The Director General

Maisons-Alfort, 19 July 2021

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

on the systematic literature review of current knowledge on the characterisation of the hazards associated with asbestos ingestion

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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 19 July 2021 shall prevail.

On 3 January 2018, ANSES received a formal request from the Directorate General for Health (DGS) to undertake the following expert appraisal: “systematic literature review of current knowledge on the characterisation of the hazards associated with asbestos ingestion”.

1. BACKGROUND AND PURPOSE OF THE REQUEST

On 31 May 2017, the Agency received a formal request from the Directorate General for Health (DGS), in order to i) conduct a critical analysis of the articles by Di Ciaula and Gennaro (2016) and Di Ciaula (2017)[1], which state that the risk of gastrointestinal cancer associated with asbestos ingestion, in particular through the daily consumption of drinking water (DW) flowing through asbestos cement pipes, is underestimated, and ii) recommend any steps to be taken following this analysis in terms of health risk assessment (Request No 2017-SA-0138). This work, whose main conclusions and recommendations are set out below, were published in the form of a Scientific and Technical Support Note (AST) in November 2017 (ANSES 2017).

Concerning the critical analysis of the two literature reviews by Di Ciaula *et al.,* ANSES underlined that they were conducted using a non-systematic approach, without any description of the process implemented to identify and select the studies (documentary databases

[1] The article from 2017 provides more or less the same information as the article from 2016 but is better structured and more detailed.

explored, search years, search queries, method of selection, inclusion and exclusion criteria, etc.). Moreover, the way in which the quality of the studies was assessed was not explained.

ANSES considered that the arguments put forward did not provide any new evidence in relation to the monograph of the International Agency for Research on Cancer (IARC), concerning the relationship between exposure to asbestos through the ingestion of DW and the development of gastrointestinal cancer (IARC 2012). In fact, the epidemiological studies specifically dealing with DW ingestion, and the experimental studies analysed, were relatively old and limited in number; they had methodological limitations with varying results. Furthermore, the recent studies cited by Di Ciaula *et al*. that provided additional evidence regarding the existence of a relationship between occupational exposure to asbestos and the development of digestive cancers did not enable any conclusions to be drawn as to the contribution of the various exposure routes in the occurrence of these cancers.

In 2017, in light of the above, ANSES recommended:

- Conducting a systematic literature review of epidemiological studies assessing asbestos exposure *via* the ingestion of DW, experimental studies on the hazards associated with asbestos ingestion, and studies investigating the mechanisms of action of asbestos related to different exposure routes;
- Documenting asbestos contamination in French DW.

Due to the issues related to asbestos, the DGS submitted a formal request to ANSES in January 2018 to conduct a systematic literature review on current knowledge on the characterisation of the hazards associated with asbestos ingestion.

The Working Group set up to carry out this expert appraisal identified four key questions to meet this objective:

- Key Question 1 (KQ1): What is the link between asbestos exposure *via* ingestion, in particular of water, and digestive cancers (oesophagus, stomach, small intestine, colon, rectum, liver, bile ducts, pancreas, and peritoneum), ovarian cancer, and inflammatory bowel disease (IBD), based on human studies?
- Key Question 2 (KQ2): What is the link between occupational asbestos exposure and digestive cancers (oesophagus, stomach, small intestine, colon, rectum, liver, bile ducts, and pancreas)[2] and IBD?
- Key Question 3 (KQ3): What is the link between asbestos exposure *via* ingestion and the development of digestive tumours (oesophagus, stomach, small intestine, colon, rectum, liver, bile ducts, pancreas and peritoneum), ovarian cancer, and IBD, based on animal studies?
- Key Question 4 (KQ4): Do the kinetic and mechanistic data on the fate of fibres in the body and their migration to the digestive organs (including the inhaled part ingested secondarily, translocation[3], and carcinogenicity mechanisms) support the potential links observed in KQ1 and KQ2?

This work focused specifically on digestive health effects potentially related to the route of exposure by ingestion (digestive cancers and IBD) and also those for which there is evidence in the scientific literature of carcinogenicity after inhalation (ovaries and peritoneum) (IARC 2012). Laryngeal and pharyngeal cancers were not considered since they are part of the ear-

[2] The link between occupational asbestos exposure and peritoneal mesothelioma on the one hand and ovarian cancer on the other is proven according to the conclusions of IARC (2012). The Working Group therefore did not carry out a new assessment for these sites.

[3] In this context of this expert appraisal, the word "translocation" refers to the crossing of a physiological barrier.

nose-throat system. In animals, the results of studies by ingestion dealing with effects other than the development of digestive and ovarian tumours and IBD, and those of studies by inhalation dealing with the development of digestive tumours, were also discussed by the Working Group.

The aim of KQ1 and KQ3 was to directly answer the question of the hazards associated with asbestos ingestion. KQ2 could provide relevant data as to the effects of asbestos ingested secondarily following exposure by inhalation. Indeed, the digestive organs can be affected *via* various pathways:

- The direct passage of fibres to the gastrointestinal tract *via* the ingestion of contaminated air ("aerophagia"[4]) and their translocation through the intestinal epithelial barrier to the accessory digestive organs;
- The migration of inhaled fibres from the respiratory tract to the digestive organs *via* two mechanisms: mucociliary clearance followed by swallowing, and translocation from the deep lungs to the lymphatic and blood system.

