA dissemination site, consulted on 16 June 2022)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Exposure Scenario (ES) name** | **PROC** | **Product category (PC) and Sector of use (SU) covered** |
|  | No identified uses |  | Other reactant in an imported polymer |
| I | Uses at Industrial sites | 1, 2, 3, 8b, 15 | SU9: manufacture of fine chemicals |

**Exposure information based on registrations**

For all the exposure scenarios via inhalation, modelling with either ECETOC TRA v3.0 or ART v1.5 was used in the registration dossiers. The following scenarios were described in the lead registration dossiers (CSR, 2019).

Manufacturing

The manufacturing scenario describes the process of the manufacturing of carbon disulfide itself. The substance is produced based on the reaction of sulfur and methane.

Carbon disulfide is manufactured in closed systems, under strictly controlled conditions due to its high flammability, resulting in a high risk of explosion at even low concentrations of carbon disulfide in indoor air. The only place where exposure is expected to occur is in the tanker loading areas.

For this use, both modelling estimates and measured data at the tanker loading area were available. Range of exposure levels are provided in table 7 below.

Industrial use in the manufacturing of regenerated cellulose

Carbon disulfide is used to form viscose that can be used to manufacture regenerated cellulose (viscose rayon, cellulose, sponge). Close, semi-close or open processes are described.

Range of exposure estimates based on modelling are provided in the table 7 below.

Industrial use as an intermediate for the production of plant protection products, biocides, processing aids

In general, a wide range of processes has been indicated. Biocidal products and plant protection products are manufactured in closed systems and also in semi-closed process (PROC 4) and carbon disulfide is used as an intermediate.

Range of exposure estimates based on modelling are provided in the table 7 below.

Industrial use as a solvent in the production of polymer preparations and compounds

Carbon disulfide is used as a solvent in many different processes within the polymer manufacturing industry. The application of solvents occurs during the production of preparations or articles by tabletting compression, extrusion and palletisation (PROC 14). In this process, an increase in indoor concentrations of carbon disulfide is expected (not a closed process).

Range of exposure estimates based on modelling are provided in the table 7 below.

Use as a laboratory reagent

Carbon disulfide is exclusively used in industrial settings, except for the use as laboratory chemical which is also registered for professional workers. The use as a laboratory reagent was described by one member of the join submission but was not proposed by the lead registrant. The use of carbon disulfide as a laboratory reagent, has to be performed under strictly controlled safety measures due to its high volatility and toxicity. Handling of the substance is reported to be done under the fume hood.

Sector of end-use for professional workers are reported to be health services and research and development.

In the registration dossier discussing the use by professional workers, estimates were modelled using TRA workers and exposure concentration was 15.07 mg/m3 (PROC 15).

Uncertainties on exposure assessment

For the manufacture of carbon disulfide, a measured value from personal samplers was provided in the tank loading area (PROC 1 “chemical production or refinery in closed processes with equivalent containment conditions”). Although the Tier I modelling tool ECETOC TRA is normally conservative, the modelled exposure value obtained with by ECETOC TRA was not worst case compared to the available air monitoring exposure measurements. Indeed, air monitoring value proposed in the dossier was more than 50-fold higher than the modelling value obtained with ECETOC TRA Workers. An explanation for the difference between the measured and the modelled values was not provided. Few information and no contextual information are available with the measured data that may explain the difference in results (number of measurements, year of measurements, duration of exposure, occupational conditions (OC) and risk mitigation measures (RMMs)).

In addition, according to ECETOC TRA, 2018 technical report, TRA does allow to assess exposures to very volatile liquids, such as carbon disulfide, and the technical report did not set an upper bound for vapour pressure. Nevertheless, the report noted that the estimate for very volatile compounds is really likely relevant for PROCs that do not describe open conditions of use, such as PROC 1. The underestimation of the exposure value obtained from the modeling for PROC1 compared to air measurements is unknown but leads to uncertainties on exposure assessment and safety concern mainly in case of open conditions (e.g. open spin bath during regenerated cellulose manufacturing).

In addition, the lack of dermal exposure modelling or human biomonitoring data provide uncertainties on exposure assessment which is based on inhalation exposure only. The fact that carbon disulfide vapour may be readily absorbed via the skin may lead to underestimation of the exposure.

Overall, there are significant uncertainties in the exposure estimates provided in the 2019 CSR as modelling may underestimate actual exposure.

**Table 7 Summary of worker exposure scenarios and exposure ranges (lead registration dossier)**

|  |  |  |  |
| --- | --- | --- | --- |
| **ES n°** | **Exposure Scenario (ES) name** | **PROC** | **Exposure ranges** |
| Manufacture |
| 1 | Manufacture of Carbon Disulfide | 1 | 1.5 mg/m3 (0.50 ppm) (based on measured data)0.022 mg/m3 (0.0070 ppm) (TRA workers) |
| Use at industrial sites |
| 2 | Manufacturing of regenerated cellulose | 1, 2, 4, 8a, 8b, 15, 19 | 0.032-11.89 mg/m3 (TRA workers)(0.01-3.77 ppm) |
| 3 | Industrial use as an intermediate, use in the manufacture of plant protection products and biocides | 1, 2, 3, 4, 8b, 15 | 3.17- 13.32 mg/m3 (TRA workers)(1-4.2 ppm) |
| 4 | Industrial use as a solvent | 1, 8b, 15 | 0.032- 4.76 mg/m3 (TRA workers)(0.01-1.5 ppm) |

**Exposure information based on literature**

In the literature, there are some data available on worker exposure in the EU in viscose production plants. Exposure was assessed using air monitoring (personal or static measurements) and/or biomonitoring. Indeed, thiazolidine-2-thione-4-carboxylic acid (TTCA), a urinary metabolite of carbon disulfide, can be used as a marker of exposure of carbon disulfide. The literature data (published period: 2010-2020) report exposure to worker slightly above the IOELV.

In two cross-sectional studies in a German viscose rayon industry published by Göen *et al.*, the cumulative external exposure and the cumulative internal exposure were calculated for each worker (Göen *et al.*, 2014). Ambient air monitoring were carried out for 362 male workers in 1992 and individual air concentration was measured in 290 carbon disulfide-exposed workers in 2009. In addition, company-internal sample measurements were taken during the period 1993 to 2008. Biological monitoring was carried out in the years 1993, 1995, 1997, 1998, 1999, 2002, 2006 and 2007 on the exposed workers. It is stated that OC and RMM have continuously been improved since 1992. External and internal carbon disulfide exposures of the employees decreased from 1992 (medians 4.0 ppm, 95th percentile 15.4 ppm and 1.63 mg TTCA/ g creatinine) to 2009 (medians 2.5 ppm, 95th percentile 6.74 ppm and 0.86 mg TTCA/g creatinine). Large variations were observed between departments (spinning of textile rayon, spinning of technical rayon, washing of textile rayon spools, post-treatment, rayon ageing and filter cleaning). According to the authors, company-internal carbon disulfide data do not show a straight trend for this period (1992-2009). The annual medians of the company internal measurement of external exposure to carbon disulfide have varied between 2.7 and 8.4 ppm, in which median values exceeded 5 ppm generally since 2000. The annual medians for the company-internal biomonitoring assessment ranged between 1.2 and 2.8 mg TTCA/g creatinine.

According to the study by Kilo *et al.* (2015), although internal exposure, as measured by biomonitoring of the employees, correlated with the individual external exposure to carbon disulfide (measured by personal air monitoring), several factors such as physical work load or dermal exposure can affect the uptake of carbon disulfide. Dermal absorption may be an important factor for internal exposure to carbon disulfide, particularly at low or medium ambient carbon disulfide levels (mean 1.6 ppm and 2.8 ppm). Moreover, they also noted that direct dermal contact to wet spinning spools (during manufacture of regenerated cellulose) results in an increase in relative internal exposure to carbon disulfide. This study highlights the potential underestimation of exposure using inhalation data only.

