Director General

Maisons-Alfort, 25 April 2019

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on "Updating knowledge on the hazards, exposures and risks associated with crystalline silica"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 25 April 2019 shall prevail.

On 16 November 2015, ANSES issued an internal request to carry out an expert appraisal to update knowledge on the hazards, exposures and risks associated with crystalline silica and to propose possible risk reduction and prevention measures.

1. Background and purpose of the request

In the context of the work of the "Emergence" group of the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P), an alert concerning the risk of severe silicosis associated with the use of reconstituted stone containing high percentages of crystalline silica (≥ 85%) was sent to the relevant Ministries on 26 June 2015 (Reference: 2015-rnv3p-016).

In fact, several publications have reported cases of severe silicosis associated with the use of reconstituted stones (artificial stones made from quartz and resin) in manufacturing kitchen countertops and bathroom coverings in various countries, particularly Israel, Spain, Italy and the United States. The concerned workers are those who cut and/or produce the material and/or install it in private homes, especially when cutting is done while dry. These types of silicosis can affect very young workers, and latency times may be shorter than those commonly observed for silicosis.

In the United States, the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) published an alert bulletin in February 2015 concerning workers' exposure to silica during the cutting of manufactured countertops, following the identification of several cases of silicosis affecting these workers.

Although the main diseases associated with occupational exposure to silica are known and give rise to compensation under the official recognition of occupational diseases, these cases of silicosis (some of which have required lung transplants) are a warning signal that should raise questions about exposure associated with the use of new materials and products, particularly those containing high levels of silica. ANSES was also asked about the growing use of cat litter containing silica and the associated risks for individuals and also, even more importantly, for the professionals who manufacture or use it in the course of their occupational activity.

Crystalline silica has been classified as "carcinogenic to humans" (IARC, Group 1). It is not currently covered by any European classification (Regulation (EC) No 1278/2008 on Classification, Labelling and Packaging, known as the "CLP" Regulation).

Data from the 2010 SUMER survey indicate that exposure to crystalline silica affects around 294,900 employees in France.

Regulatory occupational exposure limits over eight hours (8h-OELs) have been established by the French Labour Code (Article R. 4412-149) for the three main forms (or polymorphs) of crystalline silica: for quartz at 0.1 $mg.m^{-3}$, and for cristobalite and tridymite at 0.05 $mg.m^{-3}$.

Silicosis associated with work involving inhalation exposure to dust containing crystalline silica can be recognised as an occupational disease under the general compensation scheme (Table 25 pursuant to Articles L. 461-1 to 3 of the French Social Security Code) or the agricultural compensation scheme (Table 22 also pursuant to Articles L. 461-1 to 3 of the Social Security Code).

Lastly, recent research suggests that silica particles may be involved in triggering conditions other than silicosis and bronchopulmonary cancers, namely systemic inflammatory diseases (sarcoidosis, systemic lupus erythematosus, progressive systemic scleroderma, rheumatoid arthritis, etc.) and other diseases (chronic obstructive pulmonary disease, kidney failure, etc.).

The expert appraisal aimed to carry out the following tasks:

- Conduct a review of studies and data on the hazards and health effects of crystalline silica, focusing in particular on carcinogenicity studies, as crystalline silica has been classified as a Group 1 carcinogen by IARC;
- Identify all the diseases associated with exposure to crystalline silica and assess their relevance and cause-and-effect relationships;
- On the basis of this review, explore the feasibility of a proposal for classification and labelling at European level under Regulation (EU) No 1272/2008 (CLP) taking into account the work of IARC, the regulatory context – in particular, the work in the framework of REACh – and discussions on the nanoscale forms of crystalline silica;
- Conduct a study of the crystalline silica sector in order to identify the different uses of crystalline silica, from its extraction to the production and marketing of products containing it, mainly for professionals but also for consumers;
- Assess exposure to different forms of crystalline silica by carrying out a literature review of the available studies;
- Identify the practices/uses involving the highest exposures for professionals and carry out field measurements if necessary. Particular attention should be paid to the emergence of new forms of exposure, as well as to new exposure patterns relating to activities already known to involve exposure;
- Conduct a review of the main regulatory provisions on prevention, protection and compensation for diseases associated with occupational exposure to crystalline silica;
- After considering the relevance of conducting a quantitative health risk assessment for professionals exposed to crystalline silica, the Agency should, where appropriate, propose measures to eliminate or reduce the identified risks.

Amorphous silica was excluded from the scope of the formal request. The hazards and health effects concerning amorphous silica have therefore not been developed in the expert appraisal, although for didactic and comparative purposes, some parts of the report do address amorphous silica.

During the course of the expert appraisal, "work involving exposure to respirable crystalline silica dust generated by a work process" was added to the list of substances, preparations and processes in Annex I to Directive 2004/37/EC[1], as a carcinogenic process according to Directive (EU) 2017/2398 of 12 December 2017. This - in addition to the fact that no uses by consumers of crystalline silica as a substance or mixture resulting in significant inhalation exposure were identified - prompted ANSES's decision not to propose classification or labelling at European level.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal falls within the sphere of competence of the Expert Committee (CES) on "Assessment of the risks related to air environments". ANSES entrusted the expert appraisal to an *ad hoc* working group set up after a public call for applications (the "Crystalline silica" WG). The methodological and scientific aspects of the work were presented to the CES between September 2016 and March 2019. The work was adopted by the CES on "Assessment of the risks related to air environments" at its meeting on 14 March 2019.

The expert appraisal work drew on a summary and critical analysis of the data published in the literature (scientific articles, institutional reports, analytical standards).

Information needed for conducting this expert appraisal was also collected through hearings with representatives of various professional federations, experts and external individuals likely to provide additional information and data relating in particular to the crystalline silica sector and the analysis of crystalline silica in the ultrafine particle fraction.

Various databases were also consulted to supplement the information provided during the hearings or identified in the literature:

- The "quarries and materials" database managed by the French Bureau of Geological and Mining Research (BRGM) in partnership with the Ministry of Ecological and Inclusive Transition. This database is available from the Minéralinfo website (http://www.mineralinfo.fr/).
- The COLCHIC database, which includes all occupational exposure data collected in French companies by the Occupational Health and Pension Insurance Funds (CARSAT) and the French National Research and Safety Institute (INRS).
- The SCOLA (System for the Collection of Information from Accredited Organisations) database, managed by the INRS, which encompasses the results of occupational exposure assessment measurements carried out by accredited organisations as part of the regulatory control of chemical agent exposure values.
- The database of the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P), managed by ANSES, which records data on consultations carried out in occupational disease consultation centres (patient demographics, diseases, exposure, industry sectors, occupations).

[1] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work

- The database of the National Health Insurance Fund for Salaried Workers (CNAMTS) on occupational diseases.
- Databases managed by the Directorate for Research, Studies and Statistics (DARES), centralising the results of the 2010 and 2017 SUMER surveys on medical surveillance of exposure to occupational risks.

The extractions from the COLCHIC and SCOLA databases have been described in *ad hoc* reports produced by INRS. These results have been incorporated into the collective expert appraisal report.

Lastly, an international consultation was carried out with national agencies or authorities in the fields of public health and/or occupational health (Europe, North America, Australia) to collect information on exposure of the occupational and general populations to crystalline silica, on health risk assessments conducted at international level, on occupational diseases, and on current recommendations regarding preventive measures for workers associated with their occupational activities and for the general population.

ANSES analyses the links of interest declared by the experts before their appointment and throughout their work, in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.
The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. Analysis and conclusions of the WG and the CES

The CES on "Assessment of the risks related to air environments" adopted the work of the "Crystalline silica" WG and its conclusions and recommendations as described in this summary, at its meeting of 14 March 2019, and informed the ANSES General Directorate accordingly.

3.1. Summary of results

Crystalline silica (or silicon dioxide, SiO_2) is a naturally occurring mineral in the Earth's crust. Among the three most frequently encountered polymorphs, quartz is the most common, followed by cristobalite and tridymite. Quartz is found in most types of rock, from trace amounts up to levels of over 90%, such as in sand, for example. As for cristobalite, it occurs naturally in volcanic rocks or bentonites[2]. Tridymite is rarer than the other two forms. Crystalline silica is found in most natural mineral-based materials at levels above 0.1%. Of all the minerals, crystalline silica is the most widespread throughout the Earth's crust, and is also a component common to all telluric planets.

- **History and sociology of knowledge of the health risks associated with exposure to crystalline silica**

Regarded as one of the major occupational diseases, a 20th century disease comparable to what cholera may have represented for infectious diseases in the 19th century, pulmonary silicosis has for a long time epitomised (almost) all the health risks associated with occupational exposure to crystalline silica. Nevertheless, medical, toxicological and epidemiological knowledge on the possible diversity of the health effects of crystalline silica (particularly autoimmune diseases) has long been reported, especially in the United Kingdom in the first half of the 20th century, on the initiative of Edgar Leigh Collis, the second medical inspector of His Majesty's Factories, and statistician George Udny Yule.

The International Conference on Silicosis held in Johannesburg in 1930 under the collaborative auspices of the International Labour Office (ILO) and the employers' union of the Transvaal Chamber of Mines led to the recognition of silicosis as an occupational disease associated with exposure to crystalline silica in the social security systems of several countries in the following decades. However, the resulting definition of silicosis was restrictive (limited to the chronic form) and mainly associated with the mining sector. In addition, other health effects potentially associated with occupational exposure to crystalline silica were not taken into account. This event contributed to the field of study of the health risks of crystalline silica and of silicosis itself being restricted for several decades.

The work of the "Crystalline silica" WG serves as a contemporary French chapter in this history. The context coincides with the recent updating of the regulations on occupational exposure to crystalline silica by other health agencies (such as the Occupational Safety and Health Administration, OSHA, in 2016), and recognition by the European Union of the carcinogenic nature of production processes involving crystalline silica (Directive (EU) 2017/2398).

The WG's mission extends the history of the health risks of crystalline silica, encompassing both an expert appraisal approach and a social definition of the diseases in question, and aims to better understand the health effects associated with exposure to crystalline silica by updating knowledge

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[2] Bentonites are colloidal clays, often generated by the modification of tuff (a type of rock with a vacuolar structure) or volcanic ash.

on this topic, in order to propose prevention and management measures that will ultimately be more relevant from a public health perspective.

Sector study

The sector study revealed that many industry sectors are concerned by the issue of crystalline silica, due to its ubiquity in natural materials and its industrial utility. The crystalline silica sector is shown in the diagram in Figure 1.

