COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Regarding the "expert appraisal for setting occupational exposure limits for chemical agents"

Assessment of the health effects and methods for the measurement of exposure levels in workplace atmospheres for

octamethylcyclotetrasiloxane, CAS No. 556-67-2

This document summarises the work of the Expert Committees on “health reference values”, “Characterisation of substance hazards and toxicity reference values” and “expert appraisal for recommending occupational exposure limits for chemical agents” (OEL Committee) and the Working group on metrology.

Presentation of the issue

On 3 February 2012, ANSES received a formal request from the French Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limits for octamethylcyclotetrasiloxane (D4).

France does not currently have any occupational exposure limits for D4.

The Directorate General for Labour asked ANSES to assess this substance and propose occupational exposure limits based on health considerations for D4.

Scientific background

The French system for establishing OEL values has three clearly distinct phases:

- independent scientific expert appraisal (the only phase entrusted to the Agency);
- proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELs) was entrusted to AFSSET in the framework of the 2005-2009 Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

Occupational exposure limits, as proposed by the Committee are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (workers) is one that excludes both children and the elderly.

These concentration levels are determined by the Committee experts based on information available from epidemiological, clinical, animal toxicology studies, etc. Identifying concentrations that are safe for human health generally requires adjustment factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent in the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the air of a worker's breathing zone over the course of an 8-hour shift. In the current state of scientific knowledge (in toxicology, medicine, epidemiology, etc.), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working lives from the medium- and long-term health effects of the chemical in question;
- short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the atmospheric concentration of a chemical in the workers' breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure;
- ceiling value: this is the limit of the atmospheric concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$, only for liquid and solid aerosols;
- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OEL may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;
- the value of the STEL, when it exists, is not exceeded.

In addition to the OELs, the Committee assesses the need to assign a "skin" notation, when significant penetration through the skin has been identified (ANSES, 2017). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The Committee also assesses whether or not it is necessary to assign a "noise" notation, indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended exposure limits, to enable preventionists to implement appropriate measures (collective, individual and medical).

The Committee also evaluates the applicable reference methods measuring exposure levels in workplace atmospheres. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated the Committee on “Characterisation of substances hazards and toxicity reference values” (Substances Committee) for the health assessment effects and the Working Group on Metrology to assess the methods for measuring atmospheric concentrations in the workplace.

The methodological and scientific aspects of the expert appraisal work were regularly submitted to the OEL Committee.

The report produced takes into account the comments and additional information provided by the members of the OEL Committee.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities”.

Prevention of risks of conflicts of interest

ANSES analyses the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.

The experts’ declarations of interests are made public *via* the ANSES website (www.anses.fr).

Description of the method

<u>For the assessment of health effects:</u>

A summary report was prepared by ANSES and submitted to the Substances Committee and the OEL Committee, which commented on and added to it.

The summary report was based on bibliographic information taking into account the scientific literature that had been published on this substance up to 2016. The literature search was undertaken in the following databases: Medline, Toxline, HSDB, ToxNet (CCRIS, GENE-TOX, IRIS), ScienceDirect, Scopus, and ECHA, as well as the SCCS[1] report of 2010 ("Opinion on Cyclomethicone").

[1] SCCS: Scientific Committee on Consumer Safety

For the assessment of the methods for measuring exposure levels in the workplace:

A summary report was prepared by the WG on Metrology and submitted to the OEL Committee, which added its own comments.

The summary report presents the various protocols for measuring D4 in workplace atmospheres, which were identified and grouped according to the methods used. These methods were then assessed and classified based on the performance requirements set out particularly in the French Standard NF EN 482: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents" and the decision-making criteria listed in the methodology report (ANSES, 2017).

A list of the main sources consulted is detailed in the methodology report (ANSES, 2017).

These methods were classified as follows:

- Category 1A: the method has been recognised and validated (all of the performance criteria in the NF EN 482 Standard are met);
- Category 1B: the method has been partially validated (the essential performance criteria in the NF EN 482 Standard are met);
- Category 2: the method is indicative (essential criteria for validation are not sufficiently clear);
- Category 3: the method is not recommended (essential criteria for validation are lacking or inappropriate).