**Overall, in view of the uncertainties identified on exposure assessment, FR MSCA would welcome any information or comments provided during the consultation on this document to complete exposure assessment, in particular potential exposure of professional workers during the use as laboratory chemical, where OC and RMMs may be difficult to implement.**

## Hazard information (including classification)

Carbon disulfide toxicological profile is available in ANSES conclusion report on substance evaluation published in ECHA disseminated website (ANSES, 2022).

Information on classification and labelling of the substance is available in Annex 1.

**From IOELV to DNEL**

ECHA guidance document R8 noted that when an EU IOELV exists, the registrant may, under certain conditions, use the IOEL in place of developing a DNEL. This was the approach used by the lead registrant of carbon disulfide.

**SCOEL IOELV recommendation**

Discussions regarding an IOELV for carbon disulfide were conducted by the SCOEL (Scientific Committee on Occupational Exposure Limits) in 2008, the SCOEL recommended an 8-hr TWA OEL of 5 ppm or 15 mg/m3. In addition, based on the determination of the metabolite thiazolidine-2-thione-4-carboxylic acid (TTCA) in urine, a biological limit value of 1.5 mg TTCA/g creatinine was proposed by the SCOEL.

Carbon disulfide IOELV was based on the effects on the nervous and the cardiovascular systems (SCOEL, 2008).

In 2011, the Health Council of the Netherlands (HCNL) published a report on carbon disulfide based on the conclusion of SCOEL and including a supplementary literature search up to January 2010 (HCNL, 2011).

Both Committees (SCOEL and HCNL) concluded that the available human studies clearly showed that carbon disulfide affects both the cardiovascular and the nervous systems. The SCOEL considered that the earliest non clinical subtle changes on these systems were observed between 3 and 10 ppm in the human epidemiological studies, with the most reliable human studies relating to the upper end of this range. The SCOEL considered a point of departure for the critical health effects at a presumed threshold of 10 ppm (30 mg/m3) and applied an uncertainty factor of 2 based on the severity of the effect and considering the extensive human database leading to a 8h-TWA of 5 ppm (15 mg/m3).

The HCNL concluded that 15 mg/m3 (5 ppm) is a LOAEC for cardiovascular effects based on the induction of minor cardiac ischemic findings in human, observed in Takebayashi *et al.,* 2004 study. The Committee recommended a value of 5 mg/m3 (2 ppm) as a health-based occupational exposure limit applying a factor of 3 to the LOAEC of 15 mg/m3 (5 ppm). Furthermore, the HCNL also took the study published by Godderis *et al.* (2006) into account, in spite of its weaknesses in the determination of average exposure levels and data analysis, as supporting the lower value (neurological findings starting to appear at 3 ppm), while SCOEL did not consider this study as a key study.

Carbon disulfide was included in the Community rolling action plan (CoRAP) for evaluation in 2013 by France according to REACh regulation. Based on the evaluation of the available data, it was concluded that there was a need to request further information to clarify the concerns related to Endocrine Disruption, reproductive and neurodevelopmental toxicity potential. The decision to request an Extended One-Generation Reproductive Toxicity Study (EOGRTS) was agreed by the ECHA’s Member state Committee in October 2015. The EOGRTS was submitted in December 2019.

In 2022, ANSES published a substance evaluation conclusion and evaluation report on carbon disulfide as required by REACh Art. 48. The report was prepared based on the updated REACh registration dossier from December 2019, including the new EOGRTS. In addition, a literature review from 2013 to 2019 was performed in the online database Medline. It was concluded that the revision of the current OEL could be necessary. In order to assess if the revision of the indicative OEL of 5 ppm is warranted, the studies carried out by Takebayashi *et al.* (2003 and 2004), new relevant epidemiological studies available since the published report of SCOEL and HCNL (Yoshioka *et al.* 2017; Schramm *et al.*, 2016) and the new EOGRTS requested during the Substance Evaluation were assessed. Overall, four observational studies (detailed in Annex 4) and one experimental animal study were considered as potential point of departure for OEL derivation.

- Regarding the effects on the thyroid hormones, in a follow-up cohort study in Japanese rayon workers, Takebayashi *et al.* observed a significant decrease in thyroxine (T4) level in the blood of the group of workers exposed to carbon disulfide compared to the referent worker group (Takebayashi *et al.*, 2003). However, though the effect on thyroxine level may be considered biologically relevant, it was of small magnitude in the study (8.34 µg/dl ± 1.53 in CS2 workers vs 8.61 µg/dl ± 1.54 in referent workers, p=0.04), no relation was observed by job types or 6-year TTCA levels. Therefore, the results of the study are judged irrelevant for revising the IOELV.

- With regards to cardiovascular toxicity, the minor cardiovascular findings (ECG waveform anomalies noted using Minnesota code) observed in the same follow-up cohort study in Japanese rayon workers (Takebayashi *et al.,* 2004) are considered potentially relevant but are not considered sufficiently critical to revise the current IOELV in the absence of confirmed clinical alteration at 5 ppm when rigorous “symptomatic” ECG criteria of ischemia were applied. Similarly, the findings reported in Schramm *et al.* in a transversal study in German rayon worker exposed to carbon disulfide on the increase in intima media thickness (marker of atherosclerosis) were in normal biological range, without sign of atherosclerosis (Schramm *et al.,* 2016). In addition, major limitations were identified in this study (e.g. potential bias) and the effect on intima thickness was not confirmed in other epidemiological studies. Therefore, the results of this study are irrelevant for revising the current IOELV.

- With regards to the effects on the nervous system, Yoshioka *et al.* published the results of the 6-year prospective Japanese cohort study (same cohort as in Takebayashi *et al.*) on the effects of carbon disulfide on the nervous system (Yoshioka *et al.,* 2017). At baseline, motor nerve conduction (MCV) and sensory nerve conduction velocity (SCV) were not different between the exposed and the unexposed workers. At follow-up, MCV was not affected around a mean level of 6 ppm. Nevertheless, SCV was statistically significantly reduced in exposed workers compared to unexposed workers or workers previously exposed to carbon disulfide but no more exposed at follow-up. The SCV reduction effect was still observed after adjustment for potential confounding factors (*e.g.* aging) in exposed workers compared to non-exposed workers. The neurological system is a critical target of carbon disulfide-induced toxicity, but the SCV findings were of low magnitude and it was noted by the authors that the effect may be reversible at 4 ppm. Therefore, these earliest subtle neurological findings are also not considered sufficient to revise the current IOELV on this basis.

- Regarding reproductive effects: in a recent EOGRTS (Unpublished report, 2019), similar to OECD TG 443, rats were exposed by gavage to 0, 1.2, 12 or 120 mg/kg bw/d carbon disulfide. The study is detailed in the ANSES conclusion report (ANSES, 2022, table 15) available in ECHA website. The study was requested during SeV with the aim to further investigate potential ED properties of carbon disulfide and the occurrence of reproductive effect that would not be covered by the current IOELV. In this study, a decrease in serum total T4 concentration was noted in F0-generation males and females and in F1-generation males at 120 mg/kg bw/day. In addition, a significant increase in sperm cells with detached head and a significant decrease in ovarian primary and primordial follicles were observed in the F1 generation at the top dose. The NOAEL for these effects was 12 mg/kg bw/d. With regards to other systemic effects, at 120 mg/kg bw/d, a significant decrease in absolute brain weight in F0 generation males and females and males of the F1 generation (postnatal day 22) and retinal atrophy also noted in F0 and F1-generations adult animals. These findings were considered indicative of neurotoxicity. The effects observed in the EOGRTS are judged relevant for OEL derivation. Indeed, in human, consistent data exist on effects of carbon disulfide on reproductive system (e.g. sperm, libido or estrous cycle disturbance) but characterization of dose-response in the available human studies on reproductive toxicity was not possible (ANSES, 2022). Regards to ED properties, it was considered plausible that the effects were secondary to other non-endocrine mediated systemic toxicity. So, the EU ED criteria are not considered met.