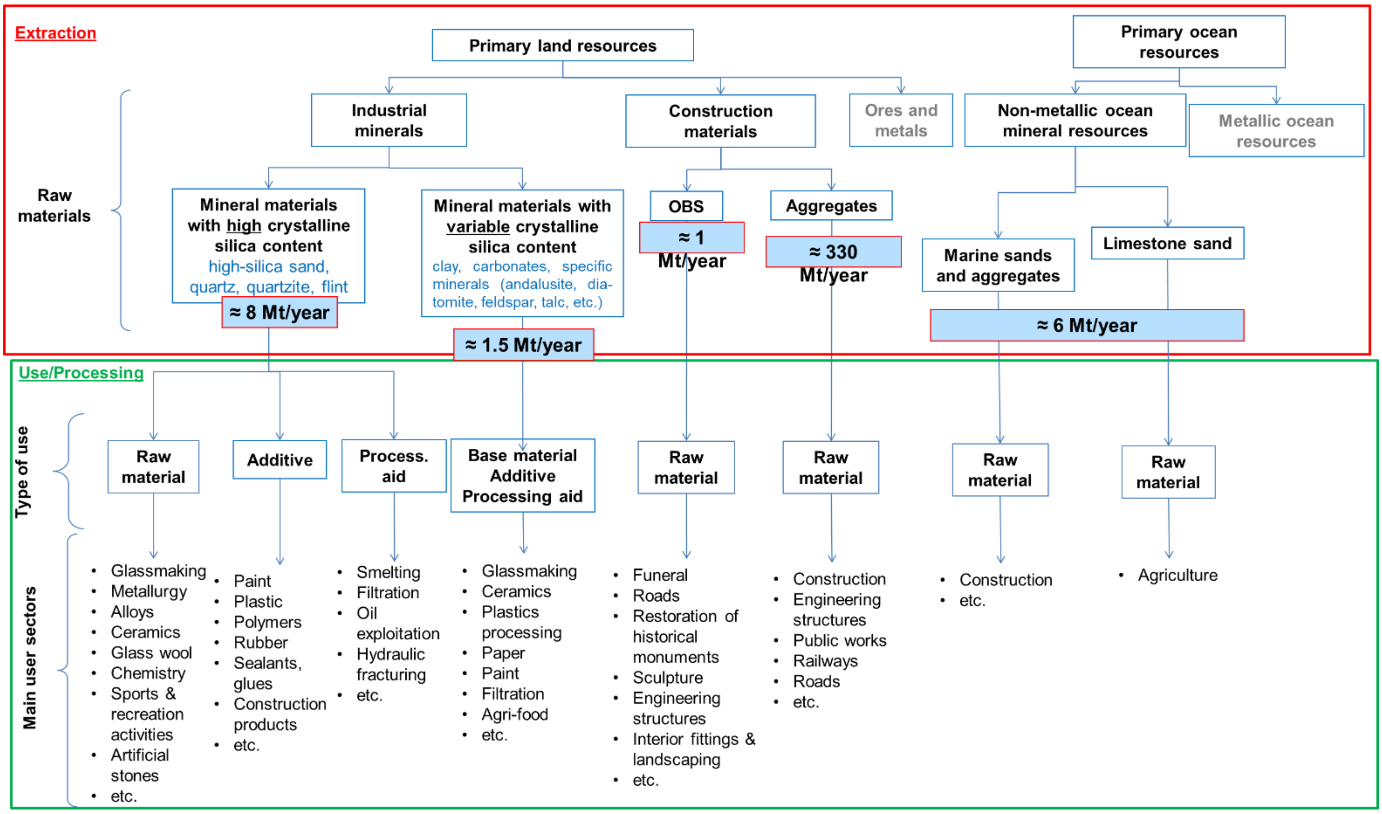

Figure 1: Diagram of the crystalline silica sector

<u>Extraction</u>

The mineral materials extracted for their high crystalline silica content (> 80%) are mainly high-silica sand, quartz and flint. Other industrial minerals with variable crystalline silica content are also extracted.

There are around 4,200 mineral and construction material extraction quarries in France, including around 3,200 aggregate[3] quarries, around 500 ornamental and building stone (OBS) quarries and around 500 industrial rock or mineral quarries. Of these, 68 quarries specifically produce industrial silica. Mining and quarrying directly account for 60,000 jobs, and involve extraction and initial processing operations (crushing, screening).

In France, 16 million tonnes of industrial minerals are extracted per year, including 8 million tonnes of quartz and cristobalite. High-silica sand (characterised by a crystalline silica content above 98%) represents 6.4 Mt/year.

[3] Small pieces of rock (<125 mm) intended to be used for public works, building and civil engineering works.

Around 6 million tonnes of marine aggregates and limestone sand are also extracted annually.

Use/Processing

Industrial minerals are used in raw form or more often processed, which gives them greater added value, either as a raw material (in glassmaking, ceramics, etc.), processing aid[4] (foundry moulds, drilling fluid, etc.) or functional additive[5] *(*paper/paint/varnish/rubber, etc.).

The sector study highlighted that there was no manufacture of "artificial stone" countertops (consisting of more than 85% quartz) in France but that this type of material was imported in the form of slabs and then custom machined by stonemasons in France. Marginal adjustments may then be carried out by stonemasons or kitchen fitters in the customer's home.

With regard to building materials, namely OBS and aggregates, they all contain varying levels of crystalline silica. As a result, all the sectors using these natural materials and all the sectors working with materials manufactured from these natural materials – mainly construction and public works – are potentially affected by exposure to crystalline silica.

Aggregates are used for works on road, railway and utilities networks, containment and other infrastructure uses (58%), for manufacturing concrete (32%, mainly ready-mixed concrete) and, to a lesser extent, for road surfaces (9%) and ballast (1%). The structures mainly concerned are therefore concrete buildings, civil engineering works and roads.

Construction waste is recycled at dedicated facilities, either in quarries or at specific sites. The volumes processed are constantly increasing to meet voluntary or legislative recycling targets (French Act of 17 August 2015 on energy transition for green growth).

Recycled aggregates are used in road construction, mainly for manufacturing road surfaces, or for rehabilitating quarries. In France at present, these aggregates from demolished concrete are only rarely ever recycled to formulate new concrete, which is not the case in other European countries.

As far as OBS is concerned, the sectors mainly concerned are construction, funeral stones and roads.

Lastly, any work in the natural environment, when it involves the manipulation of soil, may, depending on the nature of the soil, generate exposure to crystalline silica (agricultural operations, surveys, earthworks, etc.).

- **Regulatory provisions – Occupational disease tables**

In France, occupational diseases related to exposure to crystalline silica and the associated recognition and compensation criteria are defined in two occupational disease tables: Table 25 under the general compensation scheme (GCS) and Table 22 under the agricultural compensation scheme (ACS). There are some differences between these two tables, in terms of both the recognised diseases and the recognition criteria. For example, systemic lupus is recognised in ACS Table 22 but not in GCS Table 25, while time limits for compensation concerning diseases other than acute silicosis are longer in the agricultural scheme (see Table 1).

[4] An element needed for the implementation of a manufacturing process.
[5] An element used in the composition of certain products to give them particular properties.

Table 1: Occupational diseases associated with crystalline silica

Disease		Table 25	Table 22
Acute silicosis	Pneumoconiosis characterised by bilateral alveolar-interstitial lesions revealed by X-ray or computed tomography examinations, or by anatomopathological findings (lipoproteinosis) when available: this evidence or these findings may or may not be accompanied by rapidly evolving functional respiratory disorders.	X	X
Chronic silicosis	Pneumoconiosis characterised by bilateral micronodular or nodular interstitial lesions revealed by X-ray or computed tomography examinations, or by anatomopathological findings when available; this evidence or these findings may or may not be accompanied by functional respiratory disorders. **Complication**: Pathological manifestations associated with radiological evidence or lesions of a silicotic nature: - **primary bronchopulmonary cancer**; - pleural-pneumoconiotic rheumatoid lesions (Caplan's syndrome).	X	X
Progressive systemic scleroderma		X	X
Disseminated lupus erythematosus (now referred to as systemic lupus erythematosus (SLE) or systemic lupus by this disease specialists)			X
Diseases due to inhalation of mineral dust containing crystalline silicates (kaolin, talc) or graphite: Kaolinosis – Talcosis – Graphitosis		X	X
Diseases due to inhalation of coal dust: Pneumoconiosis	Bilateral interstitial lesions revealed by X-ray or computed tomography examinations or by anatomopathological findings when available, whether or not this radiological evidence or these findings are accompanied by respiratory functional disorders.	X	X
Non-regressive diffuse interstitial pulmonary fibrosis, primary in appearance.		X	

Among the occupational diseases recognised in the tables, bronchopulmonary cancer (BPC) is recognised only as a complication of silicosis. However, it may be recognised under the complementary system[6] if it has been established that it was essentially and directly caused by the victim's normal work. The coexistence of extra-occupational risk factors such as smoking usually prevents this recognition.

Most European countries also have lists of diseases that can be recognised in a compensation system after occupational exposure to crystalline silica. However, unlike the French tables, these lists do not contain any recognition criteria (medical criteria, administrative condition for eligibility of the application, exposure); at most, some of the lists associate an indicative series of occupations with the disease.

These countries also use an "off-list" or "complementary" system of recognition, in which the victim has to prove the occupational origin of his or her disease. Silicosis is recognised in all these countries. Bronchopulmonary cancer (BPC) caused by crystalline silica is recognised as an

[6] The primary health insurance fund may recognise the occupational origin of the disease after a reasoned opinion from a Regional Committee for the Recognition of Occupational Diseases (CRRMP).

occupational disease in Germany and the United Kingdom, systematically in association with silicosis. It can be recognised as an occupational disease in Italy under the "off-list" system.

The information collected did not reveal whether other diseases caused by crystalline silica have already been recognised as occupational diseases under the "off-list" system in other countries.

- **Regulatory provisions – Occupational exposure limits (OELs)**

Under the French Labour Code, crystalline silica is currently recognised as a hazardous chemical agent, but not as a carcinogen. The rules specific to control of chemical risks apply. A binding 8h-OEL has been defined for each polymorph: 0.1 $mg.m^{-3}$ for quartz, 0.05 $mg.m^{-3}$ for cristobalite and tridymite. In the presence of respirable dust containing one or more forms of crystalline silica and other non-silicogenic dust, an exposure index (EI) taking into account the exposure levels to each polymorph and to non-silicogenic respirable dust is also defined[7] and must be less than 1.

Directive (EU) 2017/2398 of the European Parliament and of the Council of 12 December 2017[8] amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work classifies "work involving exposure to respirable crystalline silica dust generated by a work process" as carcinogenic, and defines a limit value for respirable crystalline silica dust of 0.1 $mg.m^{-3}$ over 8 hours, regardless of the crystalline silica polymorph.

In 2016, OSHA established an 8h-TWA of 0.05 $mg.m^{-3}$ for respirable crystalline silica and proposed the value of 0.025 $mg.m^{-3}$ as the action level. The latter value also corresponds to the limit value for crystalline silica established by the American Conference of Governmental Industrial Hygienists (ACGIH) in 2010.

All these 8h-OELs are average values that do not take exposure peaks into account.

In France, the Public Health Code and environmental regulations have not defined any regulatory limit values for the general population.

It should be noted that under the regulations relating to classified installations for environmental protection (ICPE, within the meaning of Article L.511 of the French Environmental Code), certain activities[9] subject to authorisation require dust emissions to be monitored, but do not specifically take crystalline silica emissions into account. Crystalline silica concentrations may be measured during impact assessments, but the data are not centralised.

- **Measurement methods**

Standardised and recognised methods for measuring crystalline silica involve sampling the respirable fraction of the aerosol[10], followed by an analysis of crystalline silica. Regarding sampling,

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[7] $EI = C_{NSRD}/V_{NSRD} + C_Q/V_Q + C_C/V_C + C_T/V_T$, where C_{NSRD}, C_Q, C_C and C_T are the measured concentrations of non-silicogenic respirable dust, quartz, cristobalite and tridymite, and V_{NSRD}, V_Q, V_C and V_T are the respective limit values.

[8] Published in the Official Journal of the European Union of 27 December 2017.

[9] Quarrying activities (Section 2510 of the ICPE nomenclature), facilities for grinding, crushing, screening, bagging, spraying, cleaning, sieving, mixing stones, pebbles, ores and other natural or artificial mineral products or inert non-hazardous waste (Section 2515 of the ICPE nomenclature), transit stations for unbagged powdered mineral products such as cement, plaster, lime, filler sands or powdered inert non-hazardous waste (Section 2516 of the ICPE nomenclature), and transit stations for mineral products or inert non-hazardous waste (Section 2517 of the ICPE nomenclature).

[10] The respirable fraction is defined by EN 481 "Workplace atmospheres - Size fraction definitions for measurement of airborne particles" and corresponds to the mass fraction of inhaled particles that penetrate the unciliated airways. The respirable convention defines the target specifications for respirable fraction samplers: the percentage of the inhalable fraction convention to be collected at an aerodynamic diameter in micrometres shall be given by a cumulative log-normal distribution with a median of 4.25 µm and a geometric standard deviation of 1.5 (CEN, 1993).

many devices are available and can be classified according to their sampling rates: highflow rate (> 4L.min^{-1}), or low flow rate (< 4 L.min^{-1}).

Among the high flow rate samplers, the CIP-10 has the disadvantage of underestimating the finest fraction (< 2.5 µm). However, according to several field and laboratory studies comparing several analytical devices and techniques, the different measurement methods for crystalline silica do not lead to statistically distinct results.

The two main methods for analysing crystalline silica are X-ray diffraction (XRD) and Fourier-transform infrared (FTIR) analysis. These techniques can be implemented directly or indirectly (see Figure 2). XRD can identify crystalline materials present in the sample, unlike FTIR, which only analyses the vibrations of molecular bonds. It has the advantage of being able to anticipate possible interference during quantitative analysis, and therefore to choose the most suitable diffraction peak (non-interfered and sufficiently sensitive).

For 8h sampling durations, the limits of quantification range from 0.012 to 0.17 mg.m^{-3}, depending on the sampling device and analytical technique.