A detailed comparative study of the methods in Categories 1A, 1B and 2 was conducted with respect to the various validation data and the technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The report, as well as the summary and conclusions of the collective expert appraisal were adopted by the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents on 15 May 2017.

This collective expert appraisal work and the summary report were submitted to public consultation from 22/11/2017 to 22/01/2018. The people or organizations who contributed to the public consultation are listed in appendix 2 of the report (only available in French). The comments received were reviewed by the Committee on Health Reference Values (term of office 2017-2020) who finally adopted this version on the 21/06/2018.

Results of the collective expert appraisal on health effects

Toxicokinetics data

Absorption

In a study of 12 volunteers exposed for one hour to 10 ppm of inhaled D4, the average deposition fraction was 8% (Utell *et al.*, 1998). In animals, the results were very similar: following single or repeated exposure to various concentrations in rats, absorption ranged from 5% to 6% (Plotzke *et al.*, 2000).

By the oral route, studies showed that absorption was dose-dependent (the absorbed fraction in rats was lower for high doses than for the lowest doses, Dobrev *et al.*, 2008) as well as vehicle-

dependent: the absorption of ^{14}C-D4 was respectively 52%, 12% and 28% in corn oil, simethicone or neat (ECHA, 2016; SCCS, 2010).

By the dermal route, *in vivo* studies in rats mentioned a similar absorption percentage through viable human skin, i.e. less than 1% irrespective of the applied dose (Jovanovic *et al.*, 2008; Reddy *et al.*, 2007; Zareba *et al.*, 2002). The *ex vivo* study by Jovanovic *et al.* (2008) estimated dermal absorption of D4 through human skin to be approximately 0.5% of the applied dose.

Distribution

Due to its low blood:air partition coefficient (around 1), D4 is rapidly eliminated through exhaled air, but because of its high fat:blood partition coefficient, the non-eliminated fraction of D4 is easily stored in fat reserves. In addition, a fraction of the absorbed quantity also persists in bound form, especially through blood sequestration *via* lipoproteins (Dobrev *et al.*, 2008; Plotzke *et al.*, 2000; Reddy *et al.*, 2003; Sarangapani *et al.*, 2003).

Studies in volunteers confirmed the rapid and non-linear clearance of D4 in plasma and blood: free D4 was rapidly exhaled or metabolised whereas bound D4 was persistent in blood (Reddy *et al.*, 2003; SCCS, 2010; Utell *et al.*, 1998).

Results in animals described radiolabelling widely distributed throughout the body. Some tissues (adipose tissue, lungs, liver, ovaries) contained higher levels of radioactivity than plasma (by three to 10 times) whereas others (testicles, uterus, vagina) contained similar or slightly higher levels. The maximum concentration (Cmax) was observed at the end of exposure for the majority of tissues, and one hour after exposure for blood, three hours after exposure for plasma, and 12 hours after exposure for fat.

Metabolism

Fractions of non-metabolised D4 and its metabolites vary depending on the analysed matrix: in urine samples, only metabolites of D4 are present, whereas in the lungs, non-metabolised D4 has mainly been quantified. In urine, two major metabolites have been identified in rats: dimethylsilanediol ($Me_2Si(OH)_2$) and methylsilanetriol ($MeSi(OH)_3$). They account for 75% to 85% of urinary metabolites (SCCS, 2010). The five other minor metabolites identified are likely the result of hydrolysis and/or oxidation of the metabolites formed after oxidation of D4 by cytochromes P-450 (Plotzke *et al.*, 2000).

D4 is thought to be metabolised in the liver by a single metabolic pathway following saturable (Michaelis-Menten) kinetics (Sarangapani *et al.,* 2003). Several hepatic cytochromes P-450, CYP 2B and CYP 3A in particular, were identified as being involved in hepatic metabolism (Dobrev *et al.,* 2008).

Excretion

In humans, a study described the rapid elimination of D4 in exhaled air and plasma due to its low molecular weight and lipophilic nature (Utell *et al.*, 1998). In addition, around 25% to 30% of the dose absorbed is found in urine, in metabolite form only (SCCS, 2010).