The goal of KQ4 was to provide information about the fate of fibres in the body; in particular, it aimed to identify the main pathway through which inhaled asbestos fibres are transferred to the digestive organs (relevant for KQ2) and determine whether the mechanisms of action of asbestos in the gastrointestinal tract differ from those that are known in relation to the respiratory tract (relevant for KQ1 and KQ3).

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 issues being appraised lie within the scope of the Expert Committee on Water (CES "Water"). ANSES entrusted the expert appraisal to the Working Group (WG) on Asbestos ingestion. Expert rapporteurs from outside the Working Group were appointed to provide support for the assessment of publications examining occupational asbestos exposure and digestive cancers. The methodological and scientific aspects of the work were presented to the CES "Water" between 6 March 2018 and 6 April 2021. They were adopted by the CES "Water" at its meeting on 4 May 2021.

ANSES analyses interests declared by experts before they are appointed 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 following website: https://dpi.sante.gouv.fr/.

[4] For this expert appraisal, the word "aerophagia" encompasses direct air swallowing and the swallowing of fibres deposited in the mouth.

3. ANALYSIS AND CONCLUSIONS OF THE WG ON ASBESTOS INGESTION AND THE CES "WATER"

3.1. Expert appraisal method

Before carrying out its systematic literature review, the Working Group checked existing literature reviews dealing with the hazards or risks associated with asbestos ingestion, in order to identify their conclusions and limitations. Of the 13 identified reviews, 10 considered literature published before 1997. Most did not use a systematic literature review method with a weight-of-evidence analysis. None drew formal conclusions as to the link between asbestos ingestion *via* the consumption of contaminated water and cancers of the gastrointestinal tract.

To answer the first three questions of the expert appraisal designed to assess the link between the ingestion or inhalation of asbestos and digestive health effects, the Working Group conducted a systematic literature review with a weight-of-evidence analysis. The method selected was that developed by the Office of Health Assessment and Translation (OHAT) of the National Toxicology Program (NTP) (NTP OHAT 2019). This approach positively stands out from other assessment methods because it is transparent and highly directive. It also facilitates the harmonisation of criteria for assessing the quality of studies and the weight of evidence, both between the various experts and between the various bodies of evidence. The seven steps of the method, applied in parallel for KQ1, KQ2 and KQ3, are presented in Figure 1.

To answer KQ4 regarding the mechanisms of action and toxicokinetics of asbestos, the first two steps were similar (Figure 1). However, a narrative analysis of the results of the studies considered as being of interest was conducted in order to discuss the associations observed with the three other key questions. For the purposes of KQ4, a hearing was also conducted with an expert and pharmacokinetic modelling was carried out.

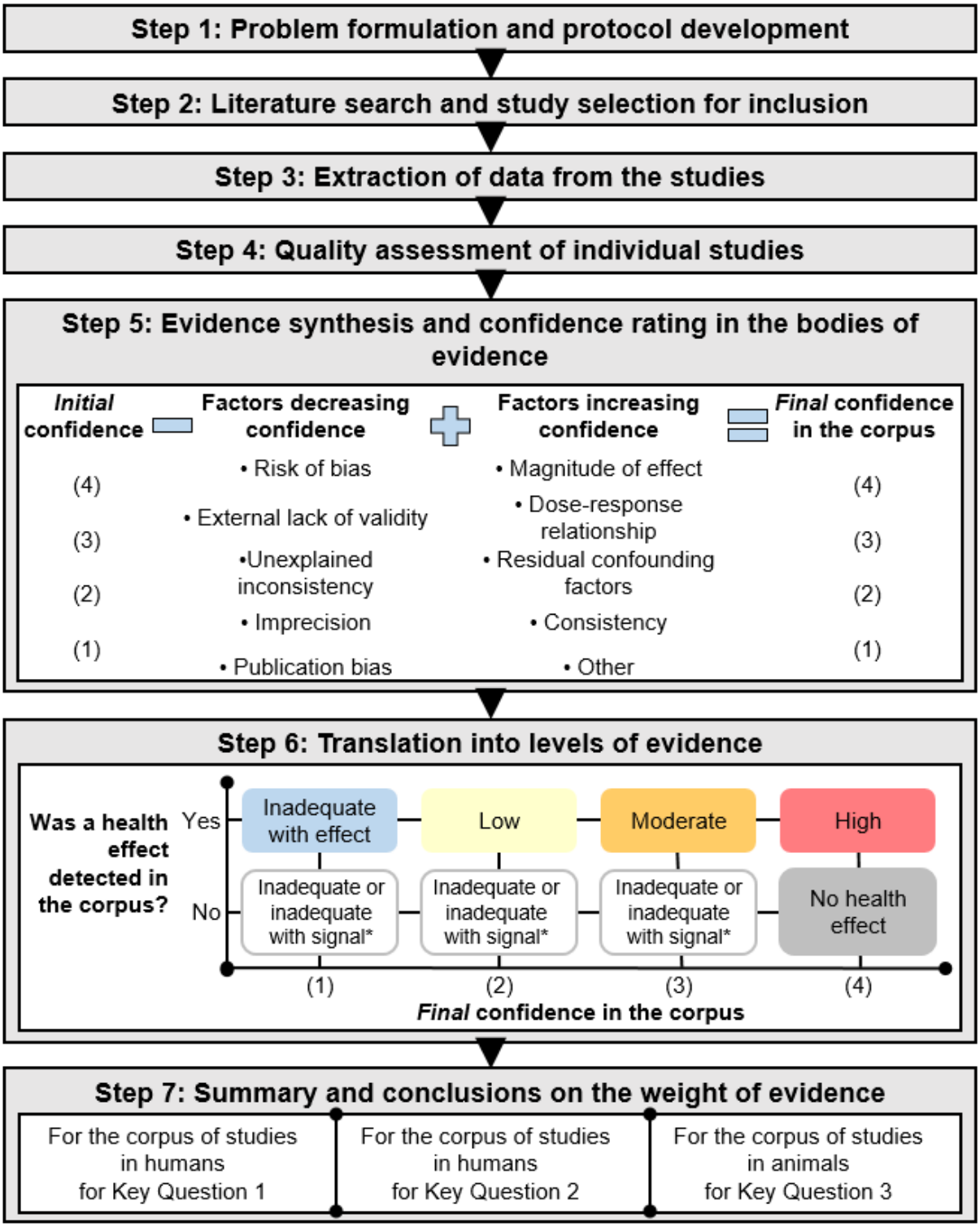
3.1.1. Problem formulation and development of the protocol