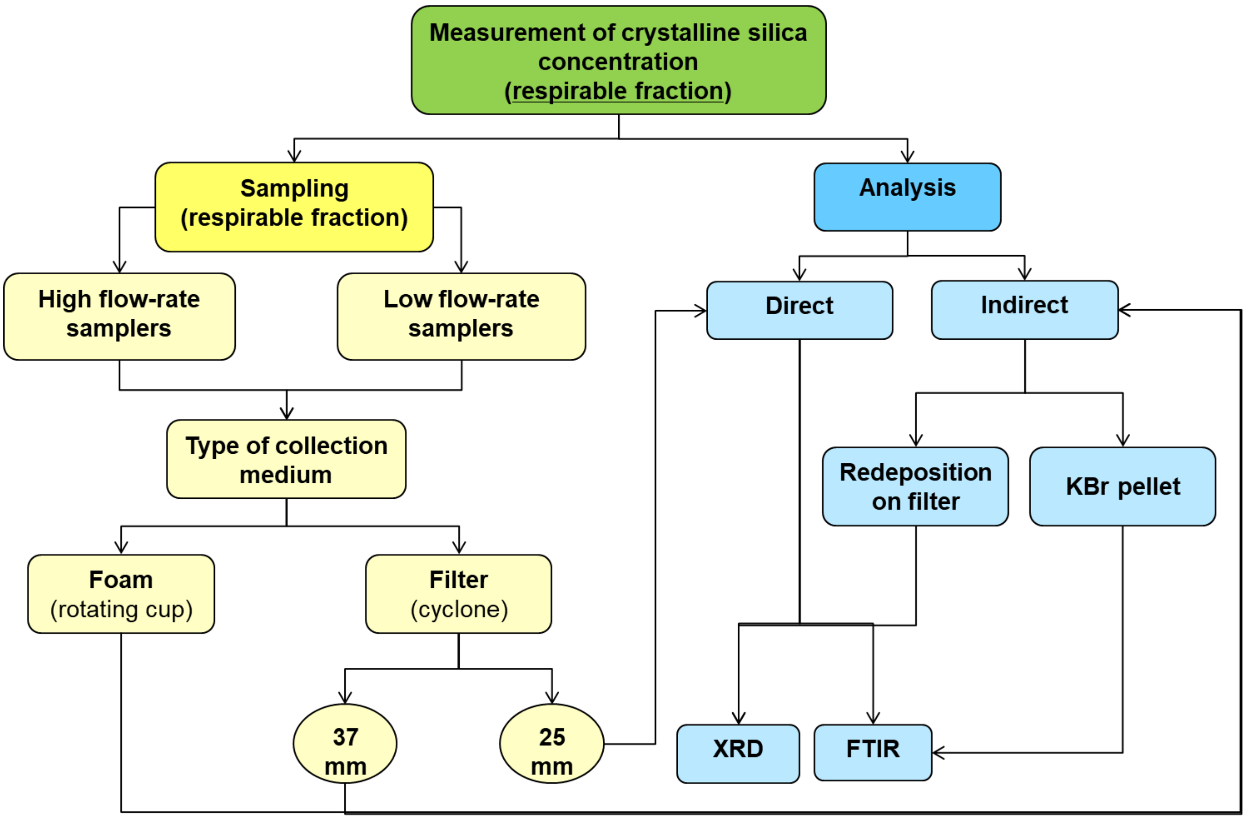

Figure 2: Methods for measuring crystalline silica in air

However, it should be noted that the sampling and analysis methods currently used are unable to take into account three parameters liable to modify the biological and therefore pathological response: exposure peaks during the work shift and *a fortiori* over the duration of each job concerned, the particle size distribution in the respirable fraction (especially the fine and ultrafine fraction), and the surface of the inhaled particles (particularly the surface reactivity associated with freshly fractured particles).

It should also be noted that environmental measurement methods for crystalline silica are not standardised. Crystalline silica has sometimes been analysed in the PM_4 fraction (similar to the respirable fraction) and also in the $PM_{2.5}$ or PM_{10} fractions. There are no standardised methods for determining crystalline silica in ultrafine particles.

- **Crystalline silica exposure data**

Extraction from the COLCHIC and SCOLA databases

The measurements recorded in the COLCHIC and SCOLA databases were carried out with different objectives (prevention for COLCHIC and regulatory control for SCOLA) and provide additional insights into exposure levels. The data provided to ANSES cover the periods 1997-2016 for COLCHIC and 2007-2016 for SCOLA. Only individual measurement data were analysed because they were considered more representative of occupational exposure.

It should be noted that in each of the two databases, more than 40% of the quartz measurements, more than 90% of the cristobalite measurements and almost 100% of the tridymite measurements were below the limit of quantification.

For the period 2007-2016, the SCOLA database contains 10 times more crystalline silica measurements than the COLCHIC database. The industry sectors investigated were different. The most represented industry sectors in terms of number of measurements in the SCOLA database over the period 2007-2016 were "mining and quarrying" (36% of the measurements), "manufacture of rubber and plastic products and other non-metallic mineral products" (36% of the measurements) and "manufacture of basic metals" (7% of the measurements). In COLCHIC over the same period, the most frequently measured industry sectors were: "manufacture of basic metals" (29%), "construction" (22%), and "manufacture of other non-metallic mineral products".

Overall, exposure levels in the construction sector declined from 1997 to 2003 (COLCHIC data) and then stabilised. There was no clear trend for the other industry sectors. A more specific analysis of the data for the 2009-2011 and 2015-2016 periods (corresponding to the 2010 and 2017 SUMER surveys) indicated, for most of the industry sectors in which this analysis could be carried out, a statistically significant increase in the number of measurements exceeding 0.1 $mg.m^{-3}$, 0.05 $mg.m^{-3}$ and 0.025 $mg.m^{-3}$ between the two periods.

The industry sectors with the highest levels of exposure were construction, mining and quarrying, manufacture of basic metals and manufacture of non-metallic mineral products.

The tasks with the highest exposure medians for each of these two databases were as follows:

- COLCHIC: "finishing operations: other tasks not otherwise codified" in "casting of iron" (NAF 2451Z); "structural works: other tasks not otherwise codified" in "operation of historical sites and buildings and similar visitor attractions" (NAF 9103Z); "deflashing, manual deburring (grinding wheel, abrasive belt, knife)" in "casting of iron" (NAF 2451Z); "mechanical abrasion machining" in "casting of iron" (NAF 2451Z) (medians ranging from 0.07 to 0.13 $mg.m^{-3}$);
- SCOLA: "other structural works, not otherwise codified" in "construction of other buildings" (NAF 4120B), "machining, assembly, welding, gluing, assembly lines, other jobs not otherwise codified" in "construction of other buildings" (NAF 4120B), "concrete surface works: bush hammering, abrading, etc." in "manufacture of concrete products for construction purposes" (NAF 2361Z), "operation and supervision of mixers in the manufacture of ceramic tiles and flags" (NAF 2331Z) (medians ranging from 0.138 to 0.472 $mg.m^{-3}$).

The tasks with the greatest proportion of exposure measurements exceeding the current 8h-OEL (0.1 $mg.m^{-3}$) were "other structural works, not otherwise codified" and "machining, assembly, welding, gluing, assembly lines, other jobs not otherwise codified" in the "construction of other buildings" sector (NAF 4120B), as well as "operation and supervision of mixers" in "manufacture of ceramic tiles and flags" (NAF 2331Z).

The occupations for which exposure levels most frequently exceeded the current limit value of 0.1 mg.m^{-3} were:

- SCOLA: finisher ("construction of other civil engineering projects" sector), industrial mason-assembler ("construction of other buildings" sector), palletiser ("manufacture of concrete products for construction purposes" sector) (medians from 0.264 to 0.443 mg.m^{-3});
- COLCHIC: stonemason ("cutting, shaping and finishing of stone" sector), finishing worker (deburring, casting ("casting of iron" sector)), deflasher-deburrer (manufacture of basic metals ("casting of iron" sector)) (medians from 0.081 to 0.0865 mg.m^{-3}).

<u>Data from the scientific literature:</u>

A literature review starting in 2000 and relating to North American and European data was conducted to supplement the exposure data from the COLCHIC and SCOLA databases. It highlighted the fact that depending on the industry sector, the geometric means (GM) of measured exposure could be much higher than 0.1 mg.m^{-3} (road construction sites (Hammond 2016, Middaugh *et al*. 2012), coal-fired power plants (Hicks and Yager, 2006), hydraulic fracturing (Esswein *et al*., 2013)).

The review focused on the most widely investigated industry sector: construction. According to the selected studies, the occupations involving the highest exposure (8h average) are sanders (maxGM = 1.28 mg.m^{-3}), demolition workers (GM = 1.1 mg.m^{-3}) and concrete workers (maxGM = 0.72 mg.m^{-3}) (IRSST 2011, Garcia *et al*. 2014, Van Deussen 2014). These studies show that overexposure to crystalline silica is possible even with the use of a vacuum device at the source. Several studies have demonstrated that even with exposure levels to respirable dust containing (or potentially containing) crystalline silica below 5 or even 3 mg.m^{-3}, exposure levels to crystalline silica exceeded 0.1 mg.m^{-3} (Garcia *et al*. 2014, Van Deurssen *et al*. 2014, Bakke *et al*. 2001, Kirkeskov *et al*. 2016, Tjoe Nij *et al*. 2002). Most of these studies did not mention whether collective or personal protective measures were implemented at the time of sampling.

In general, the exposure levels measured during a task are higher than the exposure levels measured over an 8-hour period.

No specific literature search was conducted to document the effectiveness of preventive measures. The available devices and their effectiveness depend mainly on the tools used, the tasks performed and the environmental conditions. Nevertheless, some of the reviewed studies aimed to assess this effectiveness and mainly concerned work on concrete (cutting, drilling, sawing or grinding concrete). They confirm a significant reduction in crystalline silica concentrations with the use of local exhaust ventilation (LEV) or during wet work – one possibly combined with the other – with variable effectiveness depending on the methods used, and sometimes with residual values exceeding the 8h-OELs.

A few recent studies have focused on the artificial stone countertop sector (Simcox *et al*. 1999, Phillips *et al*. 2013, Zwack *et al*. 2016, Qi & Echt 2016, Qi & Lo 2016, Cooper *et al*. 2016 and Johnson *et al*. 2017), and especially the cutting, polishing, chamfering, etc. of these countertops using portable hand tools (pneumatic or electric). The aim was to document:

- Operators' exposure levels related to the activities and preventive measures over the duration of the work shift;
- The effectiveness of the preventive measures used to limit this exposure.

Levels of exposure to crystalline silica measured during these tasks can be high (0.0578 to more than 4 mg.m^{-3}) and although wet work, coupled with LEV, can reduce exposure to respirable dust and crystalline silica by a factor of 10 (or more), exposure levels remain high (> 0.05 mg.m^{-3}).

The review also focused on the agricultural sector, since it is not investigated in the COLCHIC and SCOLA databases. Very few studies with individual measurements of exposure to crystalline silica were identified. They point out that (i) exposure levels to crystalline silica can be high (> 0.1 $mg.m^{-3}$), especially in cases where the soil contains a high percentage of quartz, and (ii) for the same soil type, the quartz content in respirable dust can vary greatly. Many determinants influence exposure levels, in particular the nature of the crops grown, the processes used, the soil type and certain environmental conditions (soil moisture, air humidity, wind speed) (Swanepoel et *al*. 2010, 2011, 2018, Archer *et al*. 2002, Lee *et al*. 2004).

Ambient air exposure data/general population

No studies seeking to assess environmental concentrations of crystalline silica in outdoor air in France were identified. Several studies in the United States, the United Kingdom and Italy measured crystalline silica in urban areas in PM_{10}[11] at concentrations on average below 3 $\mu g.m^{-3}$, and in PM_4[12] at concentrations on average below 0.34 $\mu g.m^{-3}$. Several studies have focused on the contribution of certain activities to background levels of crystalline silica (measurements of crystalline silica in PM_{10} or PM_4): around sand quarries, near waste heaps, around work sites (construction, demolition), etc. Measurements of environmental concentrations of crystalline silica generally remain below 20 $\mu g.m^{-3}$. When higher values have been measured locally, it is generally because the samples were taken in the immediate environment of an industrial site with crystalline silica emissions and/or under climatic and meteorological conditions that significantly contributed to increasing atmospheric crystalline silica levels (windy weather, dry climate, warm air currents from Africa, etc.).

Although no published studies documenting the exposure of individuals to crystalline silica during DIY activities have been identified, they may be exposed to levels in excess of 0.1 $mg.m^{-3}$. Regarding the use of cat litter, its handling can lead to crystalline silica exposure levels of up to 0.107 $\mu g.m^{-3}$ over 24 hours (hearing with IMA Europe[13] and Eurosil[14] on 07/09/2018).