**8h-TWA OEL derivation**

Considering reproductive toxicity as a critical effect of carbon disulfide, the recent EOGRTS in rats can be considered as a key study for reproductive toxicity. Based on the decreased ovarian primary and primordial follicles and the significant increase in sperm cells with detached head in the F1-generation, a LOAEL of 120 mg/kg bw/d can be identified. The NOAEL in the study is 12 mg/kg bw/d. Based on the comparative toxicokinetic study (Unpublished report, 2019b), the LOAEL is considered to be equivalent to about 300 ppm (948 mg/m3) and the NOAEL equivalent to 30 ppm (94 mg/m3).

According to ECHA guidance document R8, the NOAEC of 30 ppm is converted from rat to human (x 6.7 m3/10 m3) into 20 ppm (63 mg/m3).

Using default assessment factors recommended in the ECHA guidance document chapter R8 (ECHA, 2019), a global assessment factor of 25 could be applied (2.5 for interspecies differences, 5 for intraspecies differences, 2 for exposure duration), resulting in an OEL of 0.8 ppm (2.5 mg/m3).

There are major uncertainties on the derivation of this OEL on the basis of the EOGRTS:

- the absence of a clear pattern on the effects observed: absence of effect on other sperm parameters (e.g. morphology), on fertility or implantations,

- an absence of a dose-response relationship in the observed effects that may be due to the inappropriate dose-range spacing,

- the extrapolation from dose levels by oral route to inhalation route (e.g. the use of a toxicokinetic study performed with a unique dose, in male only, to extrapolate the exposure dose from oral to inhalation route).

Based on these elements, the dose-response relationship and the OEL derived from this study are uncertain. In addition, because a large amount of human data are available, the derivation of the OEL based on human data is considered more appropriate than based on animal data, being therefore less influenced by potential differences between species.

Therefore, new data published since 2011, either in the scientific literature or within the registration dossier do not warrant to revise the current OEL due to the uncertainties on the derivation of OEL based on the EOGRTS and also acknowledging the revised OEL based on the EOGRTS study would be in the same range as the current OEL.

However, the differences between the starting point and the uncertainty factors proposed by SCOEL and HCNL require discussion. Considering the IOELV derived by SCOEL, no major issue has been noted by FR-MSCA. The uncertainty factor of 2 for the severity of the effect is considered relevant. Due to the large amount of human data on workers, an uncertainty factor of 1 for intraspecies differences seems also appropriate. Considering the approach used by HCNL, no major issue was also noted in the methodology and uncertainty factor. Regards to the point of departure, FR-MSCA agrees with SCOEL that the effects observed in Takebayashi *et al*., 2004 are subtle changes with doubtful biological significance.

**In conclusion, the DNEL by inhalation for long-term systemic exposure used by the lead registrant, based on the European IOEL of carbon disulfide of 5 ppm (15 mg/m3) can be considered appropriate. The new data are not judged sufficiently convincing to revise this IOEL. In the framework of the public consultation, FR-MSCA would welcome comments on the conclusion that no action is needed on the current IOEL.**

## Risk characterisation

The risk characterization was performed using the exposure estimates by ECETOC TRA in the lead registration dossier (CSR, 2019) keeping in mind its related uncertainties and the long-term DNEL for systemic effect by inhalation of 5 ppm (15 mg/m3). The risk characterisation ratio (RCRs) were only calculated for inhalation.

Based on modelling data, although RCR were closed to 1, all the RCR were below 1 (range: 0.01 to 4.2 ppm) in the CSR of the lead registrants. In addition, the highest RCR was obtained for the use as a laboratory reagent by professional workers, calculated to be equal to 1.

Overall, RCR > 0.5 were noted for PROC 4 “Use in batch and other process (synthesis) where opportunity for exposure arises” and PROC 15 for the professional use as a laboratory reagent. **Considering the underestimation of potential dermal exposure and of the modelling data, risk cannot be excluded during these processes**. **In the framework of the public consultation,** **FR-MSCA would welcome further exposure data, such as biomonitoring data and air measurement data, are available to confirm the potential risk identified.**

Table 8 Risk characterisation (Exposure scenario with RCR > 0.5)

| **Identified use** | **Process Category(PROC)** | **RCR**(DNELinhal=5 ppm) | **RMM** |
| --- | --- | --- | --- |
| Manufacturing of regenerated cellulose | **PROC 4** (indoor, process temp. ≤ 40°C, 8h/d) | **RCR =0.602****(TRA**) | - Enhanced general ventilation (70% effectiveness)- LEV, 90% effectiveness- Dermal protection 95% effectiveness |
| Use at industrial sites - Industrial use asan intermediate, use in the manufacture of plant protectionproducts and biocides | **PROC 4** (indoor, temperature process ≤ 40°C 4h/d)  | **RCR = 0.843**(TRA) | - General ventilation ( 30% effectiveness)- LEV (90% effectiveness)- Dermal protection, (95% effectiveness) |
| Professional use of laboratory chemical | **PROC 15** | **RCR=1** | Ventilation (90.5% efficiency) |

Additional occupational conditions (OCs) and risk management measures (RMMs) may be implemented at industrial sites. However, additional OC and RMM may be difficult to implement by professional workers outside industrial installation.

## Information on alternatives

Information on alternatives are not found. **In the framework of the public consultation, FR MSCA asks if data exists on this point, in particular if a restriction of certain uses is necessary.**

# Justification for the (no) need for regulatory risk management action at EU level

Carbon disulfide is a high tonnage and wide-dispersive compound where risks need to be managed. The following legislative instruments have the direct or indirect potential to reduce worker exposure concern (neurotoxicity, cardiotoxicity, reproductive toxicity) and are discussed below.

* CLP (EC/1272/2008)
* REACh (EC/1907/2006)
	+ Evaluation
	+ Authorisation
	+ Restriction
* Other Regulations
	+ CAD (EC/98/24)

### 2.1 CLP regulation

In the SEv conclusion (ANSES, 2022), it was pointed out that the effects observed in the EOGRTS and the prenatal developmental toxicity study in rabbit were not available at the time of the discussion on the harmonised classification. So, there is a need to discuss whether these additional data could challenge the current classification for reproductive toxicity. In the EOGRTS (Unpublished report, 2019), a statistically significant decrease in ovarian primary and primordial follicles (considered a marker of female reproductive toxicity) compared to control was observed in the first generation. No effects were observed in the fertility parameters. A slight decrease in post-implantation losses and total number of implants was also noted, supporting an effect on fertility. However, the slight decrease was not statistically significant. Therefore, the effects are not considered sufficient to upgrade the current classification from category 2 to category 1B. In addition, some sperm parameters were changed at the top dose in the F1-generation. However, in the absence of a clear pattern, these effects are also not considered sufficient to upgrade the classification from category 2 to category 1B.

With regards to developmental toxicity, a rabbit prenatal developmental toxicity study was not taken into account during initial TC C&L (Unpublished report, 1991). The study is summarised in annex 4. The increase in the number of malformations and post-implantation losses was significant only at the top dose level where overt maternal toxicity was observed (1200 ppm). The increase in hydrocephaly was of particular concern with 2 cases in 2 litters at this top dose. In the absence of significant maternal toxicity (≤ 600 ppm), only 1 case of hydrocephaly at 100 ppm and at 600 ppm were noted (not observed in control, at 60 or at 300 ppm). The low incidence (one case in one litter) leads to some uncertainties on the treatment-relationship of the effect at dose levels below 1200 ppm. The significant increase in post-implantation losses was of small magnitude at 600 ppm (0.64± 1.00 at 600 ppm vs 0.3±0.63 in controls and vs 7.0 ± 3.94 at 1200 ppm). Therefore, these findings are insufficient to upgrade the classification to category 1B.