The first step of the expert appraisal led to the reformulation of the key questions as presented above. This step also involved the definition of PECOTS (Population, Exposure, Comparators, Outcomes, Timing, Setting) criteria for each of the key questions.

3.1.2. Literature search and study selection for inclusion

A literature search in the PubMed and Scopus search engines led to the identification of literature of interest to answer the four key questions. The queries were performed in September 2018 and included broad concepts (ingestion, asbestos, cancer) without any restrictions in this step. References were identified as being eligible after an initial screening (with double reading) of the titles and abstracts. After an evaluation of the full text, with double reviewing based on the PECOTS criteria, 17 studies[5] were considered as being of interest for KQ1, 41 studies[5] for KQ2 and 19 studies for KQ3.

[5] One study grouped together publications examining the same population or cohort in different time periods. A study could therefore refer to one or more publications.



**Within the "inadequate" level of evidence, the notion of "signal" was introduced secondarily by the Working Group to express the observation of statistically significant isolated associations that suggested the detection of a health effect but for which no firm conclusion could be drawn due to the limited number of studies and/or their methodological limitations.*

Figure 1. Process of the approach adopted by the Working Group for the weight-of-evidence assessment (adapted from NTP OHAT (2019))

3.1.3. Data extraction and analysis of the quality of the individual studies

All of the studies were analysed by two reviewers (Working Group members and/or external rapporteurs) in order to collect descriptive data and other key data, using an analysis grid adapted from that proposed by NTP OHAT. These grids summarise information concerning: the subjects (humans or animals), the methods (protocol, monitoring period, definition of health outcomes, exposure characterisation method, statistical analyses, etc.), and the key results and conclusions.

The risk of bias was assessed for each study using an adapted version of the approach developed by NTP OHAT. This method involves a tool that takes a parallel approach to rating risks of bias in human and animal studies. The tool comprises 15 questions classified into seven domains (selection, confounding, performance, attrition, detection, reporting, other). Each question corresponds to a potential risk of bias in the publication. The risk of bias for each study was assessed independently by two examiners (Working Group members and/or external rapporteurs) and then discussed to obtain a final rating.

An initial confidence level was attributed to each study by adding together the answers to four questions (1 if yes, 0 if no) defining important characteristics related to the study design: Was the exposure controlled? Was the exposure prior to the effect? Were the outcome data individual? Was a comparison group used? Experimental studies (animal experimentation, controlled clinical trials, etc.) generally have a maximum initial confidence level (4). Observational studies generally have an initial confidence level of 2 or 3, which never exceeds 3 due to the lack of controlled exposure.

3.1.4. Summary of the evidence and assessment of the confidence level in the corpora of studies

The studies were grouped into bodies of evidence according to various criteria for each key question; these bodies of evidence were included in a set of lines of evidence. A line of evidence therefore brings together integrated information of the same type, to meet the objective of assessing the weight of evidence contained in the literature (Figure 1, Step 5). The criteria for grouping the studies into lines of evidence were as follows:

- KQ1: studied site (individual sites and combinations, n=13), studied health outcome (incidence or mortality), and initial confidence level. In total, 33 lines of evidence were set based on the 17 studies included.
- KQ2: studied site (all individual sites, n=9), studied health outcome (incidence or mortality), and initial confidence level. In total, 18 lines of evidence were created from the 41 studies included.
- KQ3: route of administration (ingestion or gavage), studied site (individual sites and combinations, n=10), species (rodents or primates), asbestos type (chrysotile or amphiboles), exposure duration (single or chronic administration), and initial confidence level. In total, 75 lines of evidence were created from the 19 studies included.