Crystalline silica measurements in ultrafine particles (UFPs)[15]

Since measurements of exposure to crystalline silica only concern the respirable fraction of the aerosol, the Working Group questioned the presence of crystalline silica in UFPs. Some studies show that high-energy processes can emit large quantities of UFPs. However, no studies have investigated crystalline silica in the ultrafine fraction of the aerosol.

During a hearing with the WG (08/02/2019), the National Institute for Industrial Environment and Risks (INERIS) reported the results of an experimental study on the cutting and drilling of construction materials, preliminary work carried out at the request of the national grouping of occupational physicians in the construction sector (GNMST-BTP). This study revealed the generation of crystalline silica nanoparticles. In practice, no data are currently available in the literature that could be used to assess the health risks associated with ultrafine crystalline silica particles.

- **Prevalence of exposure: 2010 and 2017 SUMER surveys**

[11] PM_{10}: refers to particles with an aerodynamic diameter less than 10 micrometres.
[12] PM_4: refers to particles with an aerodynamic diameter less than 4 micrometres.
[13] IMA Europe (Industrial Minerals Association) – this manufacturers' association brings together European associations specific to industrial minerals and includes more than 500 companies.
[14] Eurosil (European industrial silica producers) – this association brings together European producers of industrial silica and has 40 members.
[15] UFPs: particles with an aerodynamic diameter less than 0.1 micrometres, also known as unintentional nanoparticles

According to the 2010 SUMER survey, 294,852 employees (adjusted headcount) were exposed to crystalline silica, accounting for 1.36% (weighted rate) of the employee population covered by the survey. According to the 2017 survey, the number and proportion of employees exposed to crystalline silica are increasing. Thus 365,194 employees were exposed to crystalline silica (1.47% of the employed population), which represents an increase of 0.11 points (source DARES). These results may be underestimated, due to the way in which these surveys are conducted. Indeed, estimates of exposure to crystalline silica are based on employees' declarations of their activities during the week preceding the medical examination and on the occupational physicians' knowledge of the jobs.

In 2017, as in 2010, the sector with the highest proportion of exposed employees was construction, with 170,414 workers exposed to crystalline silica (compared to 156,800 in 2010), accounting for 12.3% of workers in the sector (weighted proportion identical to that observed in 2010). The next largest sectors were "other manufacturing; repair and installation of machinery and equipment" (9.3% in 2017 compared to 3.5% in 2010), "manufacture of basic metals and manufacture of fabricated metal products except machinery and equipment" (7.9% compared to 5.3%) and "manufacture of rubber and plastic products and manufacture of other non-metallic mineral products" (6.8% compared to 5.5%).

■ Characterisation of occupational exposure

The purpose of characterising the exposure of the French occupational population to crystalline silica was to estimate the number of people exposed above a certain threshold, for different industry sectors. To do this, data from the COLCHIC and SCOLA databases were cross-referenced with prevalence data from the 2010 and 2017 SUMER surveys (see Figure 3:).

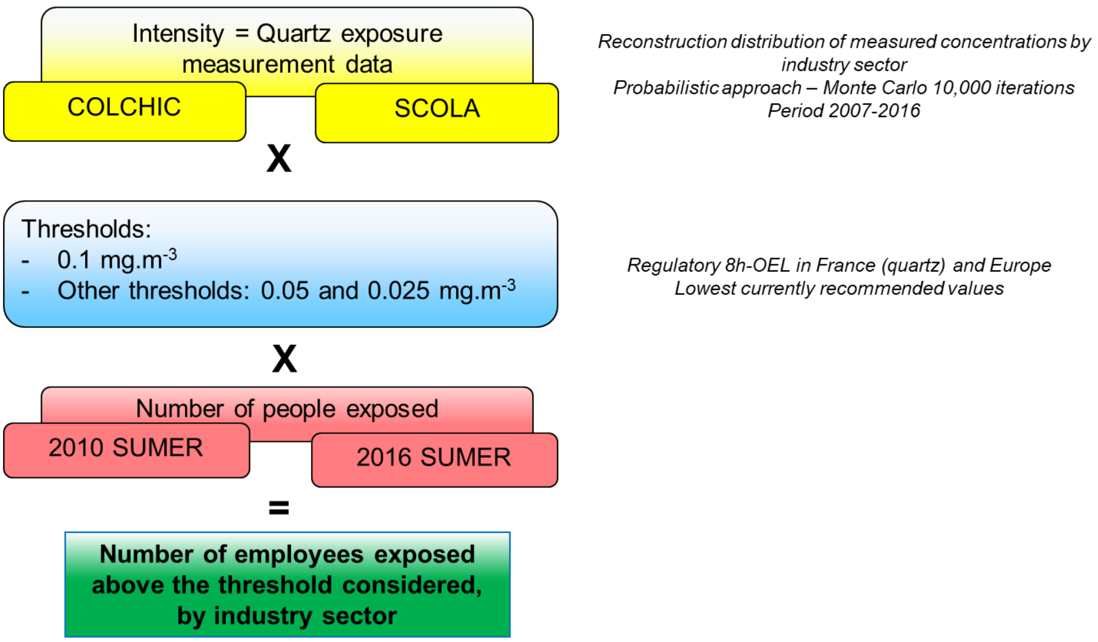

Figure 3: Methodology of exposure characterisation

The thresholds taken into account correspond to the regulatory 8h-OEL in France for quartz (0.1 mg.m^{-3}), the 8h-OEL for crystalline silica recommended by various organisations including

SCOEL[16] and OSHA[17] (0.05 mg.m^{-3}), and the lowest current 8h-OEL (0.025 mg.m^{-3}), defined by ACGIH and adopted as the action threshold by OSHA.
Given the small quantity of exposure data available for cristobalite and tridymite, this characterisation was only performed using quartz exposure data.

Several estimates were calculated: an overall estimate based on exposure data recorded in COLCHIC and SCOLA over the period 2007-2016, as well as a more detailed estimate based on exposure data determined over a period of time similar to that of the 2010 and 2017 SUMER surveys. These estimates could only be made for those industry sectors for which exposure measurements were available in sufficient number, and for which employees were identified in the SUMER surveys as exposed to crystalline silica (see Annex 1).

Depending on the method used, between 23,000 and 30,000 employees may be exposed above 0.1 mg.m^{-3}, which represents about 8% of employees exposed to crystalline silica (and 0.1% of the total wage-earning population, of which the SUMER surveys are representative[18]). Among these employees, between 14,600 and 22,400 come from the construction sector[19] (i.e. 66 to 75% of the total population exposed above 0.1 mg.m^{-3}).

Around 61,000 to 70,000 employees are estimated to be exposed above 0.025 mg.m^{-3}, representing around 19 to 21.5% of employees exposed to crystalline silica (around 0.3% of the total employee population). The construction sector accounts for 61 to 69% of the population exposed above 0.025 mg.m^{-3}.

The analysis by industry sector indicated that the proportion of employees exposed above the thresholds tended to increase between 2009-2011 and 2015-2016 for the following sectors:

- According to the SCOLA data: Other mining and quarrying[20] (NAF08), Manufacture of chemicals and chemical products (NAF 20), Manufacture of other non-metallic mineral products[21] (NAF 23), Manufacture of basic metals[22] (NAF 24), Manufacture of fabricated metal products, except machinery and equipment (NAF 25);
- According to the COLCHIC data: Civil engineering (NAF 42), Specialised construction activities (NAF 43).

Health effects

To update knowledge on the health effects associated with crystalline silica, the WG first identified and critically reviewed three recent summary reports published by European and international health agencies (IARC 2012; OSHA 2013; and SWEA[23] 2014). In order to supplement the data identified in these reference reports, a review of the scientific literature was carried out. This search concerned publications appearing since 2009, which is the most recent release date of the publications cited in the reference reports. Given the large number of scientific papers relating to crystalline silica published since 2009 (more than 8,000 publications identified), the WG first focused on identifying and analysing review papers, in particular by implementing the R-Amstar (modified) method for assessing the methodological quality of reviews. Additional bibliographical research was then carried out to investigate the questions that still remained unresolved on completion of these analyses.

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[16] SCOEL: Scientific Committee on Occupational Exposure Limits
[17] OSHA: Occupational Safety and Health Administration.
[18] Note that SUMER, since its 2017 edition, is representative of more than 95% of employees working in metropolitan France.
[19] NAF 41 – Construction of buildings, 42 – Civil engineering and 43 – Specialised construction activities
[20] These results take into account SUMER data obtained from a raw number of respondents less than 100.
[21] These results take into account SUMER data obtained from a raw number of respondents less than 100.
[22] These results take into account SUMER data obtained from a raw number of respondents less than 100.
[23] SWEA: Swedish Work Environment Authority

The diagram in Annex 2 shows the general method used by the WG to conduct the literature review on health effects.

Silicosis

Chronic silicosis is a potentially fatal progressive fibrous lung disease induced by occupational exposure to crystalline silica. There are other forms of silicosis – accelerated silicosis and silicoproteinosis – which are observed in cases of intense to very intense exposure. The causal link between respiratory exposure to crystalline silica and silicosis is well established. Silicosis specifically results from the inhalation of silica in crystalline form. According to OSHA, several exposure factors are positively associated with the progression of silicosis and are also involved in onset of the disease onset:

- The average concentration of crystalline silica,
- Cumulative exposure to respirable quartz or crystalline silica,
- The duration of occupational exposure (duration of occupation of a job).

Once silicosis has been diagnosed, the progression of the disease continues, even in the absence of further exposure. However, subjects who continue to be exposed after diagnosis of the disease are more likely to see their disease progress, compared to those without any further exposure.

The recently analysed reviews confirm the information presented in OSHA's conclusions. Additional information is available on the links between exposure to crystalline silica and severity/progression of the disease. Several epidemiological studies describe significant dose-response relationships between cumulative exposure to crystalline silica, expressed in $mg.m^{-3}$-years, and silicosis observed on chest X-rays (for cumulative exposure below 1 $mg.m^{-3}$-years) or mortality by silicosis (from cumulative exposure to crystalline silica of 0.02 $mg.m^{-3}$-years). Variations between the different estimates are due to differences in the definitions used to calculate cumulative exposure, the diversity of the studied sectors, the characteristics of the studies and their design (in particular the duration of exposure or follow-up), and the consideration of additional factors that vary from one study to another.

Several studies question the relevance of using chest scans (computed tomography or CT) compared with standard chest X-rays in the detection of silicosis. CT has a higher sensitivity than a simple chest X-ray, especially for the detection of certain abnormalities such as emphysema or micronodules. In addition, inter-reader variability is lower than for standard chest X-rays (Leung *et al*. 2012). However, there are no validated monitoring recommendations for subjects exposed to crystalline silica. Unlike asbestosis and other diffuse interstitial diseases, only very few large datasets are currently available that enable assessment of the relevance of CT scans in silicosis screening and surveys.

Other interstitial diseases

Several studies report an association between occupational exposure to crystalline silica and the presence of diffuse interstitial pneumonia (DIP) mainly of the idiopathic pulmonary fibrosis type (IPF). However, most of these studies predate the current stricter diagnostic criteria for IPF, or are based on small numbers of subjects, or on imprecise or incomplete assessments of occupational exposure. These associations therefore need to be clarified.

Sarcoidosis is a multi-systemic disease, characterised by the formation of epithelioid granulomas without necrosis. The causes are still unknown, but the combination of genetic, infectious and/or environmental factors is now well accepted (Valeyre *et al.* 2014), as the disease's two main targetorgans – the respiratory system and the skin – are in direct contact with the environment. Exposure to silica is one of the suspected environmental factors. This suspicion is based on cases of silicosis associated with sarcoidosis (for which the term silicosarcoidosis has been proposed), on different clinical histories and on some epidemiological studies.

Bronchopulmonary cancer (BPC)

Many studies in the occupational population have shown a link between crystalline silica inhalation and bronchopulmonary cancer. IARC concluded that there was sufficient evidence of carcinogenicity in humans for quartz and cristobalite, and in animals for quartz, and limited evidence in animals for tridymite and cristobalite, and has classified crystalline silica as carcinogenic to humans (Group 1) since 1997 (IARC, 2012). Other government agencies have also classified crystalline silica as a pulmonary carcinogen for humans (NIOSH 2002; NTP 2014).