There is no new human data available that would allow to classify the substance in category 1A.

As proposed by the lead registrant, additional classification of the substance as Acute Tox. 4; H332 is warranted. The specification of the nervous system and the cardiovascular system is also relevant for STOT RE 1 to better communicate on the hazards of the substance. Although a few notification propose to classify carbon disulfide as STOT SE, H335, Acute Tox. 4 (H302) and Aquatic Chronic 3 (H412), these classifications are not considered warranted based on the available data (See conclusion document and report on substance evaluation of carbon disulfide, 2022).

**Overall, an update on the existing harmonised classification is needed. Acute toxicity by inhalation is not a priority endpoint according to Art. 36 of CLP regulation for the need for Harmonised Classification and Labelling but the differences in self-classification may justify that action is needed at community level unless registrants align their self-classifications.**

### 2.2. Substance Evaluation

France started a substance evaluation process in March 2013; it was finalized in April 2022.

The conclusion of the SEv was that there is a need for follow-up regulatory action at EU level to be discussed in an RMOA.

### 2.3. Authorisation

**Identification as a substance of very high concern, SVHC (first step toward authorisation)**

The human health classification of carbon disulfide in Annex VI of CLP regulation doesn’t provide *per se* identification as a SVHC and possible inclusion in Annex XIV (not a CMR 1A or 1B).

However, carbon disulfide is a known neurotoxicant that can induce damages in the central nervous system (CNS) and peripheral nervous system (PNS) in experimental animals and in humans. Carbon disulfide induces also toxicity to the cardiovascular system. The substance is classified as STOT RE 1, in high potency class, under the CLP Regulation. So, identification under Article 57(f) based on equivalent level of concern (EloC) for STOT RE could be considered.

In case of adequate control, there will be no more risks; for the substances following the route of Art. 57(f), it should be demonstrated that it shows adverse effects on human health of EloC compared to CMR effects. Factors identified as relevant are discussed below.

Seriousness of health concern

The severity of health effects due to exposure to carbon disulfide on the nervous system ranges from sub-clinical effects on the peripheral nervous system (reduced sensory and motor nerve velocities) to polyneuropathy with reduction in velocity of both motor and sensory nerves. Eye findings (optic atrophy, retrobullar neuritis) can lead to altered function, mobility and sensitivity in human. Moreover, adverse effects on hearing, such as a reduction in auditory threshold and loss of hearing have also been reported. Neurobehavioral changes have also been noted in some human studies. In experimental animals, nerve conduction velocity changes, changes in neurobehavior, and neuropathology (degeneration and axonal swelling in spinal cord and peripheral neurons, usually accompanied by an increase in neurofilament accumulation due to the formation of cross links) were observed.

The effect on the cardiovascular system is serious as it may lead to death in human. Cardio-vascular toxicity at the workplace may also be serious and of concern.

Overall, serious health concerns (nervous system, cardiovascular system) have been identified and justify the current classification as STOT RE 1.

Irreversibility of health effects

Central nervous system (CNS) induced by carbon disulfide are considered to be irreversible. Reversibility of the effects on the PNS may depend on the severity of the effect and exposure levels.

The irreversible nature of the potential effects on the central nervous system is of high concern.

Similarly, excess mortality from coronary heart disease observed in human in viscose rayon factories is of concern.

Delay of health effects

The onset of nervous system and cardiovascular system manifestations is insidious and the course is slowly progressive. Studies revealed chronic encephalopathy and microangiopathy in the CNS after prolonged carbon disulfide exposure (Sieja, 2018).

Quality of life

The manufacture of the substance and the manufacture of regenerative cellulose is known to lead to occupational diseases. In France, professional sulfocarbonism is covered by the General regime table 22 (French decree, 13 July 1945, updated 13 September 1955). Between 2010 and 2020, there were only 3 dossiers of occupational diseases related to table 22 and resulting to compensation (there is no information on the number of submitted dossiers).

A long-term illness can reduce the quality of life for the worker.

Table 9 Professional sulfocarbonism (French decree; table 22)

|  |  |  |
| --- | --- | --- |
| **Designation of diseases** | **Time to take care** | **Indicative list of the main jobs likely to cause these diseases** |
| Acute neuro-digestive syndrome manifested by vomiting, violent gastralgia, diarrhea with delirium and intense headache. | Acute accidents: 30 days Subacute or chronic intoxications: 1 year | Preparation, handling, use of carbon sulfide and products containing it, including:- Manufacture of carbon sulfide and its derivatives;- Preparation of viscose and all manufacturing processes using the regeneration of cellulose by decomposition of viscose, such as the manufacture of artificial textiles and cellulose films - Extraction of sulfur, cold vulcanization of rubber by dissolving sulfur or sulfur chloride in carbon sulfide;- Preparation and use of rubber dissolutions in carbon sulfide;- Use of carbon sulfide as a dissolver of gutta-percha, resins, waxes, fats, essential oils and other substances. |
| Acute psychic disorders with mental confusion, dreamlike delirium. |
| Chronic psychic disorders with depressive states and morbid impulses. |
| Polyneuritis and neuritis, of any degree, with disorders of electrical reactions (especially chronaximetric). |
| Optic neuritis |

Societal concern

Neurotoxic effects and cardiovascular toxicity at the workplace may be serious and of concern.

There are no consumer uses registered under REACh for the substance. With regard to viscose and cellophane production, the substance is not bound to the end product and is mainly expected to end up in the atmosphere. Carbon disulfide is released from various natural sources from soil and plants. Regional release to the environment were calculated to be high in the EU in the air and water compartment due to the use on regenerated cellulose. Emissions from other uses are negligible if the RMM, as described in the CSR are in place. Nevertheless, no risk for human via the environment was identified and only regional general population concern could be anticipated.

Is the derivation of a safe exposure concentration possible?

A safe exposure level may be established for carbon disulfide neurotoxicity and cardiovascular toxicity (current IOELV).

Overall, serious health concern has been identified for carbon disulfide which is a highly potent cardiovascular and nervous system toxicant. Identification under Article 57(f) could be considered towards other possible risk management options.

The primary aim of authorisation under REACh is to substitute SVHCs and it has proven to be an effective driver for this substitution. However, it is unknown whether safer technically feasible alternatives are available for all uses regarding carbon disulfide.

**Identification as SVHC/Candidate listing with inclusion in Annex XIV**

A prerequisite for a substance to be included on the Annex XIV of REACh is to be identified as a SVHC. Once listed on the Annex XIV, its continued use, beyond an agreed sunset date, will only be allowed if an authorisation for a specific use. Application for authorisation are scrutinized by the ECHA committees RAC and SEAC and finally granted by the European Commission. Some of the uses may be exempted from authorisation requirements.

The prioritisation for inclusion in Annex XIV from the candidate list is mainly hazard-based (triggered by SVHC identification). Priority is driven by several criteria that are set by Article 58 of REACh.

Carbon disulfide has been registered as a full registration dossier (joint submission) under REACH accordingly to Article 10 of REACh Regulation. Regarding the uses falling under the scope of authorisation, authorisation does not cover the following uses of carbon disulfide: manufacturing, intermediate uses or research and development. If carbon disulfide is placed on Annex XIV, this would probably mostly cover the manufacturing of regenerated cellulose and the industrial uses when the substance is not used as an intermediate. Consequently, only the uses as a solvent and viscose manufacturing could be covered by REACh authorisation.