The quality of the bodies of evidence in each of the lines of evidence was assessed on the basis of 10 factors proposed by NTP OHAT and adapted for the needs of the Working Group (Figure 1, Step 5). These factors either increased or decreased confidence in the results of the body of evidence. The final confidence level for the body of evidence was the initial confidence level (i) from which the number of confidence-reducing factors was subtracted, and (ii) to which the number of confidence-increasing factors was added. Four final confidence ratings were

used, ranging from 1 (very low) to 4 (high). These ratings reflected the overall quality of the body of evidence and summarised the level of confidence in the results. Each line of evidence was independently assessed by a Working Group member and then discussed in a plenary session. The decisions were taken after reaching a consensus.

In the end, for each line of evidence, the Working Group drew a conclusion as to whether (or not) a health effect had been detected according to the results provided by the corresponding body of evidence.

3.1.5. Translation into levels of evidence

The conclusion for each line of evidence, called the "level of evidence", combined the final confidence level of the body of evidence with the detection of a health effect (Figure 1, Step 6). There were five levels of evidence: high, moderate, low, inadequate, and no health effect. The level of evidence characterised the plausibility of the association between asbestos exposure and the health outcome for each line of evidence:

- "**High**" level of evidence: there is high confidence in the body of evidence to support the association between exposure and the health outcome.
- "**Moderate**" level of evidence: there is moderate confidence in the body of evidence to support the association between exposure and the health outcome.
- "**Low**" level of evidence: there is low confidence in the body of evidence to support the association between exposure and the health outcome.
- "**Inadequate**" level of evidence: confidence in the body of evidence is inadequate to rule as to whether or not there is an association between exposure and the health outcome.
- "**No health effect**" level of evidence: there is high confidence in the body of evidence to support the lack of an association between exposure and the health outcome.

The first three levels of evidence (high, moderate and low) directly characterise the degree of plausibility for the association between asbestos exposure and the health outcome (in red, orange and yellow in Figure 1, Step 6). The "inadequate" level of evidence is used when confidence in the body of evidence is too low to rule as to the plausibility of the association ("inadequate with effect", in blue in Figure 1, Step 6) or to support the lack of an association ("inadequate", in white in Figure 1, Step 6). Within the "inadequate" level of evidence, the notion of "signal" was introduced secondarily by the Working Group to express the observation of statistically significant isolated associations that suggested the detection of a health effect but for which no firm conclusion could be drawn due to the limited number of studies and/or their methodological limitations ("inadequate with signal", in white in Figure 1, Step 6). The "inadequate with signal" level of evidence suggests the possibility of an association between asbestos exposure and the health outcome.

3.1.6. Summary and conclusions

The conclusions below summarise and compare the results from the weight-of-evidence assessment (KQ1, KQ2, KQ3) and the narrative literature review (KQ4).

3.2. Main results of the expert appraisal

The results presented in this opinion are a summarised version of the literature review and weight-of-evidence assessment carried out by the Working Group. The full process of

translating the levels of evidence of asbestos effects by cancer site is available in the collective expert appraisal report.

The main results of this expert appraisal by key question are summarised in Table 1. It should be noted that no publications examining the link between asbestos exposure (by ingestion or inhalation) and IBD were identified in the literature.

The epidemiological studies available for KQ1 dealt exclusively with the ingestion of water contaminated by asbestos, whether of anthropogenic (related to asbestos cement pipes or industrial contamination) or natural (rocky outcrops) origin. The animal experimentation studies available for KQ3 examined various sources and routes of exposure: ingestion of contaminated feed or water, gavage, and intragastric administration.

The data from the epidemiological studies published to date that have assessed the risk of cancer associated with the ingestion of asbestos-contaminated water are insufficient to establish a formal link between consumption of this water and an increased risk of digestive cancer (KQ1) (all "inadequate" levels of evidence). However, the Working Group underlines:

- **The methodological limitations related to the design of the available studies (primarily ecological studies), which were not suitable for the demonstration of a health effect, and the fact that these studies were old;**
- **The existence of "signals" within the "inadequate" levels of evidence, suggesting the possibility of an association, both in the corpora examining incidence and in those examining mortality, for several organs: oesophagus, stomach, colon (colorectal cancer) and pancreas.**

The data from the epidemiological studies examining the health effects observed in workers exposed to asbestos (KQ2) support the "signals" mentioned for the oesophagus, stomach and colon (colon-rectum), with low to moderate levels of evidence for these three organs. However, these results give no indication as to the mechanism causing asbestos to reach the digestive organs after inhalation (mucociliary clearance followed by swallowing, or haematogenous or lymphatic transport of the fibres from the lungs).