The new data analysed in this report confirm these conclusions and provide additional information on the dose-response relationship between crystalline silica exposure and bronchopulmonary cancer (Lacasse *et al*., 2009; Delva *et al*., 2016). (for cumulative exposure to crystalline silica from 0.5 $mg.m^{-3}$-years). Significant standardised mortality ratios (SMRs) are observed for both silicotic and non-silicotic workers, although lower for the latter. Silicosis is therefore an aggravating factor in the risk of BPC. Moreover, no threshold has been formally identified. Lastly, as with other conditions attributed to silica, the available epidemiological data cannot be used to test the influence of certain exposure characteristics (dose rate, particle size distribution, freshly fractured silica).

Studies that have assessed the interaction between tobacco and occupational exposure to crystalline silica with regard to the risk of bronchopulmonary cancer are more in favour of an additive or even multiplicative effect (Delva *et al.*, 2016).

Extrapulmonary cancers

A few studies report increases in digestive cancers (gastric, intestinal and gastrointestinal cancers), oesophageal cancer and kidney cancer, in the event of exposure to crystalline silica. However, because of limitations in the studies (small sample sizes, design, lack of consideration of confounding factors, etc.), no dose-response relationship has been established between these cancers and exposure to crystalline silica.

More specifically, for gastric cancer, a significant relationship was found in a meta-analysis (Lee *et al.*, 2016), but it remains to be confirmed given the limited quantitative exposure data available and the lack of consideration of co-exposures.

For laryngeal cancer, only one study (Chen and Tse, 2012) concluded that there was a weak association with crystalline silica exposure or silicosis. These results lack robustness as they draw conclusions from a reconstitution of exposure based on subjects' declarations and they take into account confounding factors in a questionable manner.

As emphasised by the Agency for Toxic Substances and Disease Registry (ATSDR), it should be noted that most of these cancers have been observed in studies which were initially designed to study the association between crystalline silica exposure and BPC. Therefore, in these studies adjustments for specific confounding factors in possible associations with non-lung cancers were not made (Chen and Tse, 2012; NIOSH, 2002).

Non-malignant respiratory diseases other than silicosis

Many studies indicate that occupational exposure to crystalline silica is associated with non-malignant respiratory diseases other than silicosis. According to OSHA, exposure to respirable crystalline silica increases the risk of chronic bronchitis, emphysema, respiratory function impairment and mortality from non-malignant respiratory diseases. OSHA concludes that there is a dose-response relationship between exposure to respirable crystalline silica and the risk of these effects occurring, even in the absence of silicosis. For emphysema, exposure to crystalline silica does not appear to increase the risk in non-smokers. For all these diseases, the effect of smoking can be additive or multiplicative.

The reviews analysed in this expert appraisal report support OSHA's conclusions regarding the links between crystalline silica exposure and respiratory function impairment (decline in forced expiratory volume per second – FEV1 – and the Tiffeneau ratio). These reviews investigated the dose-response relationship between crystalline silica exposure and changes in the results of respiratory functional explorations, but were unable to define a threshold for exposure to respirable crystalline silica associated with an increased risk of lung function disorders based on current knowledge.

The spirometric analysis parameters traditionally employed to assess respiratory function in epidemiological studies (i.e. FEV1 and the Tiffeneau ratio) cannot be used to assess associations with the earliest respiratory diseases (small airway diseases) revealed by other parameters (i.e. peak expiratory flow – PEF 25-75).

In the case of obstructive respiratory diseases, one study suggested that intermittent exposure to high concentrations (or exposure peaks) of crystalline silica may be responsible for inducing an inflammatory response and the onset of long-term effects (Hoet *et al*., 2017).

The importance of the "smoking" confounding factor in analysing associations between crystalline silica exposure and the prevalence of COPD and chronic bronchitis is reiterated.

New methods for measuring inflammation (fraction of exhaled nitric oxide (FeNO) and biomarker measurement in exhaled air condensates) remain to be assessed in the monitoring of people exposed to crystalline silica dust.

<u>Tuberculosis and other respiratory infections</u>

The risk of developing silicotuberculosis – a complication of silicosis by lung infection caused by mycobacteria, particularly Koch's bacillus – increases with the duration of exposure and the dose of inhaled crystalline silica. Some studies of workers have also reported an increased risk of tuberculosis among those who are exposed to silica in the absence of silicosis.

The risk of developing silicotuberculosis is higher in the event of HIV co-infection and with smoking.

Diagnosis of active tuberculosis in patients with silicosis is difficult, due to non-specific clinical manifestations and observation on the chest X-ray of lesions that may be difficult to distinguish from silicotic lesions. In countries with a low prevalence of tuberculosis, tests to screen for latent forms by IGRA[24] may be worthwhile.

<u>Kidney diseases</u>

Crystalline silica is responsible for two types of kidney damage: (1) direct toxic effects associated with the accumulation of excessive amounts of crystalline silica in the kidney, and (2) indirect toxic effects secondary to an autoimmune disease (AID). The association between crystalline silica exposure and the risk of kidney disease has been investigated in several studies. An increased risk of kidney disease is highlighted in these studies, but to date it is not possible to confirm that this association is due solely to crystalline silica exposure. Indeed, most of these studies reported an association between crystalline silica exposure and the risk of death from kidney failure without taking into account the underlying or associated causes of kidney failure such as diabetes, high blood pressure, co-exposure to heavy metals. The difficulty of studying kidney failure due to its late and asymptomatic nature and the usual absence of a renal biopsy for making a precise diagnosis also explains the lack of scientific evidence. Studies establishing dose-response relationships

[24] IGRA: Interferon-Gamma Release Assays – screening test for latent tuberculosis infection that detects the production of interferon gamma.

between kidney disease and silica exposure have small sample sizes and show conflicting results. A recent study showed an increase in the prevalence of kidney disease in people with silicosis.

Autoimmune diseases

Several types of studies (clinical case series, cohort studies, case-control studies) have reported an association between crystalline silica exposure and a broad spectrum of autoimmune diseases including systemic scleroderma (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ANCA+[25] vasculitis. Overall, the results of these studies indicate that occupational exposure to crystalline silica in some workers who may also have other risk factors for autoimmune diseases (genetic predisposition, exposure to other chemicals) may lead to an increased risk of developing an autoimmune disease.

Several studies have shown a clear link between crystalline silica exposure and the occurrence of SSc for nearly half a century. Recent work indicates that case-control and cohort studies lead to the conclusion of a significant association, whether the analyses are conducted separately by study type, or considered together (Rubio-Rivas *et al.* 2017). The association between SSc and silica appears to be more pronounced in male patients and possibly associated with more severe forms of the disease (McCormic *et al.* 2010, Miller *et al.* 2012 & Rubio-Rivas *et al.* 2017).

The data analysed for RA support a definite association between the occurrence of RA and exposure to silica. This association is described as Caplan's syndrome. The impact of co-exposure with tobacco and the influence of silica exposure on serological status with the presence of ACPA ("anti-citrullinated protein antibodies" specific to the disease) cannot be reliably assessed epidemiologically, given the data currently available.

The analysed data for SLE confirm the higher prevalence of a history of occupational exposure to crystalline silica in SLE patients compared to non-SLE control populations. Some studies suggest that exposed patients may suffer from more severe forms of SLE, with higher mortality in exposed subjects, and a higher frequency of hospitalisations.

For ANCA+ vasculitis, two recent studies (systematic review and meta-analysis) reported an increased risk of ANCA+ vasculitis in patients exposed to silica. However, several factors limit the generalisation of these results, including the fact that the inclusion criteria for ANCA+ vasculitis were disparate and often defined by renal impairment associated with ANCA vasculitis, and not by the diagnosis of ANCA+ vasculitis *per se.*

A summary of the causality criteria associated with these four autoimmune diseases is provided in the table below.

[25] Anti-Neutrophil Cytoplasmatic Antibodies

Table 2: Assessment of the causal link between crystalline silica exposure and four autoimmune diseases

AID/Causality criteria	Rheumatoid arthritis	Systemic scleroderma	Lupus	ANCA+ vasculitis
Strength of the association	Risk > 2	Risk > 15	Risk > 2 or even 4 for the most exposed subjects	Risk > 1.5
Temporality	Over 50 years	Over 50 years	Over 25 years	Variable data
Specificity	Yes	Yes	Questionable	No data
Chronological consistency	Cohort work	Cohort work	Cohort work	Variable data
Biological gradient	Yes	Yes	Yes	No data
Coherence	Yes	Yes	Yes	Yes
Analogy	Tobacco, other inorganic dust	Solvents	Solvents	No unequivocal data
Biological plausibility	NLRP-3 Citrullination Joint action with tobacco	NLRP-3 and fibrosis	NLRP-3 and antinuclear antibodies NETosis Apoptosis/necroptosis	Silica and NETosis
Experimental evidence	NLRP-3[26] and citrullination More speculative relationships between silica and mouse models	NLRP-3 and fibrosis: validated in some mouse models of inflammatory fibrosis. Direct impact of silica to be clarified in systemic scleroderma models	Silica and ANAs[27] in lupus mouse models	Data on NETosis and silica but no direct relationship with ANCA vasculitis
Conclusion on the causal relationship	**Certain** **+**	**Certain and Strong** **++**	**Certain** **+**	**Possible** **+/-**

However, the data currently available for each disease considered individually are inadequate for determining quantitative dose-response relationships, and it is therefore possible that a low dose of exposure may be sufficient to develop one of the autoimmune diseases induced.

Cardiovascular effects

The results of a recent study of more than 42,000 workers in China showed a significant positive trend for cumulative exposure to crystalline silica and heart disease mortality (Liu *et al*., 2014).

An analysis of the mechanisms underlying all the previously identified diseases associated with crystalline silica is given in the following section.

Mechanisms of action of crystalline silica particles

Many studies have focused on the mechanisms of action of crystalline silica and have identified several major mechanisms involved in silica-induced lung damage:

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[26] NOD-like receptor family, pyrin domain containing 3

[27] Antinuclear antibodies

- Direct damage to lung cells due to the specific surface properties of silica particles;
- Activation by silica particles of alveolar macrophages and/or alveolar epithelial cells leading to (i) the release of cytotoxic enzymes, reactive oxygen and nitrogen species, inflammatory cytokines and chemokines, (ii) cell death with release of the silica particle, and (iii) recruitment and activation of additional neutrophils and macrophages, in particular alveolar ones;
- The role of the negative charge on the surface of the particles as an important contributor to silica's cytotoxicity.

Regarding the surface properties of crystalline silica particles, *in vitro* and *in vivo* tests (cellular tests as well as on animal models) have shown much greater toxic effects with freshly ground crystalline silica particles than with "aged" particles (Vallyathan *et al.*, 1988; Dalal *et al.*, 1990a; Vallyathan *et al.*, 1995), suggesting that the surfaces of freshly fractured crystalline silica particles are far more chemically reactive, in terms of both the nature and intensity of the biological response induced by the crystalline silica particles.

The surface of a freshly generated quartz particle is very active with regard to the three major mechanisms involved in diseases associated with crystalline silica exposure: oxidative stress, persistent inflammation and DNA damage (IARC, 2012; Pavan and Fubini, 2017). Persistent inflammation is regarded as the main cause of the development of silicosis, lung cancer and autoimmune diseases (Borm *et al*., 2011; IARC, 2012). Reactive oxygen species and silanols[28] are present predominantly or at least greatly increased on the surface of freshly fractured particles, suggesting their involvement in the toxic mechanism of silica particles.

Any modification or occultation of the surface of crystalline silica particles could modify, increase or inhibit their toxicity. The following four groups of surface impurities have been studied:

- Metallic impurities. It is generally accepted that aluminium salts inhibit the pathogenicity of silica (Bégin *et al.*, 1987; Donaldson *et al*., 2001; Duffin *et al*., 2001; Knaapen *et al*., 2002; Le Bouffant *et al*., 1977; Nolan *et al*., 1981; Schins *et al.*, 2002) while iron salts have a more complex action: they activate toxicity at low concentrations (Castranova *et al*., 1997; Elias *et al.*, 2002; Fubini *et al.*, 1995) and inhibit it at high concentrations (Ghiazza *et al.*, 2011).
- Minerals in close contact with silica. It has long been established that silica associated with clay is less toxic or even non-toxic (IARC, 1997). Experimental studies indicate that carbon associated with quartz can also reduce its biological reactivity (Ghiazza *et al.*, 2013).
- Polymers deposited on the surface of the particles. The use of outer coating agents, such as lipid surfactants, proteins and polymers (in particular, the polyvinylpyridine-N-oxide or PVPNO polymer) induces a reduction in silica toxicity (Donaldson and Borm, 1998; Nolan *et al.,*1981).
- Surface functionalisation. Functionalisation of the chemical groups (mainly silanols) found on the surface of the silica particle, usually with organosilanes, is implemented to reduce the toxicity of quartz (Ferenc *et al.*, 2015; Vallyathan *et al.*, 1991).