For the widespread use of the substance as a laboratory reagent, it is not clear whether all the uses would be in the aim of research or development or if some uses would be in the scope of authorisation. There are few information on this known use of the substance as it was not evaluated by the lead registrant of the full registration dossier of the substance.

For intermediate uses, the establishment of a BOELs (CAD directive) and a BLVs or a binding DNEL under a restriction would be a more suitable RMO to address occupational risks above the current IOELV (see section 2.5 below).

**Despite the fact that the identification of carbon disulfide as SVHC would send a strong signal about its hazardous nature, authorisation might not be considered as an appropriate risk mitigation measure since manufacture, intermediate uses or research and development are not covered by this process.**

### 2.4 Restriction

A restriction proposal under REACh has to meet the REACh Annex XV requirements aiming at tackling a risk by reducing the exposure to the hazardous substance down to a safe level, otherwise at removing it.

Although an Annex XV restriction proposal would show several advantages over the REACh authorisation procedure (e.g. cover transported isolated intermediates), an “unacceptable risk has to be demonstrated”. So, the risk should be robustly addressed. Regarding the available data in the registration dossiers, there are exposures to carbon disulfide but the exposure assessment, is mainly based on modelled data. In particular for uses, such as manufacturing of regenerated cellulose (PROC 4) and industrial use as an intermediate, use in the manufacture of plant protection products and biocides (PROC 4), models lead to RCR > 0.5.

In addition, for the widespread use by professional users of carbon disulfide as a laboratory chemical (PROC 15), exposure data at the current IOELV was modelised. These data are questionable regarding the relevance and robustness as the model may underestimate the exposure for very volatile substances like carbon disulfide and as dermal exposure was not taken into account. Considering these estimated exposures and the IOELV, the RCR was set at 1. In contrast, high exposure levels to carbon disulfide have been reported for workers in the literature, above IOELV.

**In the framework of the public consultation, FR-MSCA asks if additional recent modelling data (static and personal sampling, biomonitoring, dermal exposure) is available to robustly demonstrate safe use of carbon disulfide. Otherwise, a restriction of these uses to ensure safe use of carbon disulfide would be an option. Adequate control of the substance could be ensured defining mandatory inhalation and dermal DNELs.**

Factors to be considered to decide on the relevance of this management measure are:

- the number of workers exposed to carbon disulfide above the IOELV?

- possibility of substitution, in particular for laboratory uses

- Existing OC and RMM available at industrial settings

- OC and RMMs feasibility for professional workers

### 2.5 Other EU-wide regulatory risk management measures: CAD

The main concern related to the use of carbon disulfide is worker exposure*.* In the case of carbon disulfide, an IOELV has been set meaning that all Member states must set a national OEL for the substance, taking the IOELV (and scientific documentation) into account. However, national OELs do not have to be equal to the IOELV. As seen in table 3*,* national OELs lower or higher than the IOELV have been set within the EU. The rationale behind the differences in the OEL derivation is not available.

**Given the severity of the effects (mainly cardiotoxicity and neurotoxicity) and the RCR close to 1 for some uses, it should be ensure that national OEL does not exceed the IOELV. If it is not the case, the setting of a BOELs for this substance under the CAD could be a regulatory management option to control the risks. A BOEL value set at EU level should ensure harmonisation.**

It is noted that BOELs are mainly set for non-threshold carcinogenic substances for which IOELVs cannot be set. In addition, over the last few years, priority was to focus on carcinogens and mutagens for BOELs derivation. Only one BOEL and one binding BLV (lead metal and its inorganic compounds) has been set under CAD. Nevertheless, the severity of the effects identified with carbon disulfide would justify such BOEL. Socio-economic and technical feasibility factors will be taken into account when establishing a BOEL. Information on the number of persons exposed would help for such an analysis.

As both dermal and inhalation routes of exposure are of concern in the case of carbon disulfide, the setting of a biological limit value (BLV) in the CAD in addition to the OEL would limit worker exposure and provide higher human health safety as it would also take into account dermal exposure.

The CAD Directive also covers the evaluation of emissions and process wastes which would not be covered by a DNEL proposed in a restriction.

**Overall, setting a BLV within the framework of CAD would be an option to address the risks for workers.**

# Conclusions and actions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CAS number, substance name | Human Health Hazard | Environmental Hazard | Relevant use(s) & exposure potential | Last foreseen action | Action |
| Carbon disulfide, 75-15-0 | Neurotoxicity, cardiotoxicity, toxicity for reproduction | No hazard or unlikely hazard  | Manufacturing of regenerated cellulose, solvent in the production of polymers, Transported isolated intermediate in the production of fine chemicals, laboratory reagentHigh exposure potential | Select or type...Justification:Provide a short summary of the main elements justifying the last foreseen action | **First step:** **Next steps (if risk confirmed):** |

# References

ANSES on behalf of the French Ministry of Environment. ‘Substance Evaluation Conclusion as Required by REACH Article 48 and Evaluation Report for Carbon Disulfide (in Press)’, January 2022.

CSR 2019. Chemical safety report dated December 2019 from the lead registrant.

ECHA (2019). Guidance on information requirements and Chemical Safety Assessment. Appendix to chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace, version 1.0, August 2019.

Godderis L, Braeckman L, Vanhoorne M, Viaene M. Neurobehavioral and clinical effects in workers exposed to CS2. Int J Hyg Environ Health 2006; 209(2): 139-150.

HCNL (Health Council Netherland). ‘Health-Based Recommended Occupational Exposure Limit, Carbon disulfide’, 2011. <https://www.healthcouncil.nl>

Göen, T., Schramm, A., Baumeister, T., Uter, W., Drexler, H., 2014. Current and historical individual data about exposure of workers in the rayon industry to carbon disulphide and their validity in calculating the cumulative dose. Int Arch Occup Environ Health 87, 675–683.

Kilo, S., Zonnur, N., Uter, W., Göen, T., Drexler, H., 2015. Effect of Skin Protection and Skin Irritation on the Internal Exposure to Carbon Disulphide in Employees of the Viscose Industry. ANNHYG 59, 972–981.

Schramm, A., Uter, W., Brandt, M., Göen, T., Köhrmann, M., Baumeister, T., Drexler, H., 2016. Increased intima-media thickness in rayon workers after long-term exposure to carbon disulfide. Int Arch Occup Environ Health 89, 513–519. <https://doi.org/10.1007/s00420-015-1091-5>

SCOEL (Scientific Committee on Occupational Exposure). Recommendation from the Scientific Committee on Occupational Exposure Limits for Carbon disulfide, 2008.

Takebayashi, Toru, Yuji Nishiwaki, Tetsuo Nomiyama, Takamoto Uemura, Tsuneyuki Yamauchi, Shigeru Tanaka, Haruhiko Sakurai, Kazuyuki Omae, and Japanese Rayon Worker’s Health Study Group. ‘Lack of Relationship between Occupational Exposure to Carbon Disulfide and Endocrine Dysfunction: A Six-Year Cohort Study of the Japanese Rayon Workers’. Journal of Occupational Health 45, no. 2 (2003): 111–18. <https://doi.org/10.1539/joh.45.111>.