The data from the animal experimentation studies are insufficient to establish a link between asbestos ingestion and the development of digestive or ovarian tumours (KQ3) (all "inadequate" levels of evidence). However, the Working Group underlines that:

- **There are many methodological limitations in these studies, related in particular to the methods of administration (not comparable, and questionable for certain studies), the number of and lack of justification for the tested doses, or the small number of animals per group;**
- **There is a "signal" for the colon within the "inadequate" level of evidence.**

Table 1. Levels of evidence obtained following the weight-of-evidence assessment, and main conclusions from the narrative literature review

Key Questions (KQs)	**What is the link between asbestos exposure via ingestion, in particular of water, and digestive cancers, ovarian cancer, and IBD, based on human studies? (KQ1)**	**What is the link between asbestos exposure via ingestion and the development of digestive tumours, ovarian tumours and IBD, based on studies in animals? (KQ3)**	**What is the link between occupational asbestos exposure and digestive cancers and IBD? (KQ2)**	**Do the kinetic and mechanistic data on the fate of fibres in the body and their migration to the digestive organs support the potential links observed in the other key questions? (KQ4)**
Method	Systematic literature review and weight-of-evidence assessment			Narrative literature review
Results	Levels of evidence[B] of asbestos effects by site:			Main conclusions:
Oesophagus	**Inadequate with signal* (n=9)**	Inadequate (n=15)	**Moderate (n=23)**	● Biometrology data in humans (rare) and in animals in favour of crossing of the gastrointestinal barrier after ingestion. Presumably small fraction (between 1/1000 and 1/100,000). ● Migration of the fibres to multiple organs, including digestive organs, after inhalation. The fraction of asbestos ingested secondarily after inhalation in humans cannot be quantified. ● No conclusion can be drawn regarding the main pathway through which the digestive organs are affected following exposure by inhalation: mucociliary clearance and/or translocation. Depends on several factors relating to the sites where the fibres are initially deposited in the respiratory tract and the size of the fibres.
Stomach	**Inadequate with effect (n=15)**	Inadequate (n=15)	**Low (n=28)**	
Small intestine	Inadequate (n=5)	Inadequate (n=15)	Inadequate (n=3)	
Colon	**Inadequate with signal* (n=13)**	**Inadequate with signal* (n=17)**	**Moderate (n=17)**	
Colon-rectum	Inadequate (n=2)		**Low (n=17)**	
Rectum	Inadequate (n=14)	Inadequate (n=14)	**Inadequate with signal* (n=14)**	
Liver	Inadequate (n=6)	Inadequate (n=16)	**Inadequate with signal* (n=6)**	
Bile ducts	Inadequate (n=6)	Inadequate (n=14)	Inadequate (n=3)	
Pancreas	**Inadequate with signal* (n=14)**	Inadequate (n=15)	Inadequate (n=11)	
Peritoneum	Inadequate (n=3)	Inadequate (n=14)	*(not studied in the expert appraisal)*	
Digestive system[A]	Inadequate (n=11)	*(not studied in the expert appraisal)*	*(not studied in the expert appraisal)*	
Ovaries	Inadequate (n=4)	Inadequate (n=10)	*(not studied in the expert appraisal)*	

*IBD: inflammatory bowel disease. No publications were identified dealing with the link between asbestos exposure and IBD. A: including the gastrointestinal tract. B: the level of evidence combines the level of confidence in a body of evidence with the presence (or absence) of a detected health effect in that body (see Figure 1, Step 6 for the definition of levels of evidence and the corresponding colour code). The level of evidence characterises the plausibility of the association between asbestos exposure and the health outcome of interest. * Within the "inadequate" level of evidence, the notion of "signal" was introduced by the Working Group to express the observation of statistically significant isolated associations that suggested a health effect but for which no firm conclusion could be drawn. Thus, the "inadequate with signal" level of evidence suggests the possibility of an association between exposure and the health outcome. n=number of studies included in the body of evidence.*

Non-digestive tumours were detected in the studies by ingestion in animals (keratoacanthoma, tumours of the clitoral gland, thyroid C-cell adenoma and carcinoma, leukaemia, and adrenal gland adenoma). However, the importance of these findings was discussed by the authors, particularly with regard to the statistical analysis methods used. The Working Group considers that no conclusion on the link between asbestos ingestion and the development of these tumours can be drawn based on these data.

Of the numerous animal experimentation studies in which animals were exposed to asbestos **by inhalation**, only a few examined digestive sites. None of them reported a significant increase in the frequency of digestive tumours in these chronically exposed animals.

The identified **biometrology studies** in humans and animals suggested that asbestos can cross the wall of the gastrointestinal tract following ingestion, and migrate to various organs, including digestive organs, after inhalation. However, it could not be determined, based on the available data, whether the main pathway through which the digestive organs were affected after inhalation was mucociliary clearance followed by swallowing, or translocation from the deep lungs to the lymphatic and blood system. Moreover, the fraction of asbestos reaching the digestive tract following inhalation could not be reliably estimated in quantified terms. The same was true for the estimated fraction of asbestos crossing the gastrointestinal wall, even though this was assumed to be low (between 1/1000 and 1/100,000 according to certain authors). Nonetheless, some authors considered that the quantity of asbestos ingested annually following exposure by inhalation may have been of the same order of magnitude as that ingested annually *via* the consumption of contaminated water, according to the scenario and parameters used. Lastly, some studies indicated that ingested asbestos is capable of causing cellular toxicity, with or without cellular proliferation, in certain digestive organs.