All studies by inhalation in rats exposed to various doses of radiolabelled D4 demonstrated that the major routes of elimination for D4 are exhalation and urine. Sarangapani *et al.* (2003) observed that more than 90% of the dose absorbed was eliminated by gas exchange in the lungs and less than 10% was excreted in urine.

After ingestion, D4 was eliminated by exhalation and in urine in similar proportions (around 49%) (Sarangapani *et al.*, 2003).

Toxicity data

Acute toxicity

Data in humans

Volunteers exposed to 10 ppm of D4 by inhalation for one hour demonstrated no adverse effects (Utell *et al.*, 1998).

In addition, no health effects were observed in volunteers having received a dose of 1 or 1.4 g of D4 for 24 hours on the skin of the underarms (Reddy *et al.*, 2007).

Data in animals

D4 has a very low level of toxicity following acute exposure, regardless of the route. Of the various available studies, apart from a study by inhalation determining an LC_{50} of 36,000 $mg.m^{-3}$ and a study on oral exposure determining an LD_{50} of 1700 mg/kg, no other studies have shown mortality in animals, sometimes at very high concentrations (ECHA, 2016; Carpenter *et al.*, 1974).

Irritation and sensitisation

Data in humans

No signs of respiratory irritation were reported by volunteers after one hour of exposure to 10 ppm of D4 (Utell *et al.*, 1998). Re-exposure to the same concentrations three months later showed no immunological or biological abnormalities according to the blood tests of the volunteers, nor any changes in lung function or symptoms of pulmonary irritation (Looney *et al.*, 1998).

Data in animals

D4 is not a skin irritant or sensitiser or an eye irritant. No data are available regarding respiratory irritation or sensitisation (ECHA, 2016).

Subchronic and chronic toxicity

Data in humans

No studies on the chronic toxicity of D4 are available in humans.

Data in animals

- Hepatic effects

These were the most commonly observed effects in the panel of studies undertaken on D4. Indeed, all of the repeated toxicity studies (by oral route and by inhalation) observed at least an increase in liver weight. This increase was associated, in the study by Burns-Naas *et al.* (2002) with rats Fischer 344 exposed to 0, 35, 122, 488 and 898 ppm, with a sharp increase in gamma-glutamyltransferase (γ-GT) at the highest concentration in males (168%), and at the two highest concentrations in females (330% and 975%), and with a slight increase in alanine aminotransferase (ALT) at the highest concentration in both sexes (males: 26%, females: 15%). However, no histopathological lesions were observed in this study.

- Respiratory effects

In the study by Burns-Naas *et al.* (2002), a concentration-dependent increase was observed in the incidence and severity of alveolar macrophage accumulation and interstitial inflammation in both sexes.

A study on chronic exposure observed a significant increase in the incidence of respiratory epithelium goblet cell hyperplasia, hyperplasia of the nose squamous epithelium, a statistically significant increase in rhinitis, and moderate chronic subpleural inflammation (only in females for the latter two effects). Data on animals kept after treatment suggested the effects were reversible (Battelle Toxicology Northwest, 2004, reported by SCCS, 2010).

- Renal effects

A study on chronic exposure, observed, in addition to an increase in absolute and relative kidney weight, a statistically significant increase in the severity (but not the incidence) of nephropathies (Battelle Toxicology Northwest, 2004, reported by SCCS, 2010).

Genotoxicity

D4 showed no genotoxic potential in the various *in vitro* and *in vivo* studies undertaken (Vergnes *et al.*, 2000; SCCS, 2010).

Carcinogenicity

Data in humans

There are no data on carcinogenicity in humans.

Data in animals

A chronic study showed an increase in the incidence, in males, of mononuclear cell leukaemias at the highest dose: 73% in the control group (historical controls: 45%), 45% at 10 ppm, 43% at 30 ppm, 48% at 150 ppm, and 69% at 700 ppm. However, Fischer 344 rats, used in the study, are not good models for cancerology, since this strain is prone to lymphocytic leukaemia (Battelle Toxicology Northwest, 2004, reported by SCCS, 2010).

