COLLECTIVE EXPERT APPRAISAL:
SUMMARY AND CONCLUSIONS

regarding the expert appraisal for recommending occupational exposure limits for chemical agents
concerning the assessment of methods for measuring workplace exposure levels for titanium dioxide under nanoform ($nTiO_2$, P25) (CAS n°13463-67-7)

This document summarises the work of the Expert Committee on « health reference values » and the Working Group on Metrology

Presentation of the issue

In 2015, Anses submitted a proposal of classification to the European Chemicals Agency (ECHA) for the carcinogenicity by inhalation of TiO_2 (carcinogenic category 1B) under European Regulation (CLP) No 1272/2008 on the classification, labelling and packaging of dangerous substances and mixtures. In 2017, ECHA's Risk Assessment Committee (RAC) concluded that TiO_2 in all its forms should be classified as a suspected human carcinogen of category 2 by inhalation.

Anses was requested by the Directorate General for Health (DGS), Directorate General for Risk Prevention (DGPR) and Directorate General for Labour (DGT) on 4 July 2017 to establish a chronic TRV by inhalation for TiO_2 under nanoform. This request under the terms of the referral is the result of “the analysis of the R-Nano database indicating that many industrial sites in France use titanium dioxide under nanoform. These uses can lead to exposure of workers but also to exposure of populations via off-site emissions”. The referral notes that “the International Agency for Research on Cancer (IARC) has classified titanium dioxide as respirable particles as a possible carcinogen by inhalation”.

An opinion was published in April 2019 defining a TRV of 0.12 µg.m^{-3} applicable only to "Aeroxide TiO_2 P25“[1]. The confidence level of this TRV was rated as "moderate”. Following this opinion, and in accordance with the protocol of agreement on Occupational Exposure Limits and Biological Limits (OELs and BLVs) between the Ministry of Labour and the Anses, the Anses launched the work for the development of OELs.

The Anses published in December 2020 an opinion and an collective expert appraisal report concerning only the health effects linked to exposure to titanium dioxide under nanoform (TiO_2-NP, P25) (CAS n°13463-67-7) and recommended the following OELs (Anses 2020c):

- 8h-OEL of 0,8 µg.m^{-3}

[1] The "Aeroxide TiO_2 P25" form is a fully characterized reference form of nanoparticular titanium dioxide composed of anatase (80%) and rutile (20%) with a primary particle diameter of 21 nm and a specific surface area of 48.08 m2.g^{-1}.

- 15min-STEL of 4 µg.m^{-3}

In its opinion of 2020, Anses precised that « In the absence of a conventional nanometric fraction, the fraction to be considered by default for these values is the respirable fraction ».

Moreover, Anses recommended applying by default these two values to any form of nanometric titanium dioxide, and not only to P25, for which these values were derived. In the absence of robust data to assess the parameters determining the toxicity of the different forms of nanometric titanium dioxide, this recommendation aims, in this case, to limit exposure to all these forms, without however being able to guarantee protection from their possible specific health effects.

This document is a response regarding the assessment of methods for measuring titanium dioxide under nanoform with regard to these recommendations and supplements the work published in Decembre 2020 recommending OELs.

Note on the scope of this appraisal:

TiO_2 as nanostructured particles can exist in the air as primary particles (or nanoparticles: i.e. particles whose 3 external dimensions are on nanometric scale, i.e. in the range of dimensions between approximately 1 and 100 nanometres), aggregates and agglomerates. Emissions may occur while processing non-nanometric TiO_2 through certain thermal or mechanical processes, and not only when using nanometric manufactured TiO_2. According to a study conducted by INRS in the building and public works sector, nanostructured TiO_2 particles can distribute in all conventional fractions (respirable, thoracic and inhalable) (INRS 2019).

The purpose of this appraisal aims to assess the methods used to measure manufactured nanometric TiO_2 with regard to the recommended OELs. Considering that the aerosol generated in the key study taken into account for the construction of these OELs (Bermudez et al. 2004 in Anses, 2020) comprised aggregates of nanometric TiO_2 particles with median aerodynamic diameter ranging from 1.29 to 1.44 µm, the respirable fraction is the fraction to be considered for the assessment of the measurement methods. However, the Expert Committee wants to indicate that collecting nanometric-sized particles or the respirable fraction only may underestimate workers' exposure to nanostructured titanium dioxide particles, since aggregates and agglomerates can reach several tens of micrometres in size.

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.