Takebayashi, T., 2004. A six year follow up study of the subclinical effects of carbon disulfide exposure on the cardiovascular system. Occupational and Environmental Medicine 61, 127–134. <https://doi.org/10.1136/oem.2002.006858>

Unpublished report (2019a). ‘Extended One Generation Reproductive Toxicity Study of carbon disulfide by Oral Gavage in Rats’. Summary available in ECHA disseminated database. <https://echa.europa.eu/>

Unpublished report (2019). ‘Determination of the whole blood toxicokinetics of carbon disulfide (CS2) and the plasma toxicokinetics of the CS2 metabolite 2-thiothiazolidine- 4-carboxylic acid (TTCA) in male Wistar Han rats following a single oral (gavage) or inhalation administration of CS2 and to determine the routes of elimination and excretion of CS2 and TTCA in male Wistar Han rats following a single oral (gavage) or inhalation administration of CS2.’ Summary available in ECHA disseminated database. <https://echa.europa.eu/>

Yoshioka, N., Takebayashi, T., Nishiwaki, Y., Nomiyama, T., Iwasawa, S., Sakurai, H., Omae, K., 2017. Changes of median nerve conduction velocity in rayon manufacturing workers: A 6‐year cohort study. Jrnl of Occup Health 59, 187–193.

# Annex 1: Harmonised classifications and self-classifications reported by registrants

Data consulted on 15 June 2022

**Table 10 Harmonised classifications and self-classifications reported by registrants for carbon disulfide**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| EC/ List No | CAS No | Substance name | Harmonised classification | Classification in registrations | Classification in C&L notifications (954) |
| 200-843-6 | 75-15-0 | Carbon disulfide | Flam. Liq. 3 H225Repr. 2, H361fdSkin Irrit. 2, H315Eye Irrit. 2, H319STOT RE 1\*\*, H372Specific concentration: Repr. 2; H361fd: C ≥ 1 %STOT RE 1; H372: C ≥ 1 %STOT RE 2; H373: 0,2 % ≤C < 1 % | **Retain:**Flam. Liq. 3 H225Repr. 2, H361fdSkin Irrit. 2, H315Eye Irrit. 2, H319Specific concentration: Repr. 2; H361fd: C ≥ 1 %**Modify:**STOT RE 1, H372 (nervous system, cardiovascular system, eye)Specific concentration:STOT RE 1; H372: C ≥ 1 %STOT RE 2; H373: 0,2 % ≤C < 1 %**Add:**Acute Tox. 4, H332 | Flam. Liq. 3 H225,Repr. 2, H361fd,Skin Irrit. 2, H315,Eye Irrit. 2, H319,STOT RE 1, H372 [954 out of 954]Acute Tox. 4 H332 [500 out of 954]Acute Tox. 4, H302 [42 out of 954]STOT SE 3, H335 [5 out of 954]Aquatic Chronic 3, H412 [38 out of 954] |

# Annex 2: Overview of uses based on information available in registration dossiers

Information on tonnages and uses (status 07/2022, consulted in REACh-IT) – see separate annex for confidential data

There are seven active registrants for carbon disulfide with a full registration dossier with a total tonnage range ≥ 100 000 to ≤ 1 000 000 tonnes per year and submitted in a joint submission.

Descriptors used in section 1.4.

Process categories (PROC):

* PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
* PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
* PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
* PROC 4: Chemical production where opportunity for exposure arises
* PROC 5: Mixing or blending in batch processes
* PROC 6: Calendering operations
* PROC 7: Industrial spraying
* PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
* PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
* PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
* PROC 10: Roller application or brushing
* PROC 11: Non industrial spraying
* PROC 13: Treatment of articles by dipping and pouring
* PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
* PROC 13: Treatment of articles by dipping and pouring
* PROC 15: Use as laboratory reagent
* PROC 16: Use of fuels
* PROC 17: Lubrication at high energy conditions in metal working operations
* PROC 18: General greasing /lubrication at high kinetic energy conditions
* PROC 19: Manual activities involving hand contact
* PROC 20: Use of functional fluids in small devices
* PROC 21: Low energy manipulation and handling of substances bound in/on materials or articles
* PROC 22: Potentially closed processing operations with minerals/metals at elevated temperature. Industrial setting
* PROC 23: Open processing and transfer operations at substantially elevated temperature
* PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles
* PROC 26: Handling of solid inorganic substances at ambient temperature
* PROC 28: Manual maintenance (cleaning and repair) of machinery

Product categories (PC):

* PC 0: Other: Textile
* PC 8: Biocidal products (e.g. disinfectants, pest control)
* PC 19: Removed from PC list and relocated in the technical function list (Table R.12- 15 of ECHA guidance document, chapter R.12[[6]](#footnote-7)).
* PC 20: Products such as ph-regulators, flocculants, precipitants, neutralisation agents
* PC 21: Laboratory chemicals
* PC 27: Plant protection products
* PC 32: Polymer preparations and compounds

Sector of end-uses (SU):

* SU 0: Other: SU 3: Industrial uses of substances as such or in preparation at Industrial sites
* SU0: Other: SU 22: Professional uses: Public domain (administration, educations, entertainments, services, craftsmen)
* SU 5: Manufacture of textiles, leather, fur
* SU 8: Manufacture of bulk, large scale chemicals (including petroleum products)
* SU 9: Manufacture of fine chemicals
* SU 20: Health services
* SU 24: Research and development

# Annex 3: Overview of completed or ongoing regulatory risk management activities

Data consulted on June 2022.

**Table 13 Overview of completed or ongoing regulatory activities**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Substance | RMOA | Authorisation | Restriction | CLH | Actions not under REACH/ CLP |
|  |   | **Candidate list** | **Annex XIV** | **Annex XVII** | **Annex VI (CLP)** |  |
| Carbon disulfide | No other RMOA |  -  |  -  |  -  |  Yes |  IOELV |

# Annex 4: Background Document (not for publication)

#  Human Health

### 1.1. Additional human health hazard information

##### 1.1.1 Repeated-dose toxicity

* **Takebayashi *et al.*, 2003 and 2004**

The authors investigated associations between occupational exposure to carbon disulfide and endocrine and cardiovascular system parameters.

Both publications concern a cohort study conducted in workers from 11 viscose rayon fiber manufacturing plants. In 1992-1993, 432 male workers exposed to carbon disulfide and 402 unexposed workers from the same factory and about the same age were included in the cohort.

The follow-up phase took place in 1998-1999. The participation rate was 89.9% (4 deaths, 80 lost to follow-up.

After reclassification according to carbon disulfide exposure, the data of 744 individuals are analyzed:

- 259 still exposed,

- 133 ex-exposed (cessation of exposure due to a production stoppage in 3 plants in 1994-1995),

- 352 not exposed.

The assessment of occupational exposure to carbon disulfide is performed according to two parameters:

- Measurement of the biomarker of carbon disulfide exposure: urinary TTCA adjusted on the urinary creatinine level since 1992,

- Measurement of carbon disulfide in the inhalation zone on the same day as the urine sample since 1993.

In the 2003 publication, associations between occupational exposure to carbon disulfide and indicators of the endocrine system were studied in blood. The parameters studied were:

- glucose metabolism: fasting blood glucose, glycated hemoglobin (HbA1C), serum insulin level,

- pituitary function: FSH, LH, ACTH,

- gonadal function: testosterone,

- thyroid function: TSH, T3 T4, TBG.

In the 2004 publication, associations between occupational exposure to carbon disulfide and potential effects on the cardiovascular system was studied. The parameters studied were:

Cardiovascular risk factors: biochemical blood markers as total cholesterol, HDL-cholesterol, LDL-cholesterol, apolipoprotein AI, apolipoprotein B, lipoprotein (a), triglycerides, fibrinogen, plasminogen activator, D-dimer, plasminogen activator/inhibitor ratio-1, and thrombin and antithrombin complex III.

Indicators of vascular effect: resting blood pressure, aortic stiffness, blood flow, maximum blood velocity. Fundus was performed to evaluate microaneurysms or retinal hemorrhage.

Cardiac outcome indicator: From 12-derivation ECGs, an automated analysis of ECG abnormalities (from subclinical = minor to major abnormalities) by Minnesota model was performed (ischaemic signs, conduction disturbance, and arrhythmia). If medical treatment was initiated during follow-up, the patient was considered positive (no details provided on the type of treatment or therapeutic indication considered). A fine analysis of the ECG was then performed to specifically determine symptomatic signs of ischemia (ST shift>2mm) for comparison.