Toxicity to reproduction and development

Data in humans

No reprotoxicity data in humans are available.

Data in animals

Two studies (including one two-generation study) are available to assess the effects of D4 on reproduction (Meeks *et al.*, 2007; Siddiqui *et al.*, 2007), with highly consistent results. Both studies observed statistically significant and dose-dependent decreases in the number of implantation sites and the number of viable foetuses.

Establishment of OELs

Several effects were observed in repeated-exposure animal studies undertaken with D4:

Hepatic effects: In its guide on hepatic effects, the US EPA (2002) specifies that the increase in ALT should not be considered adverse until it is at least 2-fold to 3-fold greater than control levels. On the other hand, according to this study, an increase in γ-GT would be sufficiently indicative of a compound's toxicity to the liver. The US EPA also specifies that in the absence of histopathological lesions, serum levels for at least two parameters should be significantly elevated before they can be ascribed to hepatic toxicity. Therefore, the non-reproducibility of the increase in γ-GT between studies, and the fact that this increase was not combined with other changes in biochemical or histopathological parameters in the study by Burns-Naas *et al.* (2002), suggest an adaptive effect of the liver, not toxicity.

Respiratory effects: The respiratory effects observed were unspecific local effects, considered as related to the anatomy of rats. In fact, in rats, the olfactory epithelium is much more developed than in humans, making it difficult to transpose these effects to humans.

Renal effects: The effects observed on the kidneys did not demonstrate a dose-response relationship, and no serum markers provided evidence of functional impairment.

Reproductive toxicity: The decrease in the number of implantation sites and the decrease in the number of viable foetuses, the two effects observed in the two available studies, were statistically significant and dose-dependent, and cannot be ruled out in humans.

8h-OEL

In light of the available data, the effects on reproduction reported in studies in rats appear the most robust for the establishment of the 8h-OEL. The two parameters for which statistical significance and a dose-response relationship appeared were analysed (decrease in the number of implantation sites and decrease in the number of viable foetuses).

Of the two available studies in which these effects were observed, the study by Siddiqui *et al*. (2007) was selected as the key study for the establishment of the 8h-OEL. It exposed animals of both sexes for the longest duration (70 days; exposure time covering a complete breeding cycle) and was undertaken in accordance with the OPPTS guidelines and GLP.

Following the construction of benchmark concentrations (BMCs) from the study by Siddiqui *et al*. (2007), the decrease in the number of implantation sites seemed to occur at a slightly lower concentration. This parameter was therefore used to determine the critical dose for the establishment of an OEL.

The BMC values that were determined for the decrease in implantation sites were as follows:

- $BMC_{5\%}$: 96 ppm
- $BMC_{5\%}L_{95\%}$: 73 ppm

Dosimetric adjustment was applied using the PBPK model for D4 developed by McMullin (2016), considering the $BMC_{5\%}L_{95\%}$ of 73 ppm as the point of departure (POD). This dosimetric adjustment led to the determination of a $BMC_{5\%}L_{95\%\ HEC}$ of 80 ppm.

The following adjustment factors were then applied to calculate the 8h-OEL from the $BMC_{5\%}L_{95\%\ HEC}$:

- Inter-species variability (AF_A): 2.5

This factor was justified by the dosimetric adjustment, eliminating the toxicokinetics component (IPCS, 2005).

- Inter-individual variability (AF_H): 3

Due to the lack of quantitative data on inter-individual variability, the value of 3 was assigned by default to this factor in order to take into account variability within the population of workers.

- Subchronic to chronic transposition (AF_S): 1

The key study selected to establish the 8h-OEL was a study in which animals were exposed for 70 days. However, this exposure time covered a complete breeding cycle, and no more significant effects were observed in the studies with subchronic or chronic exposure. The application of a value of 1 for the AF_S was thus considered relevant.

Therefore, the application of an overall adjustment factor of 7.5 led to an 8h-OEL of 80/7.5 = 10.66 ppm, i.e. 10.66*12.33 = 131.4 $mg.m^{-3}$ rounded to 130 $mg.m^{-3}$.