The OELs, as proposed by the "Health reference values" Committee (HRV 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 considered as

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 (the workers) is one that excludes both children and the elderly.

The HRV Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the expert committee on health reference value (HRV Committee) and to the working group on metrology (Metrology WG).
The methodological and scientific aspects of the work were regularly submitted to the Expert Committee. The report produced takes account of observations and additional information provided by the Committee members.
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".

Preventing risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.
The experts' declarations of interests are made public on the website : https://dpi.sante.gouv.fr/.

Description of the method

For the assessment of the methods for measuring exposure levels in the workplace, an assessment report of the measurement methods was prepared by the Working Group on Metrology and submitted to the HRV Committee, for comments and validation. Several ANSES employees also contributed to this work.

The report addresses:

- the issue presented by sampling nanometric TiO_2 with regard to the recommended OELs, and the absence of a convention for the sampling of nanometric-sized particles;
- the existing sampling devices suitable for the sampling of particles in the near-nanometric size range;
- the various protocols for measuring non-nano-sized titanium dioxide in workplace air, listed and grouped according to their analysis methods. The sampling devices used are designed for sampling either the inhalable or respirable fraction. However, as the corresponding analytical validation data were obtained by doping the membranes with solutions, the analytical methods were evaluated and classified with regard to the performance requirements specified in particular in standard NF EN 482 and the decision criteria outlined in the report describing the methodology for assessing the measurement methods (Anses, 2020b).

The list of the main sources consulted is detailed in the methodology report (Anses 2020b).

These methods were classified as follows:

- Category 1A: recognized and validated methods (all of the performance criteria are met);
- Category 1B: partially validated methods (the essential performance criteria are met);

- Category 2: indicative methods (essential criteria for validation are not clear enough or else the method requires adjustments that need to be validated);
- category 3 : methods not recommended because they are unsuitable (essential validation criteria are not fulfilled)
- category 3*: methods not recommended because they cannot be evaluated (essential validation criteria are not documented).

NB : For the measurement of aerosols and substances in mixed phases, an initial classification is established with regard to the performance criteria for sampling methods. A second classification is then established with regard to the performance criteria for analytical methods. The final classification of the method corresponds to the least favourable of these two classifications.

A detailed comparative study of the methods in categories 1A, 1B and 2 was conducted with respect to their various validation data and 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 HRV Committee for public consultation on 09/12/2022.

Results of the collective expert appraisal

1. sampling issues

There is currently no convention for sampling nanometric-sized particles (dimensions approximately ranging between 1 and 100 nanometres), unlike the case for inhalable, thoracic or respirable fractions. Nanometric particles concentrations are most frequently determined by means of particles counters. These devices determine the number concentration in real time as a function of particle size (mobility diameter). Depending on the devices,the size ranges of counted particles vary and can exceed 100 nanometres.

However, the recommended OELs are not expressed in terms of number of particles, but in mass concentration. It is therefore advisable to use measurement techniques that enable the determination of the mass concentration of the aerosol.

Data on number concentration obtained from a particle counter can be converted into mass concentration, provided the particles' shape and density are known. However, this type of sampler does not allow off-line analysis of samples. Also, in the presence of various types of nanometric particles, such devices are unable to distinguish the different particles and cannot be retained for the control of the OELs for nanometric TiO_2.
In order to characterise exposure as accurately as possible, sampling must be carried out in the worker's breathing zone. This is why the microbalance and impactor devices used for fixed-position measurements are not included in this appraisal.

None of the individual samplers typically used in occupational hygiene are capable of only sampling particles that have a size below 100 nm. Some individual impactors enable particles sampling in the submicrometre range with a mass determination. These are devices with several collection stages enabling to sample particles according to different cut-off diameters (aerodynamic diameters - Dp). The sampling rate, the nature of the collection media, the number of stages and the cut-off diameters vary according to the devices. Among the most widely used individual impactors enabling the collection on the end filter of a submicrometre-sized fraction are the Marple (< 0.52 µm), the Sioutas (< 0.25 µm) and the Mini MOUDI 135-8 (< 0.18 µm). These impactors enable the determination of the mass concentration of the sampled aerosol and the quantification of the various chemical elements collected.