A questionnaire was used to collect various symptoms.

Univariate and multivariate analyses were performed. Confounding factors considered were age, BMI (kg/m2 ), education level, smoking status, alcohol consumption, shift work (yes or no), and coronary behavior (yes or no) at baseline. Systolic blood pressure and HDL-cholesterol at baseline were considered for ophthalmography, as well as arterial thickness and ECG.

Results

*Exposure levels*

- The duration of exposure was 19.3 (8.1) years for the exposed and 15.6 years for the ex-exposed.

- The average TTCA level (geometric mean) was 1.61 mg/g creatinine (1.94 for the spinning station and 0.98 for the other stations).

- The CS2 measurement: 5.02 ppm (6.11 for the spinning station and 3.08 for the other stations).

Regarding the effects on the endocrine system, very few associations were observed, the only significant differences were in HbA1C levels at baseline but no difference at follow-up and a lower T4 levels in the exposed group compared to the unexposed group (8.34 µg/dl vs 8.61 µg/dl) at follow-up only. However, there was no dose-response relationship by use or by TTCA level.

Regarding the effects on the cardiovascular system (2004 publication):

- No adverse effect on lipid biochemistry, coagulation.

- No effect (or marginal effect) on systolic and diastolic blood pressure.

- No effect on arterial stiffness.

- No significant effect on retinal microaneurysms.

ECG analysis according to University of Minnesota coding:

- Signs of ischemia: Code 1 (altered QRS pattern); Code 4.1 to 4.3 (ST-segment depression or alteration), Code 5.1 to 5.3 (negative, flat, or dimorphic T wave)

- Conduction block: Code 6 (atrioventricular) and 7 (ventricular)

- Arrhythmias; Code 8.1 to 8.9)

The baseline, follow-up, and 6-year incidence of ischemic signs based on Minnesota 82 ECG coding were statistically higher in carbon disulfide -exposed workers vs. the other 2 groups. After stratification by age, these results tend to show a correlation between the 6-year carbon disulfide and TTCA levels and these subclinical findings. (5 ppm (carbon disulfide) and 1.6 mg/g creatinine (TTCA)).

This observation is not confirmed by fine systematic analysis of ECGs (ST depression >2 mm or patients receiving treatment).

* **Schramm *et al.,* 2016**

The authors conducted a cross-sectional review of 290 exposed and 137 unexposed workers to carbon disulfide in a German rayon fiber manufacturing plant. On this cohort, they calculated cumulative (CE CS2) and individual biological (CE TTCA) exposure from 1992 to 2009. Follow-up included assessment of cardiovascular risk factors and measurement of intima-media thickness (IMT) of right and left carotid arteries. Multiple linear regression analyses were performed with IMT as the outcome with three cumulative exposure variables (exposure duration, cumulative carbon disulfide, and cumulative TTCA) as well as with maximum categorized carbon disulfide exposure, all adjusted for cardiovascular risk factors.

Exposed workers had a mean duration of exposure (CE YEARS) of 16.8 (7.8) years, a cumulative exposure dose (CE CS2) of 256.3 (158.9) ppm × year, and a cumulative exposure index (CE TTCA) of 30.2 (23.8) mg TTCA/g creatinine × year.

Among the 2 groups, only age and diastolic pressure differed (lower in the exposed group). Cardiovascular risk factors did not reveal any difference between the groups. IMT measurements revealed no difference between the 2 groups (0.62 vs 0.61 mm).

Multivariate linear regression analyses, however, showed an increase in IMT with EC YEAR, EC-CS2, and EC-CTTCA. The analyses showed a dependence of the results with age and number of pic per year.

* **Yoshioka *et al*., 2017**

Yoshioka et al. (2017) conducted a 6-year cohort study to evaluate the relationship between carbon disulfide exposure and motor and sensory nerve conduction velocities (MCV) and sensory nerve conduction velocity (SCV). The study involved male workers recruited from 11 viscose rayon facilities (same as in Takebayashi *et al*). At baseline, study subjects included 432 exposed and 402 unexposed workers with no history of cardiovascular or cerebrovascular disease. Of the exposed workers, 145 ceased carbon disulfide exposure during the follow-up period (ex-exposed workers).

Nerve conduction velocity was studied at the median nerve level using evoked currents. MCV and SCV were measured at baseline and during the follow-up period.

In this study, the confounding factors considered were age, BMI, smoking status, alcohol consumption, education level, carbon disulfide exposure status (unexposed, ex-exposed, exposed (1st, 2nd and 3rd tertile of exposure level).

For exposure assessment, the carbon disulfide concentration was measured twice a year in the workers' area of evolution and the average concentration was time-weighted over an 8-hour period. For individual exposure, urinary carbon disulfide concentration was assessed by monitoring a urinary TTCA, twice a year.

The mean carbon disulfide exposure concentrations (ppm) were:

- for exposed workers, the mean concentration were 5.96 ppm (0.8-16.0 ppm), with 2.84 ppm (0.8-4.6 ppm) for the first tertile, 5.64 ppm (4.7-6.6 ppm) for the second tertile, and 9.95 ppm (6.6-16.0 ppm) for the third tertile.

- for ex-exposed workers, the mean exposure concentrations were 3.93 ppm (0.6-9.9 ppm).

The urinary TTCA concentration was proportional to carbon disulfide exposure (r2 = 0.9807, determined by the study authors). TTCA levels were 1.38 mg/g creatinine (0.25-8.2 mg/g) in ex-exposed and 1.74 mg/g (0.25-8.2 mg/g) in exposed with 0.89 mg/g (0.25-2.28 mg/g) for the first tertile, 1.60 mg/g (0.33-3.01 mg/g) for the second tertile and 2.71 mg/g (0.89-8.22 mg/g) for the third tertile.

Measurement of sensitive nerve conduction velocity (SCV) showed no significant difference between unexposed, exposed and ex-exposed individuals at baseline. In the follow-up study, a significant decrease (p < 0.001) in SCV can be observed only in exposed individuals (48.82 ± 5.49 m/sec) compared to unexposed individuals (50.43 ± 4.97 m/sec). Further analysis of exposure shows that a significant decrease in SCV is only observed in exposed individuals belonging to the second (48.52 ± 5.70 m/sec) and third (48.64 ± 5.88 m/sec) tertiles of exposure (p < 0.05).

The measurement of motor nerve conduction velocity (MCV), at the beginning of the study, shows lower values in exposed individuals (57.66 ± 3.65 m/sec - p < 0.001) and ex-exposed individuals (57.59 ± 3.60 m/sec - p < 0.001) compared to that of unexposed individuals (58.97 ± 3.30 m/sec). Further analysis of exposure shows that lower MCV values are observed only in individuals in the second exposure tertile (57.18 ± 4.08 m/sec - p < 0.001) and the third exposure tertile (57.64 ± 3.11 - p < 0.05). In the follow-up study, lower MCV values were also observed in exposed (56.06 ± 3.63 m/sec - p < 0.001) and ex-exposed (55.98 ± 3.60 m/sec - p < 0.001) individuals compared to unexposed individuals (57.45 ± 3.31 m/sec). These lower values are also observed only in individuals belonging to the second (55.83 ± 3.87 m/sec) and third (55.83 ± 3.61 m/sec) tertiles of exposure (p < 0.001).

Nerve conduction velocity (NCV) differentials, between the beginning and end of the study, were measured in all individuals. For MCV, the conduction velocity differential was found to be non-significant in all individuals. For SCV, a significant conduction velocity differential could be observed in exposed individuals (-4.47 ± 3.94m/sec - p < 0.001). This negative differential was only found to be significant in exposed individuals belonging to the third exposure tertile (-4.89 ± 4.39 m/sec - p < 0.05).