The Committee therefore recommends an 8h-OEL of **130 $mg.m^{-3}$**.

15min-STEL

Due to the lack of available data regarding the short-term toxic effects of D4, and in order to limit the size and number of exposure peaks, the OEL Committee recommends, in accordance with its methodology (ANSES, 2017), not exceeding five times the value of the 8h-OEL, i.e. 650 $mg.m^{-3}$, over a 15-minute period.

Therefore, the Committee recommends a pragmatic 15min-STEL of **650 $mg.m^{-3}$**.

"Skin" notation

The dermal absorption of D4 appears very low, with all studies reporting absorption below 1%. In the absence of additional quantitative data, it does not appear necessary to assign a "skin" notation for D4.

"Noise" notation

None of the available studies suggest an ototoxic effect of D4. Accordingly, the "noise" notation is not assigned.

Results of the collective expert appraisal on measurement methods in workplace atmospheres

Assessment of the measurement methods for D4 in workplace atmospheres

Three methods for measuring D4 in workplace atmospheres were identified and analysed (see Table 1).

Table 1: Identification and classification of the methods for measuring D4 in workplace atmospheres

Method		Protocols	Category		
			Regulatory technical control		Monitoring short-term exposure
No.	Description		8h-OEL	Pragmatic 15min-STEL	
1	Active sampling on a tube containing Amberlite XAD-2 resin Solvent desorption, analysis by gas chromatography with flame ionisation detection (GC/FID)	NF ISO 16200-1 (2001) NF X43-267 (2014) MétroPol M19 (2007)	3 (vapour phase)		
2	Passive sampling on an SKC 575-001 badge, activated charcoal, solvent desorption, analysis by GC/FID	ISO 16200-2 (2000)	2 (vapour phase)	3 (vapour phase)	
3	Active sampling on quartz fibre filter and tube of activated charcoal, solvent desorption, analysis by GC/FID	Inrs MétroPol M-427 (2018)	2 (mixed phase or vapour phase)		

Additional validation data on Method 2 were found in the validation report for the SKC sampler published on the manufacturer's website and were analysed (SKC Report 1890, 2014).

Preliminary comment on the phase to be sampled

The vapour pressure of D4, slightly greater than 100 Pa at 20°C, suggests that a vapour sampling system should be used.

Data on each method's range of validity and limit of quantification with regard to the 8h-OEL and 15min-STEL are presented in the following two figures.