3.3. Conclusions and discussion

To the knowledge of the members of the Working Group on Asbestos ingestion and the CES "Water", this is the only expert appraisal that has taken such an in-depth and cross-cutting approach to the issue of the hazards associated with asbestos ingestion, based on a systematic literature review with a weight-of-evidence assessment of studies on asbestos ingestion in humans and animals and studies in occupational environments in humans. The mechanistic and toxicokinetic data collected also provided an opportunity to discuss the results from these various bodies of evidence.

Even though the analysis conducted for this expert appraisal did not make it possible for a formal link to be established between asbestos ingestion *via* the consumption of contaminated water and the cancers studied, the Working Group underlines that "signals" were observed within the "inadequate" levels of evidence, suggesting the possibility of an association for oesophageal, stomach and colon cancer. For these three sites, low to moderate levels of evidence of an effect of occupational asbestos exposure were also demonstrated, potentially supporting the "signals" mentioned in the studies by ingestion. A "signal" for colon cancer was also observed in the animal experimentation studies. Moreover, there were biometrological arguments supporting the biological plausibility of the association between asbestos and oesophageal, stomach and colon tumours.

Nevertheless, several points suggest that these results should be interpreted with caution.

The intrinsic limitations of the epidemiological studies examining the ingestion of asbestos-contaminated water, almost all of which were ecological in nature, prevented any conclusion

from being drawn regarding the causal relationship between asbestos ingestion and the occurrence of digestive cancers.

Concomitant exposure to substances other than asbestos was considered by the Working Group throughout the weight-of-evidence assessment process whenever this was permitted by the data reported in the publications. However, it is possible that the levels of evidence observed for the effects of occupational asbestos exposure actually reflected concomitant exposure to other carcinogenic substances.

In animal experimentation studies, the development of digestive tumours is a rare outcome making it difficult to demonstrate statistically significant differences when the groups (control and exposed) are small in size, which was the case for the majority of the examined studies.

The size of the fibres in the epidemiological and animal experimentation studies was not systematically specified and was not taken into account in the analyses. Therefore, no conclusions could be drawn as to the link between the occurrence of digestive cancers and the ingestion of asbestos fibres according to their size. In the experimental studies providing this type of data, the fibres measured in tissues after ingestion were generally short, but no general conclusion could be drawn based on the data regarding the passage of fibres according to their size. Similarly, the type of fibre ingested was generally unknown in the epidemiological studies, making it impossible to issue specific conclusions according to the type of fibre.

The conditions of exposure, and the duration and frequency of contact between the fibres and the site of interest, differ depending on whether an individual is exposed *via* the ingestion of contaminated water or *via* swallowing after mucociliary clearance. For the oesophagus, it is likely that occupational exposure (slow semi-continuous flow related to the mechanism of mucociliary clearance followed by swallowing) causes the fibres to remain in contact with tissues over a longer period than with the ingestion of water (discontinuous flow). Most of the animal experimentation studies focused on the ingestion of feed spiked with asbestos fibres, which is different from the ingestion of water considered in the epidemiological studies and may impact the availability and residence time of the fibres in the various organs of the gastrointestinal tract (in particular for the oesophagus and stomach).

Based on the data available in the literature, no formal conclusion can be drawn regarding the main pathway through which the digestive organs are affected following occupational exposure by inhalation. Although translocation of the fibres from the deep lungs to the digestive organs *via* the blood or lymphatic system is possible, it is likely that a large share[6] of the inhaled asbestos reaches the digestive tract through secondary ingestion (mucociliary clearance followed by swallowing). Extrapolating the results obtained for exposure in occupational settings (inhalation) to environmental exposure *via* the consumption of water (ingestion) is therefore difficult and associated with uncertainties.

Assuming that the digestive organs are primarily affected *via* mucociliary clearance followed by swallowing, the data from the literature and the results of the pharmacokinetic models indicate that the quantity of fibres ingested annually following exposure in occupational settings may be of the same order of magnitude as the quantity of fibres ingested annually *via* the consumption of contaminated water. Nonetheless, the quantities of fibres ingested *via* air and *via* the consumption of water should be compared with caution since fibres in air and water have different morphological and dimensional characteristics.

[6] In the literature, the estimated swallowed fractions of asbestos after mucociliary clearance ranged from 16% to 100% of the initially inhaled quantity. These largely depended on the size of the inhaled fibres.

3.4. Recommendations

The Working Group reiterates that in 2017, ANSES's CES "Water" emphasised that establishing a guideline value in drinking water (DW) would only make sense if the causal relationship between asbestos exposure *via* ingestion and the development of tumours was certain or probable (ANSES 2017).

At this point, in light of the conclusions of this expert appraisal and the limitations of the corpora of studies examined, no guideline value can be established in DW based on health criteria. The Working Group has no scientific arguments for setting a maximum number of asbestos fibres per litre of DW not to be exceeded, or for concluding as to a health risk associated with these fibres according to their size or type.