The results obtained also suggest that the effects of exposure to 4 ppm carbon disulfide may be reversible because the differential in SCV observed at the end of the study in ex-exposed individuals (-3.26 ± 3.79 m/sec) is almost identical to that observed in unexposed individuals (-3.38 ± 3.97 m/sec).

##### 1.1.2 Developmental toxicity in rabbits

In this GLP guideline study (Unpublished report, 1991), New Zealand white rabbits (24 per group) inhaled 0, 60, 100, 300, 600 or 1200 ppm (equivalent to 0, 190, 316, 948, 1896, 3792 mg/m3) carbon disulfide for 6 h/d on gestation days 6 to 18. At the top dose, ataxia, labored respiration, wheezing, and tremors were observed, as well as scant feces and low food consumption that were clearly associated with carbon disulfide treatment. Three animal deaths at 1200 ppm were considered treatment-related. At the top dose, group mean body weight was statistically significantly reduced compared to control. Haematological findings were also noted mainly at the top dose (haemoglobin and haematocrit levels, mean corpuscular volume, mean corpuscular haemoglobin neutrophils and lymphocytes). Overt maternal toxicity was considered only at the top dose level of 1200 ppm (3792 mg/m3).

At both 600 and 1200 ppm, a statistically significant increase in post-implantation losses (early and late resorptions) and reduced number of live foetuses were observed. Post-implantation losses were: 0.30 ± 0.63 in control, 0.64 ± 1.00 at 600 ppm and 7.00 ± 3.94 at 1200 ppm. Two litters of 22 in the 600 ppm group and 14 litters of 21 in the 1200 ppm group consisted of implantation sites with no live fetuses, i.e., the litters consisted exclusively of resorptions. Reduced fetal body weights were also noted at 600 and 1200 ppm. Dead fetuses were observed in the 0, 100, and 600 ppm exposure groups; yet this was not considered a treatment-related finding because dead fetuses were observed in the control group, and none was observed in the 60, 300, or 1200 ppm exposure groups.

In the 1200 ppm (3720 mg/m3) group, an increase in the incidence of hydrocephalus (2 in 2 litters) was observed. Hydrocephalus was also noted at 100 ppm and at 300 ppm (1 incidence in 1 litter) but was not observed in the control group or at 600 ppm. The total number of malformations was increased at the top dose (right-sided oesophagus, absent rish subclavian artery, swollen sublclavian artery, swollen sublingual salivary glands, malformed stomach, small thyroid and parathyroid, abnormal caudal vertebrae, fused sternebrae and split sternebrae) with low incidences for each malformation (1 incidence in 1 litter). However, the incidence of any specific skeletal or visceral malformation was not significant.

**Table 14 Selected visceral malformations summary (Unpublished, 1991)**

|  |  |  |
| --- | --- | --- |
|  |  | Carbon disulfide |
| Group |  | 0 ppm | 60 ppm | 100 ppm  | 300 ppm  | 600 ppm | 1200 ppm  |
| Total number examined | LitterFetuses | 22202 | 23201 | 22193 | 21175 | 20159 | 735 |
| Total number of malformations | LittersFetuses | 2 (9.1%)2 (1%) | 2 (8.7%)2 (1%) | 5 (4.5%)7 (3.6%) | 4 (19%)3 (2.3%) | 2 (10%)2 (1.3%) | 4 (57.1%)\*4 (11.4%) |
| Hydrocephalus | LittersFetuses | 00 | 00 | 1 (4.5%)1 (0.5%) | 00 | 1 (5%)1 (0.6%) | 2 (28.6%)2 (5.7%) |

\*p≤ 0.05; Fisher Exact

In a previous prenatal developmental study in rabbits Jones-Price *et al.* (1984b) investigated the effects of carbon disulfide on development following oral exposure of pregnant rabbits to 0, 25, 75 and 150 mg/kg bw/d during gestation days 6-19. Animals were sacrificed on gestation day 30. Retarded body weight gains and increased liver weights were measured in the dams at 75 and 150 mg/kg bw/d. Fetal malformations were statistically significantly increased in males following exposure to 150 mg/kg bw/d. Resorptions were seen at all dose levels. A LOAEC of 25 mg/kg bw/d was identified for the study (study report not available, summary available in ATSDR, 1996).

In addition, in a prenatal developmental toxicity study in rabbit performed 7 hours per day, 5 day per weeks before mating up to gestation day 21, no developmental effects were seen up to 19-38 ppm (60-120 mg/m3) (Beliles *et al*., 1980).

# Reference

ATSDR, 1996: Toxicological profile for carbon disulfide (review article or handbook), Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA, US Department of Health and Human Services, Public Health Service.

Beliles, R.P, Brusick, D.J, Mecler, F.J, 1980. Teratogenic-mutagenic risk of workplace contaminants: Trichloroethylene, perchloroethylene and carbon disulphide. (No. NTIS Document No. PB82-185075).

Jones-Price, C., Tyl, Marr, Kimmel., n.d. 1984. Teratologic Evaluation of Carbon Disulphide (CAS No. 75-15-0) Administered to New Zealand White Rabbits on Gestational Days 6 through 15. National Center for Toxicological Research, Jefferson AR. Govt. Reports Announcements and Index, Issue 15. NTIS PB 84-192350.

Schramm, A., Uter, W., Brandt, M., Göen, T., Köhrmann, M., Baumeister, T., Drexler, H., 2016. Increased intima-media thickness in rayon workers after long-term exposure to carbon disulfide. Int Arch Occup Environ Health 89, 513–519. <https://doi.org/10.1007/s00420-015-1091-5>

Takebayashi, Toru, Yuji Nishiwaki, Tetsuo Nomiyama, Takamoto Uemura, Tsuneyuki Yamauchi, Shigeru Tanaka, Haruhiko Sakurai, Kazuyuki Omae, and Japanese Rayon Worker’s Health Study Group. ‘Lack of Relationship between Occupational Exposure to Carbon Disulfide and Endocrine Dysfunction: A Six-Year Cohort Study of the Japanese Rayon Workers’. Journal of Occupational Health 45, no. 2 (2003): 111–18. <https://doi.org/10.1539/joh.45.111>.

Takebayashi, T., 2004. A six year follow up study of the subclinical effects of carbon disulfide exposure on the cardiovascular system. Occupational and Environmental Medicine 61, 127–134. <https://doi.org/10.1136/oem.2002.006858>

Unpublished report, 1991. Developmental inhalation toxicity study of carbon disulphide in the New Zealand white rabbit. (study report)

Yoshioka, N., Takebayashi, T., Nishiwaki, Y., Nomiyama, T., Iwasawa, S., Sakurai, H., Omae, K., 2017. Changes of median nerve conduction velocity in rayon manufacturing workers: A 6‐year cohort study. Jrnl of Occup Health 59, 187–193.

1. https://echa.europa.eu/understanding-assessment-regulatory-needs [↑](#footnote-ref-2)
2. Latest amendment: Directive (EU) 2022/431, published 9 March 2022 [↑](#footnote-ref-3)
3. Commission Directive 2009/161/EU of 17 December 2009 establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC [↑](#footnote-ref-4)
4. A skin notation assigned to the occupational exposure limit value indicates the possibility of significant uptake through the skin [↑](#footnote-ref-5)
5. <https://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp> (consulted in May 17th, 2022) [↑](#footnote-ref-6)
6. <https://echa.europa.eu/documents/10162/13632/information_requirements_r12_en.pdf/ea8fa5a6-6ba1-47f4-9e47-c7216e180197> [↑](#footnote-ref-7)