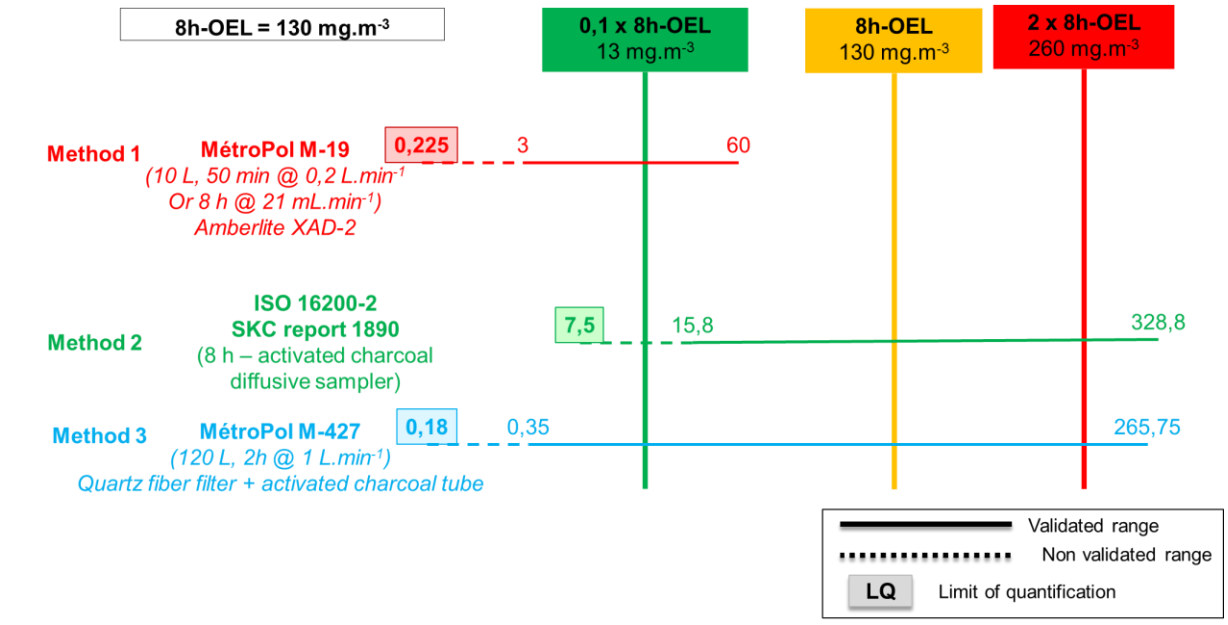

Figure 1: Range of validity and limit of quantification of the methods compared to the range from 0.1 to 2 times the 8h-OEL proposed by the Committee

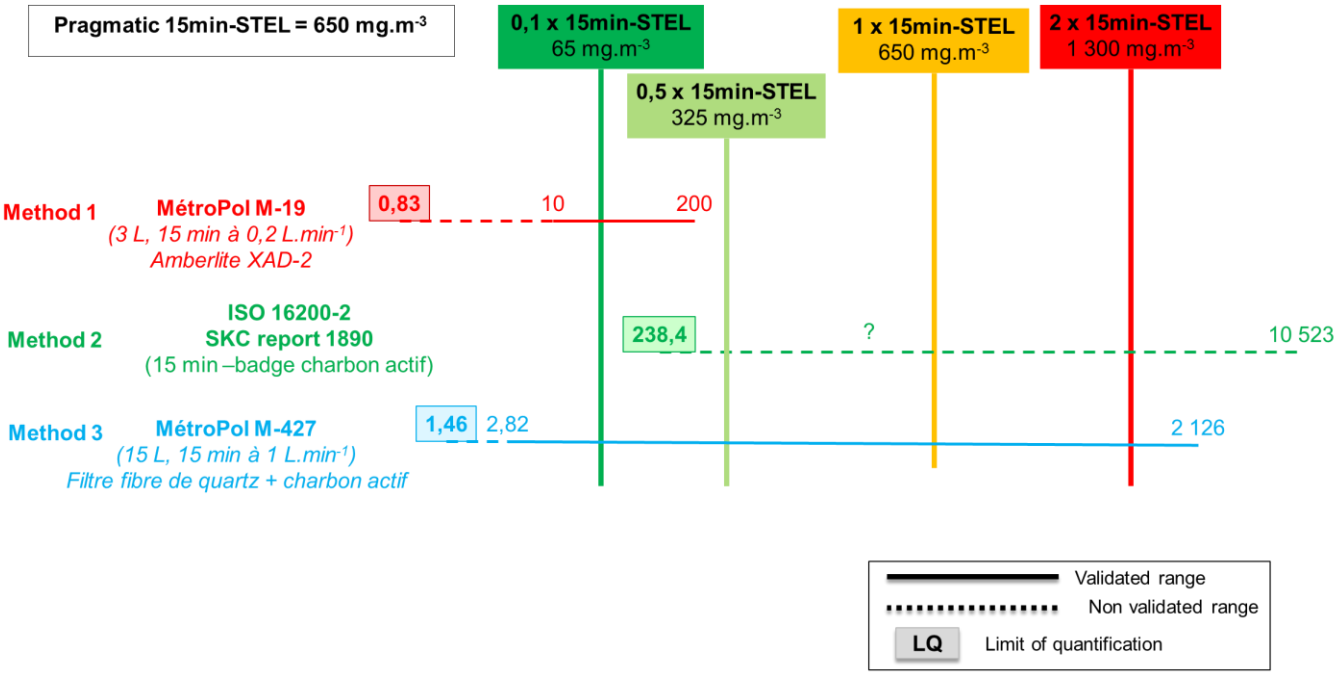

Figure 2: Range of validity and limit of quantification of the methods compared to the range from 0.1 to 2 times the pragmatic 15min-STEL proposed by the Committee

Method 1:

This method is described in the partially validated INRS – MétroPol protocol, sheets 19 (sampling and analysis) and 33 (validation data). It consists in pumping air through a tube filled with Amberlite XAD-2 resin, a copolymer of polystyrene. The resin is desorbed with 5 mL of an acetone/methanol mixture (96/4 v/v) and then soaked in an ultrasound water bath for 15 minutes. The desorbate is analysed by gas chromatography with flame ionisation detection (GC/FID).