In order to identify additional individual sampling devices capable of sampling and analysing nanometric TiO_2, a bibliographic search in the Scopus database was conducted on 18/02/2021 using the following queries:

- TITLE-ABS-KEY ("titanium dioxide" AND nano* AND "occupational exposure") = 176
- (TITLE-ABS-KEY ("titanium dioxide" AND nano* AND air* AND analysis AND sampl*) = 280

This search resulted in the identification of two sampling devices specifically dedicated to nanomaterials: the Nanoparticle Respiratory Deposition (NRD) and the Personal Nanoparticle Sampler (PENS).

The NRD is described in Cena et al.'s study (Cena, Anthony and Peters 2011). This device comprises an aluminium cyclone sampling the respirable fraction of the aerosol, followed by an impaction stage and finally a diffusion stage. The impinger possesses a cut-off diameter of 300 nm and a sampling flow rate of 2.5 $L.min^{-1}$. However, the study lacks validation data regarding to the collection of a nanometric TiO_2 aerosol. Moreover, some collection substrates used in this device may contain significant amounts of titanium (e.g. nylon mesh bed), making the use of this sampler to assess exposure to titanium dioxide nanoparticles complicated. Other authors have assessed different collection substrates (granular bed, polyurethane foam, non-woven), tested the NRD with a high sampling rate (10 $L.min^{-1}$) or studied it in comparison with a nanomoudi-type impactor. However, even though it has been used in several field studies, none of these aimed to assess nanometric TiO_2 concentrations.

The study by Tsai et al (2012) describes and evaluates the PENS. This device enables the simultaneous sampling of the respirable fraction and nanometric fraction (D50 = 100 nm). The particles are sampled with a cyclone, then pass through a micro-orifice impactor and are finally collected on a Teflon filter. In this study, they assessed the impact of particle load on the collection efficiency of the impactor by using nanometric TiO_2. However, no further tests were carried out and no validation data were obtained with this type of aerosol.

Other samplers are also described in the literature (thermophoretic sampler, mini-cyclone, sensor, inertial filter with layer mesh and capacitive sensor), but no studies implementing them with nanometric TiO_2 were found.

2. Assessment of the measurement methods of nanometric TiO_2 in workplace air

No protocol for measuring nanometric TiO_2 (sampling and analysis) could be identified during the inventory. However, three methods for measuring non-nanometric TiO_2 particles were identified (Table 1).
None of these methods involves the sampling of a nanometric fraction. For each method, air is sampled through a device that collectes the inhalable or respirable fraction onto a quartz fiber filter, or a cellulose ester (CE) membrane, or a polyvinyl chloride (PVC) membrane. The titanium dioxide is subsequently dissolved using various acid mixtures.
These methods therefore differ essentially only in the analytical technique used. Therefore, in this report, they were classified according to this criterion. These analytical techniques enable to quantify the titanium element and the protocols describing these methods are not specific to titanium but relate to the analysis of metals and metalloids

Although the identified protocols do not recommend collecting a nanometrically-sized fraction, or do not specify the sampling device to be used for the respirable fraction, the analytical methods were assessed with regard to the recommended TLVs.
Indeed, as the validation data from the different protocols were not acquired in controlled atmospheric conditions but by doping membranes with solutions, data obtained can be extrapolated for any device that employs the same type of membrane.

The mineralisation methods differ in the listed protocols, in particular according to the support used and the supposed refractory aspect of the particles. These distinctive mineralisation methods can impact the performance of the related protocols, that are implicitly evaluated with regard to the mineralisation method employed.

Table 1 displays theclassification of the identified methods for measuring the concentration of non-nanometric TiO_2 particles (measured as titanium (Ti)) in workplace air along with their respective protocols.

Table 1: Identification of measurement methods for non nanometric titanium dioxide particles (measured in Ti) in workplace air

N°	Method				Protocols
	Sampling	Sampling device and sampling medium	Mineralisation	Analyse	
1	Active	CFC, cyclone or impactor Quartz fiber filter or EC or PVC membrane	Different acid mixtures and mineralisation methods (hot plate, microwave)	Atomic absorption (AA) (absorption or emission)	NF X43-275 (2002)
		CFC + accucap Quartz fiber filter		AA electrothermal atomisation	INRS MétroPol M120
		CFC + accucap Quartz fiber filter		AA flame atomisation	INRS MétroPol M121
		CFC EC membrane		AA	OSHA id 121
2	Active	Inhalable or respirable convention compliant sampler Filter or membrane (unspecified nature)		ICP-AES	NF ISO 15202-1 , -2 et -3
		CFC + accucap Quartz fiber filter			MétroPol M122
		CFC + accucap EC membrane			MétroPol M125
		CFC + accucap EC membrane			NIOSH 7306
		CFC EC membrane			MétroPol M124
		CFC EC membrane			NIOSH 7302
		CFC EC membrane			NIOSH 7300
		CFC PVC membrane			NIOSH 7304
3	Active	Inhalable or respirable convention compliant sampler EC membrane	-	XRF	HSE mdhs 91-2
		FSP2 (respirable fraction sampler) Membrane (unspecified nature)	Acetone	total reflection X-ray fluorescence (TXRF).	IFA 8765 (2008)
		GSP3,5 (inhalable fraction sampler) Membrane (unspecified nature)			IFA 8766 (2008)