However, since a health effect cannot be ruled out, the Working Group is issuing, first of all, recommendations for monitoring asbestos fibres in water and the deterioration of asbestos cement pipes. The data thus acquired are essential to better characterise the potential exposure of populations, and to implement epidemiological studies in particular. The Working Group is also issuing recommendations on improving knowledge on the hazards associated with asbestos ingestion.

3.4.1. Recommendations for monitoring asbestos fibres in water

As a reminder, in France, there is currently no regulatory obligation to analyse DW for asbestos content, and there are no recommendations concerning the dimensional criteria that should be taken into account when measuring asbestos fibres in water. Moreover, Directive (EU) 2020/2184 of 16 December 2020 on the quality of water intended for human consumption does not include asbestos on its watch list.

In keeping with the recommendations issued in 2017 (ANSES 2017), the Working Group stresses the need to measure and characterise asbestos fibre levels in DW likely to contained them, such as in:

- **DW distributed through asbestos cement pipes;**
- **DW produced from raw water that may potentially contain asbestos fibres (natural or anthropogenic origin) and does not undergo any clarification treatment.**

The Working Group therefore agrees with the recommendation of the World Health Organization which, in its draft document for the updating of limit values in water, also advises carrying out analytical campaigns to update the available data on DW contamination concerning the concentrations, fibre sizes and types of asbestos in water from old asbestos cement pipes (WHO 2020).

Such measurements should be taken according to a harmonised, standardised protocol. Transmission electron microscopy (TEM), which in France is the recommended method for monitoring asbestos fibres in air, could be used to measure asbestos fibres levels in water, mentioning various classes of fibre lengths (≤ 5 µm, 5-10 µm, > 10 µm) in the analysis reports. Moreover, a sampling strategy needs to be defined to take into account the impact of hydraulic fluctuations in water supplies on the concentrations observed.

The Working Group stresses the need to submit the results obtained to the competent regional and national authorities, so they may be combined and used for the purposes of research or epidemiological surveillance.

As mentioned in earlier work (ANSES 2017), the risk of fibres being released from asbestos cement pipes into the water supply remains low when the pipes have been installed in stable non-aggressive soil, and when the water carried by these pipes contains calcium[7]. However, this risk cannot be ruled out in the case of badly deteriorated (friable) pipes.

Therefore, by analogy with what was recommended for assessing the deterioration of materials and products containing asbestos in buildings and the release of fibres in air (AFSSET 2009), monitoring the release of fibres from asbestos cement pipes into DW is also recommended.

The Working Group therefore recommends (i) developing non-destructive in-line inspection techniques capable of determining the state of disrepair of asbestos cement pipes (Leroy *et al.* 1996; van Laarhoven and Quintiliani 2020; White, Mordak and Wheeler 1988) and (ii) conducting studies to determine the concentration of asbestos in water that could reflect the deterioration of the materials, potentially requiring that the pipes in question be rehabilitated or replaced as appropriate.

3.4.2. Recommendations for improving knowledge on the characterisation of the hazards associated with asbestos ingestion

Characterising the hazards associated with asbestos ingestion requires the availability of high-quality data in the mechanistic, kinetic, animal experimentation, and epidemiological fields. In view of the limitations in the literature identified in this expert appraisal and the remaining uncertainties in relation to certain questions, efforts still need to be made to acquire knowledge to better understand the link between asbestos ingestion and the occurrence of health effects and to characterise the corresponding risk. Better characterisation of this risk will be made possible by the collection and communication of measured concentrations of fibres in water supply systems.

The Working Group recommends **assessing the feasibility of carrying out** new studies or of updating the existing epidemiological studies examining asbestos ingestion, and then implementing these studies where appropriate. All types of epidemiological (ecological, case-control, cohort and nested studies) and animal experimentation studies can be considered. However, in order for them to be relevant, they will need to minimise as far as possible the limitations identified in the literature and fulfil the current research criteria.

- These new epidemiological studies could draw from contemporary databases, thus improving the characterisation of exposure (in connection, for example, with the collection of measurement data resulting from the previous recommendations) and health outcomes (in connection, for example, with improved coverage by cancer registries and the combination of several data sources for the definition of cases) in the general population. As far as possible, such studies should take into account the presence of individual confounding factors, even if only qualitatively or indirectly. The priority health outcomes to be studied would be those for which a "signal", reflecting a possible association, has been observed in the literature as analysed in this expert appraisal: oesophageal, stomach and colon cancers.
- Before any new experimental studies in animals can be conducted, the Working Group recommends pooling the available data on other types of particles having dimensional characteristics similar to those of asbestos; this could, by analogy, provide useful information for the characterisation of the hazards associated with asbestos ingestion.

[7] In France, there is an obligation to supply DW in calco-carbonic equilibrium, with a pH of 6.5 to 9 and a conductivity of 200 to 1100 µS/cm at 25°C, according to the Ministerial Order of 11 January 2007 (on the quality references and limits for raw water and water intended for human consumption listed in Articles R. 1321-2, R. 1321-3, R. 1321-7 and R. 1321-38 of the French Public Health Code).