The available epidemiological and experimental data do not show any differences in toxicity or carcinogenic potential between the different polymorphs of crystalline silica.

No data are currently available in the literature that could be used to assess the toxicity of ultrafine crystalline silica particles. Nevertheless, by analogy with toxicological data comparing nanoscale and micron-scale particles of the same chemical composition, greater biological reactivity is expected of ultrafine particles with equal silica mass (Karlsson *et al.*, 2009; Guichard *et al.*, 2012; Porquin *et al.*, 2017; Ta *et al.*, 2018; Kuska *et al*., 2014; Stone *et al*., 2017).

[28] Chemical compounds containing at least one silicon atom directly bonded to a hydroxyl group.

In the absence of standardised measurements of the half-life of crystalline silica particles in organs, the lack of solubility in biological fluids (Utembe *et al.*, 2015) and the results of retention studies in workers who have been exposed to these particles (Pairon *et al.*, 1994) support the biopersistence of these particles in tissues or biological fluids. In addition, animal studies have shown that as well as their cytotoxicity, crystalline silica particles induce persistent lung inflammation even after exposure has ceased, as well as impairment of macrophage-mediated clearance, resulting in accumulation and persistence of particles in the lungs (IARC, 1997). Moreover, in the lungs of subjects with no known occupational exposure, crystalline silica is the most common mineral phase after micas, (as a percentage of the mineral species in retained mineral particles) (Paris *et al.*, 2011) .

More specifically concerning the carcinogenicity of crystalline silica particles, the mechanism in humans has not been established. According to IARC (1997; 2012), animal data indicate that three mechanisms are involved: (i) indirect genotoxicity caused by impaired alveolar macrophage-mediated clearance inducing persistent pulmonary inflammation, followed by the release of oxidants; (ii) generation of extracellular free radicals inducing exhaustion of antioxidant defences, epithelial cell lesions, then finally a proliferation of damaged cells; (iii) direct genotoxicity due to the trapping of crystalline silica particles by pulmonary epithelial cells, followed by intracellular generation of free radicals. According to IARC, the preferred hypothesis regarding the mode of action is indirect genotoxicity induced by inflammation, although other mechanisms, potentially initiated in parallel, cannot be ruled out.

The recent publications analysed provide additional information on these mechanisms and raise questions about the relationship between genotoxicity and inflammation. The existence of DNA damage induced by crystalline silica particles has been confirmed, but the direct relationship between inflammation and DNA damage is contested.

A non-quantitative (heterogeneous studies of limited number) meta-analysis supported the hypothesis that exposure to different types of particles, including silica, is associated with a significant increase in sister chromatid exchanges, and an increase in micronuclei (Bonassi *et al.*, 2016).

Exposure of animals by the airborne, intraperitoneal or gastrointestinal route causes a significant increase in DNA oxidation in tissues, blood and urine. A genotoxic effect is observed in tissues soon after exposure (single dose), suggesting genotoxicity consequences, not only in the short term but also in the long term (biopersistence). The hypothesis that the genotoxicity mechanism of crystalline silica is secondary, resulting from inflammation, is not confirmed by other studies. These have concluded that there is no direct experimental evidence in agreement with the idea that inflammation is a prerequisite for DNA oxidation in the lung.

Taking into account the results obtained with different types of particles (asbestos, diesel, quartz, nanoscale carbon), it has been observed that particles generate dose-dependent genotoxicity, without a specific threshold, with the mention that effects at low doses have not yet been extensively studied (Moller *et al.* 2013).

■ Health data in France

<u>Data from the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P)</u>

Over the period 2001-2017, 4,506 work-related health problems (WRPs) associated with silica were identified in the RNV3P database. The most numerous diseases were bronchopulmonary cancer (BPC) accounting for nearly 40% of WRPs, followed by silicosis (26% of WRPs), chronic obstructive pulmonary disease (COPD) (8% of WRPs), idiopathic interstitial pneumonia (IIP) (6% of WRPs), and systemic scleroderma (4.5% of WRPs). Emphysema accounted for 1.7% of WRPs. Regardless of disease, exposure and causality, four main industry sectors stand out:

- Construction (NAF 43+42+41+(45-NAF93)), which accounted for 36% of WRPs associated with crystalline silica exposure.
- Mining and quarrying (NAF 05+06+07+08+09+10-NAF93), which accounted for 17% of WRPs associated with crystalline silica exposure.
- Manufacture of basic metals and of fabricated metal products, except machinery and equipment (NAF 24+25), which accounted for 11% of WRPs associated with crystalline silica exposure.
- Manufacture of rubber and plastic products and of other non-metallic mineral products (NAF 22+23), which accounted for 10% of WRPs associated with crystalline silica exposure.

The construction sector had the highest number of WRPs for each disease except for silicosis: up to 48% for BPC and 47% for systemic scleroderma. Silicosis was mainly identified in the mining and quarrying sector (40%).

Silicosis and systemic scleroderma were mainly diagnosed with moderate/high causality, while the causality associated with BPC, COPD, IIP and emphysema was predominantly low.

<u>Data on occupational diseases</u>

Under the general compensation scheme, over the last five years available (2012-2016), between 200 and 275 occupational disease cases relating to Table 25 were recognised annually, accounting for between 0.4 and 0.5% of all occupational disease cases recognised over this same period. Acute or chronic silicosis accounted for 74 to 82% of the occupational disease cases recognised in this table, followed by systemic scleroderma (4 to 10%), primary bronchopulmonary cancer (4 to 9%), pneumoconiosis due to inhalation of coal dust (0 to 4%) and non-regressive diffuse interstitial pulmonary fibrosis, primary in appearance (1 to 2.5%). No cases of tuberculosis have been recognised since 2014 under Table 25.

The incidence of silicosis appears to have declined over the years, while the number of systemic sclerodermas has increased slightly, and the number of primary bronchopulmonary cancers has remained constant.

For more than half of all occupational disease cases, the industry sector was not reported. Otherwise, the industry sectors most concerned were: manufacture of basic metals and of fabricated metal products, except machinery and equipment (NAF 24 and 25), construction (NAF 41, 42 and 43), manufacture of other non-metallic mineral products (NAF 23), mining and quarrying (NAF 08), other manufacturing (NAF 32) and manufacture of motor vehicles, trailers and semi-trailers (NAF 29).

Under the complementary compensation scheme, 46 occupational disease cases have been recognised in connection with exposure to crystalline silica over the past 20 years (between 0 and 4 occupational diseases per year). The most frequently recognised were bronchopulmonary cancer in the absence of silicosis (26%) and "unspecified lung disease" (7%).

In the agricultural scheme, between 0 and 3 cases of occupational diseases were recognised annually under Table 22 depending on the year.

■ Risks for workers

In 2016, for different cumulative exposure levels, OSHA assessed the lifetime or cumulative risk estimates of mortality by lung cancer, silicosis or non-malignant respiratory diseases, as well as of silicosis morbidity. Regardless of the outcome considered, the calculated lifetime or cumulative risk estimates were greater than 1 per 1000 for cumulative exposure of 45 years to 0.1 $mg.m^{-3}$. The lifetime or cumulative risk estimates calculated for cumulative exposure of 45 years to 0.05 and 0.025 $mg.m^{-3}$, although lower, were always greater than 1 per 1000, regardless of the outcome considered.

The risk assessment carried out by OSHA on the risks of mortality from kidney failure was not considered sufficiently robust for use by the Working Group, due to the limitations on kidney diseases mentioned above.

the issue of the relevance of the cumulative risk assessment was raised: for the same cumulative exposure, are the risks associated with low long-term exposure comparable to those induced by intermittent but intense exposure? In the absence of data to answer this question, the Working Group considered the risk assessments conducted by OSHA to be relevant.

3.2. Conclusions of the CES

The purpose of this expert appraisal was to update knowledge on the hazards, exposures and health risks associated with crystalline silica, with a view to proposing risk prevention and reduction measures.

Crystalline silica (or silicon dioxide, SiO_2) is a naturally occurring mineral in the Earth's crust. Among the three most frequently encountered polymorphs, quartz is the most common, followed by cristobalite and tridymite. Quartz is found in most types of rock, from trace amounts to levels of over 90%, such as in sand, for example. As for cristobalite, it occurs naturally in volcanic rocks or bentonites[29]. Tridymite is rarer than the other two forms. Crystalline silica is found in most natural mineral-based materials at levels above 0.1%.

History and sociology of knowledge of the health risks associated with exposure to crystalline silica

Pulmonary silicosis has for a long time accounted for (almost) all the health risks associated with exposure to crystalline silica. Its worldwide recognition at the 1930 Johannesburg International Conference as an occupational disease associated mainly with the mining sector marked a significant step forward in the history of occupational health. However, this conference imposed a restrictive definition for silicosis: concentrating knowledge only on the mining sector, and overlooking the risks in other industry sectors where employees are exposed to crystalline silica, neglecting acute or early forms of silicosis, and delaying the study of possible links between exposure to crystalline silica and other health effects such as autoimmune diseases.

Based on these findings, the work conducted as part of this expert appraisal, like the recent work of other health agencies such as OSHA (2016), sought to provide a more representative view of the diversity of forms of exposure to crystalline silica and the diseases they can cause.

Sector study

Due to the ubiquity of crystalline silica, the sector study revealed that a vast number of sectors are concerned by workers' exposure to this substance. The main industry sectors concerned are mining and quarrying (industrial minerals, construction materials, ocean mineral resources, ores and metals), followed by the sectors using and processing the extracted raw materials. Secondary resources[30] are also concerned by crystalline silica, in particular through the recycling of construction waste.

[29] Bentonites are colloidal clays, often generated by the modification of tuff (a type of rock with a vacuolar structure) or volcanic ash.
[30] A resource derived from industrial waste or by-products that can be used as a substitute for primary resources extracted from quarries.

All quarries and mines are concerned by exposure to crystalline silica, but to different degrees depending on the crystalline silica content of the extracted material. Some of them, such as high-silica sand, quartz and flint, are extracted for their high crystalline silica content (> 90%); while others contain between less than 1% (limestone) and about 60% (shale) of crystalline silica. Aggregates[31] may contain up to 80% crystalline silica.

In France, construction materials, and aggregates in particular, represent around 330 million tonnes extracted per year, or 95% of the materials extracted. Industrial minerals with very high crystalline silica content (all types), like other industrial minerals, account for about 8 million tonnes extracted.

Industrial silica, as well as mineral materials and materials containing crystalline silica, are used as raw materials, additives or processing aids in their original or processed form. They can be found in a variety of applications, including glassmaking, smelting, chemistry, rubbers, paints, construction (especially concrete), and headstones, etc. Crystalline silica is therefore found in a wide variety of consumer products that may cause exposure of the general population.

Specifically concerning the artificial stone countertop sector, no countertop manufacturing site has been identified in France. These countertops are manufactured in other European countries, mainly Spain, then imported in the form of slabs into France, where they are stored, cut and adjusted to order, then installed in private homes. Marginal adjustments may be carried out by stonemasons or kitchen fitters in the customer's home.

Industry sectors operating in the natural environment, when this involves the manipulation of soil, may also be affected by exposure to crystalline silica, depending on the soil type and the work involved. This is particularly the case for earthmoving activities, tunnelling, or agricultural work during land preparation, harvesting operations or the operation of irrigation systems.

Measurement methods in industrial hygiene

Regarding the standardised measurement methods for crystalline silica, there is a wide variety of devices for individual sampling of the respirable fraction. The comparison studies did not show any significant difference in results between these sampling devices, although some appear to be more sensitive to the particle size of the collected particles. Devices with a high sampling rate (> 4 $L.min^{-1}$) can collect larger quantities of material, particularly when sampling for short-term tasks. Some devices can also be used to carry out a direct analysis, without preparation, of the collection media, limiting the variability in the analysis results. Depending on the exposure context, one device will be preferred to another.