1.1. Assessment of the compliance of sampling devices

Sampling devices were assessed for compliance with the conventional respirable fraction during the expert appraisal concerning the assessment of measurement methods for dust without specific effects (DWSE) (Anses, 2020a). Some of the devices assessed in 2020 are used in the protocols identified for this report. Their classification with respect to their compliance to conventional fractions is recalled below:

– - FSP2: classified as category 2 regarding compliance with the respirable fraction.

The 2020 Anses report identifies additional sampling devices for the respirable fraction classified in category 2 compatible with PVC membranes: cyclones (sampling flow rate of 1.5 to 2 $L.min^{-1}$), high-flow cyclones (model GK 4.162 at 9 $L.min^{-1}$, FSP10 at 10 $L.min^{-1}$).

None of the sampling devices implemented in the listed protocols allows to collect a nano-sized fraction.

1.2. Assessment of analysis methods

The protocols describing methods 1, 2 and 3 ((Table 1) use sampling devices equipped with PVC or EC membranes.

Method 1: Atomic absorption (AA)
Method 1 involves sampling by pumping onto a filter or membrane support. After sampling, the support is weighed and then mineralised in acid medium to perform an AA assay.
The identified protocols do not provide any validation data for titanium, with the exception for OSHA protocol ID 121, that notes a detection limit (LOD) of 0.04 µg(Ti).mL^{-1}. The - limit of quantification (LOQ) estimated from the LOD is 1 µg (Ti) on the substrate. To reach a LOQ equal to one tenth of either the 8h-OEL or one tenth of the 15min-STEL, it would be necessary to sample for 8 hours at a flow rate of 43.4 $L.min^{-1}$ or to sample 15 minutes at a flow rate of 1833 $L.min^{-1}$.

As reaching one tenth of the 8h-OEL and of the 15min-STEL requires sampling rates that are incompatible with both respirable fraction sampling devices and individual sampling devices mentioned earlier (impingers, PENS and NRD), this method is classified as category 3 for the technical control of the 8h-OEL, the 15min-STEL, and the short-term exposure monitoring.

Method 2: Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES)
Method 2 involves sampling particles by pumping them through a filter or membrane, which are then digested by hot acid solutions (heated by hotplate or microwave), using various mineralisation methods. Analysis is performed by ICP-AES.

The protocols provide little validation data for titanium. All the protocols, except for the INRS MetroPol M124 protocol, state the LODs and/or LOQs for titanium. However, the minimum sampling flow rate required to achieve LOQs equivalent to one tenth of the 8h-OEL with an 8 hours sampling period is 6 $L.min^{-1}$, whilst the flow rate for LOQs less than one-tenth of the 15min-STEL, with a 15 minutes sampling period, must be above 39 $L.min^{-1}$.

The minimum sampling rates required are not compatible with the individual respirable fraction sampling devices used in the listed protocols. Other individual sampling devices for the respirable fraction with compatible flow rates were evaluated as part of the expert report on DWSE (Anses 2020a): these are the CIP10-R for the respirable fraction, the PPI8 impactors, the FSP10 and the GK 4.162.

However, the CIP10 is not suitable for sampling the finest particle sizes (Anses 2020a). Moreover, PU foams are used as sampling media and the quantification limits reported in the listed protocols were established on dissimilar media, thus rendering them inapplicable. The same applies to the PPI8. The FSP10 and GK 4.162 operate at a flow rate of 10 and 9 $L.min^{-1}$ respectively and are suitable for use with PVC or EC membranes. They are classified as category 2 regarding compliance with the conventional respirable fraction due to an overestimation for particles with an aerodynamic diameter of less than 4 µm and an underestimation for particles with a diameter of between 4 and 10 µm (Anses 2020a). Considering an 8 hour sampling using a FSP10 or a GK 4.162 cyclone and the LOQ determined on PVC membrane by NIOSH (NIOSH 7300), it should be possible to reach a LOQ of 0.034 $µg(Ti).m^{-3}$, less than one tenth of the 8h-OEL. It should be noted that these devices can induce a significant pressure drop and may be restrictive owing to the heavier weight of the sampling pump.