This method is classified in Category 3 for regulatory technical control of the 8h-OEL and the pragmatic 15min-STEL, as well as for monitoring short-term exposure, due to the lack of data on the sampler capacity and the expanded measurement uncertainty, encompassing sampling and analysis. No additional publications or reports were found in the literature providing information about the missing criteria for the method.

Method 2:

This method is described in Standard ISO 16200-2, with specific information taken from a validation report for the SKC 575-001 badge published by its manufacturer and distributor.

Validation thus applies to this badge only and cannot be transposed to other passive sampling media.

The method involves passive sampling on an SKC 575-001 badge, acetone/CS_2 desorption, then analysis by gas chromatography with flame ionisation detection.

In its sampling guide, the manufacturer indicates that this badge is partially validated for D4 sampling with regard to the NIOSH validation protocol and that only the diffusion rate, desorption efficiency and storage conditions were studied. The validation data for the SKC 575-001 badge show that the requirements of the NF EN 482 Standard regarding the measurement range are met only for the regulatory technical control of the 8h-OEL. The diffusion rate was determined experimentally for durations of 15 to 480 minutes and validated for concentrations ranging from 15.8 to 328.8 $mg.m^{-3}$ for 8-hour sample times, but for 15-minute sample times this rate was validated only at the concentration of 238.4 $mg.m^{-3}$.

Due to the lack of data on the minimum face velocity of the air, its orientation with respect to the flow, and the influence of temperature and co-pollutants, the method implemented with the SKC 575-001 badge is classified in Category 2 for regulatory control of the 8h-OEL. These parameters can modify the diffusion rate and significantly lower the sampler capacity.

The measurement range for the monitoring of short-term exposure (0.5 to 2*pragmatic 15min-STEL) and regulatory technical control of the pragmatic 15min-STEL (0.1 to 2*pragmatic 15min-STEL) are not validated. The method is therefore classified in Category 3 for regulatory technical control of the pragmatic 15min-STEL and the monitoring of short-term exposure.

Method 3:

This method is described in the INRS M-427 MétroPol protocol.

The sampling device consists of a closed 37 mm cassette with a quartz fibre filter, followed by an activated charcoal tube (400/200 mg), and allows the sampling of D4 in mixed phase form. The sampling is done at a rate of 1 $L.min^{-1}$ for a maximum of 2 hours. After the sampling of the substance, it is necessary to sample pure air for 30 min by connecting an activated charcoal tube upstream of the cassette, in order to transfer the mass of D4 collected on the filter towards the first

activated charcoal range of the tube. Indeed the small amount of D4 trapped on the filter is not retained even at 4°C.

The method is validated over a concentration range covering 0.1 to 2*VLEP-8h, with a 2h sampling, and covering 0.1 to 2*15min-STEL with a 15min sampling.

In view of the risk of breakthrough, the sampling for monitoring the 8h-OEL must not exceed 2 hours, which means that 4 successive samples must be taken to cover the entire work shift. Moreover, the influence of interferences and environmental conditions on the sampler capacity is not known.

For these reasons, the method is classified in category 2 for the regulatory technical control of the 8h-OEL and the pragmatic VLCT-15min, as well as for the monitoring of short-term exposures.