From an analytical point of view, crystalline silica content can be assessed by X-ray diffraction (XRD) or Fourier-transform infrared (FTIR) spectroscopy. Although the performance of the two techniques is equivalent, XRD analysis has the advantage of identifying, in addition to crystalline silica, the mineral phases present in samples whose composition is unknown. This situation occurs frequently, especially in the construction sector, although less so in the case of mining and quarrying where the material is generally better known. Knowledge of the other mineral phases also enables possible analytical interferences to be better taken into account.

Data on crystalline silica exposure and characterisation of occupational exposure in France

The occupational exposure limit over eight hours (8h-OEL) in France is 0.1 $mg.m^{-3}$ for quartz, and 0.05 $mg.m^{-3}$ for cristobalite and tridymite.

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[31] Small pieces of rock (<125 mm) intended to be used for public works, building and civil engineering works (according to a hearing with the National Federation of Public Works, FNTP, 2015)
Granular material used in construction. An aggregate can be natural, artificial or recycled (EN 13043 standard, according to the hearing with the FNTP, 2015).

According to the 2017 SUMER survey, nearly 365,000 workers in France were exposed to crystalline silica, corresponding to about 1.47% of all employees in all industry sectors combined, a slight increase compared to the 2010 survey data[32].

The exposure data analysed as part of this expert appraisal came from several sources: the COLCHIC and SCOLA databases, job-exposure matrices and the scientific literature. All these exposure data converge to indicate that four industry sectors are especially concerned, with higher levels of exposure to crystalline silica and the current limit values frequently exceeded:

- Construction;
- Manufacture of non-metallic mineral products;
- Manufacture of basic metals;
- Mining and quarrying.

These are "historical" industry sectors, in the sense that exposure here has been documented for several years.

According to data from the COLCHIC and SCOLA databases, the tasks involving the highest exposure are structural works and machining tasks, assembly in the building construction sector, and operation and supervision of mixers in the manufacture of ceramic tiles and flags.

The occupations in which exposure levels most frequently exceed the current limit value are: finisher ("construction of other civil engineering projects" sector), industrial mason-assembler ("construction of other buildings" sector), palletiser ("manufacture of concrete products for construction purposes" sector), stonemason ("cutting, shaping and finishing of stone" sector), finishing worker (deburring, casting ("casting of iron" sector)), deflasher-deburrer (manufacture of basic metals ("casting of iron" sector)).

The analysis of these data did not reveal any "emerging" industry sectors in terms of crystalline silica exposure.

The data from the 2010 and 2017 SUMER surveys were cross-referenced with COLCHIC and SCOLA exposure data for the period 2007-2016. Among the workforce considered, representing 74 to 87% of the population exposed to crystalline silica in SUMER, between 23,000 and 30,000 workers may be exposed to crystalline silica at levels exceeding 0.1 $mg.m^{-3}$ (of whom nearly 66 to 75% are from the construction sector) and more than 60,000 workers may be exposed to levels exceeding 0.025 $mg.m^{-3}$ (of whom 61 to 69% are from the construction sector).

By cross-referencing data from the SUMER surveys with COLCHIC and SCOLA exposure data corresponding to the dates of these surveys (2007-2009 and 2015-2016 for the 2010 and 2017 surveys respectively), it can be seen that the number and proportion of workers exposed to crystalline silica levels exceeding the values of 0.1, 0.05 or 0.025 $mg.m^{-3}$ have increased, particularly for the following sectors: "mining and quarrying", "manufacture of chemicals and chemical products", "manufacture of other non-metallic mineral products", "manufacture of basic metals", "manufacture of fabricated metal products, except machinery and equipment", and the "civil engineering" and "specialised construction activities" sectors.

The few studies available in the literature that aimed to assess exposure or emissivity during machining of artificial stone countertops highlight particularly high levels of exposure during certain tasks such as chamfering and polishing.

In the agricultural sector, a few studies show exposure to crystalline silica that can, depending on the soil type and the exposure conditions, exceed the value of 0.1 $mg.m^{-3}$.

[32] In 2010, the proportion of employees exposed to crystalline silica was 1.36%.

In general, exposure levels are significantly reduced by wet work and/or local exhaust ventilation. However, the use of either of these techniques – or both in combination – is not always sufficient, as residual levels may lead to current OELs being exceeded. The dust reduction effectiveness does in fact vary, and depends on the tools and devices used.

Some studies have pointed out that the quartz content in respirable dust is not systematically correlated with the quartz content in raw materials, regardless of the industry sector. Several studies have shown particularly high levels of exposure to crystalline silica (> 0.1 $mg.m^{-3}$), even for relatively low levels of "respirable dust without specific effects". Compliance with the existing limit value for "respirable dust without specific effects"[33] as defined by the regulations does not therefore mean that measurements of exposure to crystalline silica are unnecessary.

Data on the particle size distribution of crystalline silica, and more specifically on its presence in the finest fractions, are currently very rare in the literature. Some studies indicate that high-energy processes can emit large quantities of ultrafine particles (particles with a diameter < 100 nm). A recent preliminary study seemed to confirm the presence of crystalline silica among these ultrafine particles during concrete and granite cutting operations. Only one study has investigated the mass particle size distribution of crystalline silica, without mentioning the presence of ultrafine particles.

Excluding the direct influence of emission sources, the environmental concentrations of crystalline silica in outdoor air established by various studies (none of which were carried out in France) were generally between 1 and 3 $\mu g.m^{-3}$. These levels are influenced by the immediate environment of the samples (e.g. presence of an industrial site with crystalline silica emissions) and by climatic and meteorological conditions possibly leading to higher values which, other than in exceptional cases, remain below 20 $\mu g.m^{-3}$.

No data on exposure in the vicinity of agricultural work were identified. In France, there are no data on the exposure of local residents to crystalline silica around industrial and extraction sites emitting crystalline silica.

Health effects in humans

Silicosis and other interstitial diseases

Occupational exposure to silica is definitely associated with several lung diseases, including chronic silicosis, accelerated silicosis and silicoproteinosis. The forensic definition of silicosis dates back to the 1930 Johannesburg International Conference and is based on the presence in the lung parenchyma of characteristic fibro-hyaline nodules, with the presence of lightly birefringent particles under polarised light on its periphery, namely silicotic nodules. This definition excluded early histological lesions and lymph-node-only silicosis. However, several studies have shown that isolated lymph node forms, with the presence of silicotic nodules in the hilar or mediastinal lymph nodes, constitute an early form of pulmonary silicosis, for which they are a proven risk factor, regardless the cumulative levels of exposure to crystalline silica.

A significant dose-response relationship for silicosis has been well documented, using autopsy and radiological data (based on standard chest X-rays), and also on silicosis mortality data (based on cumulative exposure to crystalline silica of 0.02 $mg.m^{-3}$-year).

While the cumulative exposure dose expressed in $mg.m^{-3}$-year is the most important factor in the development of silicosis, progression of the disease increases slowly for several decades after exposure has ceased, possibly because of the crystalline silica dust still retained in the lungs. Therefore, stopping exposure does not necessarily prevent the development or progression of the

[33] Current regulatory 8h-OEL for dust without specific effects – respirable fraction = 5 $mg.m^{-3}$ (Article R 4222-10 of the French Labour Code). It should be noted that this 8h-OEL is currently being updated.

disease. However, subjects who continue to be exposed after the silicosis diagnosis are more likely to see their disease progress, compared to those without any further exposure.

The presence of diffuse interstitial pneumonia (DIP) mainly of the idiopathic pulmonary fibrosis type (IPF) or sarcoidosis has been associated with exposure to crystalline silica, but there are insufficient current data to pinpoint the exact relationship between them.

Several studies have highlighted the contribution of thoracic computed tomography (CT or chest scans) compared with standard chest X-rays in the diagnosis of silicosis, with its improved sensitivity, as well as for some of the associated diseases, such as emphysema or the presence of DIP. However, there are no studies able to assess the specificity of CT, nor to establish a dose-response relationship based on this examination. A few protocols for monitoring and screening workers exposed to crystalline silica have been proposed, mainly based on the standard chest X-ray, but no validated recommendations have been established.

Bronchopulmonary cancer (BPC) and other cancers

Since IARC classified crystalline silica as a human carcinogen in 1997 (which was confirmed in 2012), all studies published in this field have confirmed the link between the cumulative exposure dose to crystalline silica and the development of bronchopulmonary cancer (BPC). Having pulmonary silicosis increases a person’s risk of developing BPC, although recent studies have also confirmed the existence of a significant risk even without silicosis. These studies' limitations essentially concern the accuracy of reconstructions of exposure to crystalline silica and the often insufficient consideration of confounding factors (co-exposure, smoking).

Regarding the dose-response relationship, no threshold has been identified. The risk is significant, even for the lowest levels of exposure (from 0.5 $mg.m^{-3}$-years). Recent studies show an additive or even multiplying effect of smoking on the risk of BPC.

For other cancers, there is no known association with exposure to crystalline silica, but a link with digestive cancers has been suggested.

Non-malignant respiratory diseases other than silicosis

For non-malignant respiratory diseases other than silicosis – respiratory function impairment in the form of reduced expiratory flow, chronic obstructive pulmonary disease (COPD), emphysema, tuberculosis – there is a significant dose-response relationship for mortality from non-malignant respiratory diseases.

Data from recent publications on respiratory function using flow-volume curves are insufficient to detect small airway disease in subjects exposed to crystalline silica.

Although silicotic subjects are at risk of tuberculosis, excess cases of tuberculosis have also been observed in workers exposed to crystalline silica in the absence of silicosis. There are virtually no recent data on other mycobacterial infections associated with exposure to crystalline silica. Screening by immunological blood tests such as IGRA (Interferon-Gamma Release Assays) in a country with a low prevalence of tuberculosis is interesting, especially in workers from countries with high endemic tuberculosis and exposed to crystalline silica dust. However no data are currently available in France on this topic.

New tests are being discussed for the early diagnosis of bronchial and alveolar diseases, including fraction of exhaled nitric oxide (FeNO) and measurement of biomarkers in exhaled air condensates. Few data have been published to date and the benefits of monitoring people exposed to crystalline silica dust by these methods remain to be assessed.

Kidney diseases

The association between crystalline silica exposure and the risk of kidney disease has been investigated in several studies. An increased risk of kidney disease is highlighted by the studies, but it is impossible to confirm that it is due solely to crystalline silica. Indeed, most of these studies reported an association between crystalline silica exposure and the risk of death from kidney failure without taking into account the underlying or associated causes of kidney failure (such as diabetes, high blood pressure or co-exposure to heavy metals). The difficulty of studying kidney failure due to its late and asymptomatic nature and the usual absence of a renal biopsy for making a precise diagnosis also explains the lack of scientific evidence.

Autoimmune diseases

With regard to autoimmune diseases, a significant association between exposure to crystalline silica and systemic scleroderma, systemic lupus and rheumatoid arthritis has been confirmed, particularly in men. Recent advances in knowledge of ANCA+ vasculitis, defining this entity as a heterogeneous group, do not currently make it possible to conclude that there is an overall association with crystalline silica. The current data are insufficient to establish a dose-response relationship for autoimmune diseases.

Other diseases

The existence of a relationship with other diseases, particularly cardiovascular, has been mentioned, without it being possible to conclude specifically as to the role of crystalline silica particles.

Mechanisms of action of crystalline silica particles

The main biological effects of crystalline silica observed in animals exposed by inhalation or the intratracheal route are the generation of inflammatory reactions, fibrosis and cancer. The inflammation effects are compatible with the activation of an immune response and the facilitation of an autoimmune process. Crystalline silica induces genotoxicity *in vivo*, and *in vitro* on cell cultures. Although the available data on low doses are fragmentary, on the one hand the assumption of no threshold remains the most reasonable given that the genotoxicity data suggest both a direct and indirect mechanism, and on the other hand the genotoxic effects appear to be dose-dependent.

The inflammatory effects depend on physico-chemical characteristics (size, shape, surface chemistry) and the distribution of contaminants on the surface of the particles. The relationships between the sample characteristics and the nature of the biological effects (e.g. trapping of particles by cells, production of reactive oxygen and nitrogen species, activation of the inflammatory response, DNA damage) are at this stage hypothetical, and far from being fully established.