Among the individual sampling devices described above that allow off-line chemical analysis (impactors, PENS and NRD), only the Sioutas provides a flow rate compatible with the required flow rate to reach one-tenth of the 8h-OEL. However, this device uses different collection media to those for which the LOQs have been established, and that have not been validated. Nanometric particles are collected on the end filter. As this is a stage of filtration, any type of support could be used, such as an EC or PVC membrane, subject to validation and careful management of pressure drops during sampling.

The required sampling rates to achieve 0.1 or 0.5 *15min-STEL are not compatible with the devices used for sampling the respirable fraction or with the individual samplers mentioned earlier (impingers, PENS, NRD). The method is thus classified as category 3 for the technical control of the 15min-STEL and the short-term exposure monitoring.
None of the sampling devices used in the protocols has a flow rate sufficient to reach one tenth of the 8h-OEL (greater than 6 $L.min^{-1}$). Among the individual sampling devices (respirable fraction, impactors, samplers dedicated to PENS and NRD nanoparticles), the FSP10, the GK 4.162 and the Sioutas have an adequate flow rate. The FSP10 and the GK 4.162 are classified as category 2 regarding their compliance with the conventional respirable fraction, but there is no validation data directly obtained with these devices and a PVC membrane, in particular uncertainties data. The Sioutas collection medium has not been validated for the analysis of nanometric TiO_2. However, a PVC membrane could be used as terminal filter, subject to validation and careful management of pressure drops during sampling. This measurement method is therefore classified as category 3(*) for the technical control of the 8h-OEL.

It should be noted that none of the listed protocols describes the analysis of Ti by inductively coupled mass spectrometry (ICP-MS). However, this technique, more sensitive than ICP-AES, should make it possible to obtain lower LOQs. Validation data for titanium analysis by ICP-MS on air samples was retrieved from the SCOPUS database on 10th January 2022 using the following query:

- (TITLE-ABS-KEY (titanium) AND TITLE-ABS-KEY (analysis) AND TITLE-ABS-KEY (icp AND ms) AND TITLE-ABS-KEY (air*)) = 74

This search identified 5 articles that present validation elements for the ICP-MS titanium analysis method. The validation was conducted with samples from the National Institute of Standards and Technology (NIST), specifically SRM1648/SRM1648a or 2783 types. The determination of LODs used either white filters or filters doped with Ti solutions at a concentration of 10 $mg.L^{-1}$. Available data comprises recovery rates (70 to 112% depending on the mineralisation methods), biases, fidelity and expanded uncertainties established in relation to NIST-certified values. It should be noted that these data are not validated for the Ti concentration ranges corresponding to the values expected for the 8h-OEL and 15min-STEL ((Kulkarni et al. 2003); (Pekney and Davidson 2005); (Kulkarni et al. 2007); (Celo et al. 2010); (Salcedo et al. 2014)). The LODs are about 10 ng (Ti) per filter.

These data highlight that ICP-MS has a higher sensitivity than ICP-AES. The quantification limits achieved are below one tenth of the 8h-OEL and the 15min-STEL (accounting for a sampled air volume of 960 L and 30 L, respectively).

Method 3: X-ray fluorescence (XRF)

Method 3 involves taking a sample on a filter or membrane medium. After sampling, the support is weighed and then mineralised in acidic medium for XRF analysis.

To achieve performance levels as set out in the protocol, this method requires a control of the loading rate and particle size of the sample collected. Performance may also be impacted if the sample is heterogeneous by nature or due to the sampling device's nature. If there is any doubt, concentrations obtained from this non-destructive method can still be verified using an alternative method (ICP-OES or ICP-MS after acid digestion of the samples). In addition, the protocol does not provide validation data for Ti.

IFA protocols 8765 and 8766 describe a method that involves sampling respectively the respirable fraction (using an FSP, at 2 or 10 $L.min^{-1}$) or the inhalable fraction (using a GSP at 3.5 or 10 $L.min^{-1}$), followed by extraction using acetone and analysis using total reflection X-ray fluorescence. The only available validation data consist of the limits of quantification and a coefficient of variation related to precision.