If new animal experimentation studies need to be carried out, they will have to include a sufficient number of animals per group and enable dose-response relationships to be studied, in compliance with ethical measures.

The Working Group also recommends **encouraging further research into the modes of migration** of asbestos fibres, or of particles having similar dimensional characteristics (nanoforms or elongated mineral particles, for example), to the digestive organs after ingestion and inhalation, by carrying out new studies complying with the current research standards. Such studies would also improve knowledge for these other particles.

In addition, the Working Group recommends **carrying out new biometrology studies in humans** to characterise asbestos fibre loads in the digestive organs thanks to samples collected during surgical procedures in patients with known occupational exposure, as is performed for bronchial cancers.

Lastly, for all of these recommendations designed to improve knowledge, the Working Group recommends relying on **international multidisciplinary networks** and considering their implementation at European level or even internationally, including other countries concerned by or wondering about the issue of asbestos in DW.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The critical reading of the articles by Di Ciaula *et al.*, stating that the health risks associated with asbestos ingestion are underestimated, gave rise to the publication of a Scientific and Technical Support Note (AST) by the French Agency for Food, Environmental and Occupational Health & Safety in 2017. In this note, the Agency considered that the arguments put forward by the authors did not provide any new evidence in relation to the IARC monograph (2012) and recommended conducting a systematic literature review, as described in this expert appraisal, in order to better characterise the hazards associated with asbestos ingestion.

ANSES endorses the analysis, conclusions and recommendations of the experts in the Working Group on Asbestos ingestion and the CES “Water”, regarding the systematic literature review designed to characterise the hazards associated with asbestos ingestion.

The Agency reiterates that, although the use of asbestos has been prohibited in France since 1997, its past use in the manufacture of asbestos cement pipes and the presence of natural outcrops constitute potential sources of exposure in the population *via* the consumption of water.

To answer the question concerning the characterisation of the hazards associated with asbestos ingestion, the expert appraisal drew on a weight-of-evidence assessment method applied to the systematic review of the available toxicological and epidemiological literature, accompanied by a literature review of studies examining the kinetics of asbestos; the working framework proposed by NTP OHAT (2019) was adapted by the Working Group for its specific needs. The levels of evidence obtained characterise the degree of plausibility of the association between asbestos exposure and the various health outcomes of interest, through five categories: high, moderate, low, inadequate, and no health effect (NTP OHAT 2019). Within the “inadequate” level of evidence, the notion of “signal” was introduced secondarily by the Working Group to express the observation of statistically significant isolated associations that suggested a detected health effect but for which no firm conclusion could be drawn, thus indicating a possible association between asbestos exposure and the health outcome of interest.

The expert appraisal concluded that the data from the epidemiological and experimental studies published to date were not sufficient to rule as to the plausibility of the association between asbestos ingestion and digestive cancers. Nevertheless, the inadequate levels of evidence suggested the possibility of an association between asbestos ingestion and oesophageal, stomach and colon (colorectal) cancers. For these three sites, low to moderate levels of evidence of effects of occupational asbestos exposure were also observed, although they did not provide any indication as to the mechanism causing asbestos to reach the digestive organs after inhalation (mucociliary clearance followed by swallowing, or haematogenous or lymphatic transport of the fibres from the lungs).

In view of the results, the Agency underlines the recommendations of the Working Group on Asbestos ingestion and the CES "Water" concerning the monitoring of asbestos fibres in water, in particular:

- In line with the recommendations issued in 2017 following the previous formal request, the need to measure and characterise asbestos fibres levels in DW likely to contain them, *via* targeted analytical campaigns. This is closely linked to the need to acquire new knowledge and the purpose of the request. The results will be used for research or epidemiological surveillance purposes.
- The need to monitor the deterioration of asbestos cement pipes, which may require that they be rehabilitated or replaced as appropriate.

As a reminder, since 2014, public drinking water services have been required to establish an annual detailed description of structures for the transport and supply of drinking water (Articles L. 2224-7-1 and D. 2224-5-1 of the French Local and Regional Authorities Code) specifying the lengths of pipes, the year or period of installation, the information available about the materials used, and the diameters of the pipes. Furthermore, at the request of the French Ministry of Ecological and Inclusive Transition (MTES) and the French Biodiversity Agency (OFB), the National Research Institute of Science and Technology for Environment and Agriculture (IRSTEA) was mandated to set up a national asset knowledge base for drinking water networks, operating at water agency scale (Husson *et al.* 2020). Therefore, the locations of asbestos cement pipes should be known to the bodies in charge of the production and supply of DW.

Lastly, the results of this expert appraisal relating to occupational asbestos exposure may provide input for other ongoing work on this topic at the Agency.

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KEYWORDS

Amiante, cancers digestifs, eau destinée à la consommation humaine (EDCH), effets sanitaires, évaluation du poids des preuves, ingestion.

Asbestos, digestive cancers, drinking water, health effects, ingestion, weight of evidence.

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