Regarding the intensity of the induced biological responses, the surfaces of freshly fractured silica particles are more reactive than "aged" surfaces from a chemical point of view. Few data are available on the origin of the crystalline silica samples used in experimental studies or the preparation conditions, in particular grinding, particle size distribution and physico-chemical characteristics, even though these parameters can influence the toxicological properties of crystalline silica. The study of surface state changes suggests that the variability of "quartz hazard", both for toxicological studies and for worker exposure, could come from the particle generation process (which determines size, shape and surface state), prior heat treatment, and any mineral and metal impurities present. The distribution of reactive sites on the surface of particles (radical, acidic, hydrogen-bonding), particularly silanol groups, also seems to play an important role in this variability, as silanols have a specific configuration on fractured surfaces.

Several questions remain open, including the relationship between inflammation and genotoxicity, and the role of inflammation in cancer and autoimmune diseases.

There are insufficient data in the literature to assess the role of the ultrafine fraction in the toxicity of samples of crystalline silica particles. However, by analogy with amorphous silica, the reactivity of ultrafine particles is assumed to be higher than that of respirable particles.

Risks for workers

The lifetime or cumulative risk estimates calculated by OSHA for cumulative exposure of 45 years to the current 8h-OEL (i.e. 0.1 $mg.m^{-3}$) were greater than 1 per 1000, whether for mortality from lung cancer, mortality from silicosis and non-malignant respiratory diseases or pulmonary silicosis. The lifetime or cumulative risk estimates calculated for cumulative exposure of 45 years to 0.05 and 0.025 $mg.m^{-3}$, although lower, were always greater than 1 per 1000, regardless of the outcome considered.

As a reminder, according to the exposure and prevalence data analysed for the expert appraisal, between 23,000 and 30,000 workers may be exposed to crystalline silica at levels exceeding 0.1 $mg.m^{-3}$ and more than 60,000 exposed at levels exceeding 0.025 $mg.m^{-3}$ in France.

It should also be pointed out that exposure peaks, which are frequent in the workplace, are not taken into account when assessing the health risks associated with cumulative exposure to crystalline silica. Little is currently known about the ability of these peaks to trigger inflammatory, carcinogenic or respiratory immune disorders, regardless of cumulative exposure levels.

Lastly, the work shows that there is no difference between quartz and cristobalite in terms of the associated health effects.

Risks for the general population

The few available data on exposure levels to crystalline silica in the general population do not allow a health risk assessment to be carried out.

In conclusion, in view of the exposure levels currently observed in France and the excess risks documented in the literature, a particularly high health risk (greater than 1 per 1000)[34] **for the occupational population exposed to crystalline silica is confirmed. The current 8h-OEL value of 0.1 $mg.m^{-3}$ is not sufficiently protective.**

3.3. Recommendations of the CES

Prevention in the workplace

The CES first wishes to reiterate the need to enforce the hierarchy of preventive measures as set out in Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Indeed, "work involving exposure to respirable crystalline silica dust generated by a work process" is now considered to be carcinogenic because it has been added to the list of substances, preparations and processes in Annex I to this 2004 directive by Directive (EU) 2017/2398 of 12 December 2017.

For protecting the occupational population, the CES specifically recommends:

[34] For information, this value is 10 to 100 times higher than the values conventionally used for risk management (Dankovic and Whittaker, 2015; NIOSH, 2017, 2018; ANSES, 2017)

- transposing into French law, as soon as possible, the recognition of work involving exposure to crystalline silica dust mentioned in Directive (EU) 2017/2398 as carcinogenic processes.
- revising the OELs for crystalline silica, given the identified health risks, without distinguishing between the different polymorphs.
- directly measuring the crystalline silica content by atmospheric sampling of the respirable fraction, regardless of the industry sector concerned. Exposure to crystalline silica should not be extrapolated, either from the level of crystalline silica in the raw materials or from the results of measurements in "respirable dust without specific effects" as defined by the regulations. Similarly, measurements in crystalline silica should be carried out, regardless of the levels measured in "respirable dust without specific effects", even when these levels are below their OEL.
- regarding the measurement method, choosing a high or low flow-rate sampling device according to its intrinsic limits and the sampling characteristics (duration, expected silica concentration, potential presence of ultrafine particles), and using X-ray diffraction (XRD) to more effectively account for the problem of interference. Direct analysis of the sampling medium should be preferred where possible.
- generalising the implementation of preventive measures such as wet work and/or local exhaust ventilation, systematically first checking their effectiveness according to the tools and techniques used, including on mobile work sites.
- raising awareness among professionals of the risks associated with exposure to crystalline silica and of the preventive measures, regardless of the industry sector, including both traditional sectors (mining and quarrying, construction, etc.) and more recent sectors (those using artificial stone, etc.).

Medical surveillance in the workplace

In order to improve the medical surveillance of exposed workers, the CES recommends:

- redefining the diagnostic criteria for the various anatomo-clinical forms of silicosis by including lymph-node-only silicosis, regarded as early forms of pulmonary silicosis in their own right.
- assessing the role of thoracic computed tomography (CT) in the screening of silicosis and associated diseases (emphysema, DIP, etc.) in subjects who have been professionally exposed.
- including subjects exposed to crystalline silica, even in the absence of silicosis, in the experiments planned in the 2015 HAS-INCa-SFMT recommendation on the monitoring of subjects exposed to bronchopulmonary carcinogens.
- assessing the relevance of systematically screening for the presence of lymph-node-only silicosis when treating certain diseases, including bronchopulmonary cancer.
- assessing the relevance of systematically screening for occupational exposure to crystalline silica in subjects with autoimmune diseases such as systemic scleroderma, systemic lupus and rheumatoid arthritis.
- assessing the usefulness of systematic screening for tuberculosis by IGRA in workers exposed to crystalline silica.
- using respiratory function measurement devices to produce flow-volume curves, particularly to improve early diagnosis of small airway diseases.
- assessing the value of monitoring kidney function in subjects occupationally exposed to crystalline silica.

All these steps appear necessary for establishing recommendations for the medical surveillance of subjects currently or previously exposed through their work to crystalline silica.

Compensation for occupational illnesses

Lastly, the CES recommends initiating the revision of the tables of occupational diseases related to crystalline silica, particularly in view of the identification of a risk of bronchopulmonary cancer even without silicosis, and extending the definition of silicosis to lymph-node-only silicosis.

Prevention in the general population

For protecting the general population, the CES recommends:

- monitoring crystalline silica emissions, under the regulations relating to classified installations for environmental protection (ICPE) for quarries, especially for the benefit of residents living near this type of facility. It also recommends that the data from this monitoring be centralised and accessible.
- raising awareness among individuals using materials containing crystalline silica or performing DIY operations such as cutting tiles or concrete, sanding mortar, etc. of the risks associated with inhalation exposure to crystalline silica. This may involve developing new forms of communication and information on the risks at points of sale and intended for private individuals.

Improving knowledge with a view to prevention

Regarding metrology and exposure, the CES recommends:

- supplementing the study of the prevalence of exposure to crystalline silica in the main sectors concerned, especially construction, manufacture of basic metals, mining and quarrying, and manufacture of non-metallic mineral products.
- documenting exposure in under-investigated sectors such as agriculture, and sectors where work involves short periods of exposure to materials such as concrete, granite or artificial stone.
- developing standardised measurement methods for the occupational and general environments enabling both the sampling of particles according to their size and the analysis of crystalline silica in the different particle size classes, especially that of ultrafine particles, in order to better characterise the particle size distribution of crystalline silica.
- better characterising emissive processes, by developing activity/emission/particle size matrices.
- documenting the environmental concentrations of crystalline silica in outdoor air, through studies carried out both in background stations and near sites liable to generate crystalline silica-containing aerosols, such as major roads and construction sites. Depending on the results, the value of including crystalline silica in outdoor air quality monitoring could be assessed.
- acquiring exposure data for the general population through measurements during DIY activities, for example.
- depending on the exposure data collected, possibly conducting a health risk assessment in the general population.

Regarding epidemiology, the CES recommends:

- generally including lymph-node-only silicosis in both clinical and epidemiological studies of the health effects of silica exposure.
- pursuing studies to clarify the potential association with other cancers, especially digestive cancers.
- better documenting the effects of co-exposure in malignant and non-malignant diseases associated with crystalline silica.

- better investigating kidney, autoimmune and cardiovascular diseases associated with exposure to crystalline silica, with a particular focus on dose-response relationships.
- conducting new epidemiological studies to better analyse exposure characteristics such as dose rate, particle size distribution and surface activity of particles, which may modulate the toxic response.

Given the highly variable dose rates in some industry sectors, particularly sectors with occasional highly emitting activities, such as construction or manufacture of basic metals, the CES recommends conducting studies to establish "exposure duration/crystalline silica concentration" relationships associated with specific tasks.

Regarding toxicology, the CES recommends:

- documenting all the operations involved in producing particulate samples in experimental studies and characterising them, particularly in terms of particle size and surface properties.
- assessing the associated effects and role in carcinogenicity of the ultrafine fraction of crystalline silica, in comparison with the "respirable" fraction.
- comparing the effects by using complementary determinants to the silica mass, better suited to ultrafine particles (number, specific surface area).
- studying the mechanisms of cell response to crystalline silica by identifying the signalling and metabolic pathways activated: in particular by documenting 1) the immunogenic effects of crystalline silica and its possible role in increasing autoimmunity phenomena, 2) the mechanisms of cell death.
- conducting dose-response studies of inflammatory and genotoxic effects and developing models for studying genotoxicity at low doses.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES on "Assessment of the risks related to air environments".

Dr Roger Genet

KEYWORDS

Silice cristalline, quartz, cristobalite, tridymite, fraction alvéolaire, silicose, cancer broncho pulmonaire, pathologies interstitielles, pathologies respiratoires non malignes, pathologies rénales, maladies auto immunes, santé au travail, exposition professionnelle, risques sanitaires, surveillance médicale, étude de filière.

Crystalline silica, quartz, cristobalite, tridymite, respirable fraction, silicosis, bronchopulmonary cancer, interstitial diseases, non-malignant respiratory diseases, renal diseases, autoimmune diseases, occupational health, occupational exposure, health risks, medical surveillance, sector study.

ANNEX 1: CHARACTERISATION OF WORKERS' EXPOSURE TO CRYSTALLINE SILICA

Table 1: Share of the workforce included in the cross-referencing of COLCHIC and SCOLA exposure data with the 2010 and 2017 SUMER surveys

Source of the data	Nb ISs SUMER	Total nb employees SUMER	Nb exposed ISs SUMER	Nb exposed employees SUMER	Numbers included in relation to the total number of exposed employees considered in SUMER (%)
2010 SUMER	87	21,606,951	50	294,852	-
2010 SUMER * 2007-2016 SCOLA	32	11,783,514	29	256,740 (248,083)	87.1
2010 SUMER * 2007-2016 COLCHIC	14	4,257,745	14	227,817 (219,917)	77.3
2017 SUMER	83	24,787,985	42	365,194	-
2017 SUMER * 2007-2016 SCOLA	32	11,714,938	25	272,424 (244,382)	74.6
2017 SUMER * 2007-2016 COLCHIC	14	3,943,046	13	235,230 (193,873)	64.4

Nb ISs: number of industry sectors included (NAF-2 digits)
Nb: number; Data ( ): do not take into account industry sectors in which fewer than 100 employees responded to the SUMER surveys (significance threshold established by DARES)

Table 2: Share of the workforce included in the cross-referencing of COLCHIC and SCOLA exposure data over the 2009-2011 and 2015-2016 periods with the 2010 and 2017 SUMER surveys, respectively

Source of the data	Nb ISs SUMER	Total nb employees SUMER	Nb exposed ISs SUMER	Nb exposed employees SUMER	Numbers included in relation to the total number of exposed employees considered in SUMER (%)
2010 SUMER	87	21,606,951	50	294,852	-
2010 SUMER * 2009-11 SCOLA	11	2,257,270	11	76,019 (68,119)	25.8
2010 SUMER * 2009-11 COLCHIC	4	1,557,689	4	180,170 (180,170)	61.1
2017 SUMER	83	24,787,985	42	365,194	-
2017 SUMER * 2015-16 SCOLA	11	1,799,226	10	76,545 (48,502)	21.0
2017 SUMER * 2015-16 COLCHIC	4	373,575	4	172,634 (154,021)	47.3

Nb ISs: number of industry sectors included (NAF-2 digits)
Nb: number; Data ( ): do not take into account industry sectors in which fewer than 100 employees responded to the SUMER surveys (significance threshold established by DARES)

ANNEX 2: LITERATURE ANALYSIS METHOD USED TO UPDATE KNOWLEDGE ON THE HEALTH EFFECTS OF CRYSTALLINE SILICA