The limits of quantification, based on samples taken over 8 hours or 15 minutes, exceed one-tenth of the 8h-OEL and one-tenth of the 15min-STEL. This method is therefore classified as category 3 for the technical control of the 8h-OEL, the 15min-STEL and the short-term exposure monitoring.

Conclusions of the collective expert appraisal

No method was found for measuring nanometric TiO_2, but three methods for measuring non-nanometric TiO_2 particles were identified.

- Active sampling - acid mineralisation, analysis by atomic absorption (AA)
- Active sampling - acid mineralisation - analysis by inductively coupled plasma-atomic emission spectrometry (ICP-AES)
- Active sample - analysis by X-ray fluorescence (XRF)

These methods enable the analysis of the titanium element, are not specific to titanium dioxide and involve sampling of the inhalable or respirable fraction. Although not all of the listed protocols recommend sampling of the respirable fraction, the analysis methods were assessed regarding the recommended OELs, because these data were obtained by spiking membranes with solutions.

The identified protocols offer limited validation data. The reported limits of quantification are higher than the limit values recommended by the HRV Committee.

It is worth mentionning that certain individual sampling devices enable to sample particles in sizes close to the nanometer scale, and to determine the mass concentration of the nanometric fraction of the sampled aerosol and as well as to quantify the different chemical elements present. These are some impactors (Marple (< 0.52µm), the Sioutas (< 0.25µm), the Mini MOUDI 135-8 (< 0.18 µm)) and devices specifically developed for nanomaterials (NRD and PENS). No validation data for the analysis of nanometric TiO_2 using these sampling devices were identified.

Method 1 is classified as category 3 for the regulatory technical control of the 8h-OEL, the 15min-STEL and the short-term exposure monitoring, because the quantification limit is too high and the required sampling rate is not compatible with individual sampling devices, whether they are sampler of the respirable fraction, impactors or samplers dedicated to nanoparticles (NRD, PENS).

Method 2 is also classified as category 3 for the technical control of the 15min-STEL and the short-term exposure monitoring for the same reasons. It is classified as category 3* for the regulatory technical control of the 8h-OEL. Indeed, among respirable fraction individual samplers classified as category 2 in terms of compliance with the conventional respirable fraction ((Anses 2020a), only the FSP10 and the GK 4.162 can be used with a PVC membrane (the medium with the lowest LOQ) and maintain a sufficient flow rate (10 and 9 $L.min^{-1}$) which should enable to reach one-tenth of the 8h-OEL. However, no validation data obtained directly with these devices and the PVC membrane is available, particularly regarding uncertainties. Furthermore, the Sioutas is a sampling device that can collect sized particles smaller than 250 nm on a single support (terminal filter), which could be an EC or PVC membrane. It provides a flow rate suitable for reaching one tenth of the 8h-OEL and could be used subject to validation and careful management of pressure drops during sampling.

Method 3 requires a control of the loading rate and the particle size of the sample collected in order to achieve the claimed performances. Moreover, the associated quantification limits exceed one tenth of the 8h-OEL and the 15min-STEL. It is therefore classified as category 3 for the technical control of the 8h-OEL, the 15min-STEL and the short-term exposure monitoring.

Thus, no measurement method is recommended for the technical control of the recommended OELs for nanometric TiO_2.
The expert committee recommends the development and validation of a measurement method capable of sampling the respirable fraction and measuring titanium with LOQs that equate to one tenth of both the 8h-OEL and the 15min-STEL. The ICP/MS analysis method, which is usually more sensitive for analysing metals, could be a method of interest. It is recommended to use PVC or EC membranes to optimise quantitative analysis.

In order to document exposure to TiO_2 in nanostructured forms (including aggregates and agglomerates), the committee therefore recommends implementing a measurement strategy combining:

- individual real-time measurement to objectify the nanometric nature of the aerosol

with

- a sample of the aerosol to determine titanium content. This could be a sample of the inhalable fraction, therespirable fraction, a sample using impactors to determine the granulometric distribution, or a sample using one of the devices developed to sample a granulometric fraction close to the nanometric fraction (such as the NRD and PENS samplers).

This strategy is restrictive because it requires multiple sampling devices. However, in the absence of a validated measurement method, it enables to document the presence of nano-sized particles, ensure the particle size distribution of the aerosol and consider aggregates and agglomerates.

Date of validation of the summary by the expert committee for public consultation: 08 December 2022.

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