Conclusions and recommendations

Of the two identified measurement methods of D4 only in vapour phase:

- Method 1, described in the INRS MétroPol 19 protocol, has been classified in Category 3 for regulatory technical control of the 8h-OEL and the 15min-STEL, as well as for monitoring short-term exposure. This method has an available measurement range that is too narrow as well as incomplete validation data on the sampler capacity and uncertainties not compliant with the requirements of NF EN 482.
- Method 2, described in the ISO 16200-2 protocol and using an SKC 575-001 badge, has been classified in Category 2 for monitoring the 8h-OEL and in Category 3 for monitoring short-term exposure and regulatory technical control of the pragmatic 15min-STEL. Certain parameters, such as the influence of the badge's environment and the effect of temperature and other siloxanes sometimes combined with D4, were not studied and can affect the badge's diffusion rate and capacity. Moreover, this method does not have an available measurement range compatible with the measurement of the pragmatic 15min-STEL.

For the method, allowing the sampling of D4 in the form of a mixed phase (joint sampling of the gas phase and the particulate phase):

- Method 3, described in the INRS M-427 MétroPol protocol, has been classified in category 2 for the regulatory control of the 8h-OEL and the pragmatic 15min-STEL as well as for the monitoring of short-term exposures. Indeed, although the method is validated on the desired measuring range (0.1 to 2*8h-OEL and 0.1 to 2*15min-STEL), the breakthrough conditions are restrictive: the method allows sampling for a maximum of 2 hours, and the influence of environmental conditions and interferences on the sampler capacity is not mentioned.

Thus, are recommended when D4 is present only in vapour phase:

- For the regulatory technical control of the 8h-OEL: the indicative method 2 applied with the SKC 575-001 badge as well as the indicative method 3.
- For the regulatory technical control of the pragmatic VLCT-15min and for short-term exposure monitoring: the indicative method 3.

When D4 is present as a mixed phase, only indicative method 3 is recommended for regulatory control of the 8h-OEL and of the pragmatic 15min-STEL as well as for short-term exposure monitoring.

Table 2: Recommended methods for measuring D4 in workplace atmospheres

Method		Protocols	Classification		
			For regulatory technical control		Monitoring short-term exposure
No.	Description		8h-OEL	15min-STEL	
2	Passive sampling on an SKC 575-001 badge, activated charcoal, solvent desorption, analysis by GC/FID	ISO 16200-2 (2000) *Implemented with the SKC 575-001 badge*	2 (vapour phase)	3 (vapour phase) (not recommended)	
3	Active sampling on quartz fiber filter and tube of activated charcoal, solvent desorption, analysis by GC/FID	Inrs MétroPol M-427 (2018)	2 (vapour phase or mixed phase)		

Conclusions of the collective expert appraisal

Based on the data that are currently available for D4, the Committee recommends setting an 8h-OEL of 130 mg.m^{-3}. This recommendation aims to protect against effects on reproduction (decrease in the number of implantation sites and decrease in the number of viable foetuses). These effects, considered as the most robust, have been observed in the available animal studies and cannot be ruled out in humans.

Based on the data that are currently available, no 15min-STEL can be recommended for D4. Therefore, in accordance with its methodology, the Committee recommends not exceeding five times the value of the 8h-OEL (i.e. 650 mg.m^{-3}) over a 15-minute period.

The Committee does not recommend a "skin" notation.

The Committee does not recommend a "noise" notation.

Regarding the methods for measuring D4 in workplace atmospheres, the Committee recommends:

- when D4 is present only in vapour phase, implementing,
    - for the regulatory technical control of the 8h-OEL, two indicative methods, classified in category 2 :
        - the method involving an active sampling on quartz fibre filter and activated charcoal tube, a solvent desorption then analysis by GC/FID,
        - the method involving a passive sampling on a disc badge with activated charcoal, solvent desorption, and analysis by GC/FID. The Committee draws attention to the fact that the validation data apply only to the SKC 575-001 badge. The use of other passive media should be subject to a comprehensive assessment.
    - for the regulatory technical control of the pragmatic 15min-STEL or the short term exposure monitoring, the method involving an active sampling on quartz fibre filter and activated charcoal tube, a solvent desorption then analysis by GC/FID.

- When D4 is present as a mixed phase: implementing, for the regulatory control of the 8h-OEL and the pragmatic 15min-STEL as well as for the short term exposure monitoring, the indicative method, classified in category 2, involving an active sampling on quartz fibre filter and activated charcoal tube, a solvent desorption an analysis by gas chromatography with detection by flame ionization.

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