

The Director General

Maisons-Alfort, (17 June 2019)

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

on Exposure to cadmium (CAS no. 7440-43-9) – Proposals for toxicity reference values (TRVs) by ingestion, health reference values in biological media (blood, urine, etc.) and cadmium levels in fertilizers and growing media that would control pollution of agricultural soils and contamination of crop production

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES's public health mission involves ensuring 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 the necessary information concerning these risks as well as the requisite expertise 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 17 June 2019 shall prevail.

On 22 June 2015, ANSES received a formal request from the Directorate General for Health (DGS), the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF), the Directorate General for Labour (DGT), the Directorate General for Food (DGAL) and the Directorate General for Risk Prevention (DGPR) to conduct an expert appraisal on the following issue: Exposure to cadmium – Proposals for toxicity reference values (TRVs) by ingestion, health reference value in biological media (blood, urine, etc.) and cadmium levels in fertilizers and growing media that would control pollution of agricultural soils and contamination of crop production.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Cadmium is a ubiquitous trace metal element found in the various environmental compartments (soil, water, air) due to its natural presence in the Earth's crust and to anthropogenic inputs related to industrial and agricultural activities. Cadmium is readily available for uptake by plants through their roots, by which it enters the food chain.

Cadmium metal was classified as “carcinogenic to humans” (Group 1) by the International Agency for Research on Cancer (IARC) in 2012. It is also classified as Category 1B carcinogenic, Category 2 toxic for germ cell mutagenicity and Category 2 toxic for reproduction according to the European CLP Regulation¹. Moreover, cadmium is known to induce renal tubular impairment and bone fragility in humans, following prolonged oral exposure. Reproductive disorders have also been reported.

¹ The CLP (Classification, Labelling, Packaging) Regulation refers to Regulation (EC) No 1272/2008 of the European Parliament on classification, labelling and packaging of substances and mixtures.

In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) set the provisional tolerable monthly intake (PTMI) of 25 $\mu\text{g}\cdot\text{kg}^{-1}$ body weight as the toxicity reference value (TRV) by ingestion. In 2011, the European Food Safety Authority (EFSA) adopted a tolerable weekly intake (TWI) of 2.5 $\mu\text{g}\cdot\text{kg}^{-1}$ body weight, which was the same value that had been established earlier in 2009.

Furthermore, Action 24 of the 2015-2019 Third National Environmental Health Action Plan (PNSE3) intends to assess the relevance and feasibility of measures to detect or monitor blood concentration levels in populations exposed to metals such as cadmium on priority sites, implement them when appropriate and disseminate prevention information based on the results. At national level, however, no health benchmark values have been set in biological media for screening purposes.

Apart from smoking, the main source of exposure to cadmium in the general population is food (EFSA, 2009, 2012). According to the ANSES opinion and report on the second Total Diet Study (TDS2) of June 2011 (ANSES, 2011a)², the dietary exposure of people in France to cadmium appeared to be increasing compared to the previous TDS published in 2004. The TWI defined by EFSA in 2009 was exceeded in 0.6% of adults and 15% of children. More recently, the infant Total Diet Study (iTDS) published in September 2016 (ANSES, 2016)³ drew the same conclusion as the TDS2, i.e. that the health risk associated with cadmium cannot be ruled out for children under three years of age. Following the second TDS, ANSES issued an opinion on the revision of maximum levels for cadmium in foodstuffs intended for human consumption (ANSES, 2011b). To reduce population exposure, it recommended acting on the level of contamination of environmental sources, particularly regarding the inputs (mineral fertilizers – especially phosphate fertilizers – organic fertilizers and soil conditioners, etc.) partly responsible for soil and food contamination.

Of these inputs, commercial inorganic mineral fertilizers are defined in the European Union (EU) by Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003⁴, amended by Commission Regulation (EU) No 463/2013 of 17 May 2013.

The French standard NF U 42-001-1 currently sets a regulatory maximum cadmium content for these commercial mineral fertilizers of 90 mg Cd.kg⁻¹ by mass of phosphoric anhydride (P₂O₅) equivalent. However, a new draft European regulation, extended to all fertilizers (mineral and organic fertilizers, mineral and organic soil conditioners) and growing media, was being prepared at the time of the reception of this request on 22 June 2015. Its goal was to set limit values for contaminants. The establishment of such levels will thus apply to cadmium as part of the marketing of CE-marked fertilizers and growing media. In this context, France supported the European Commission's recent proposal to submit the study published in 2013 by Fertilizers Europe⁵ (representing the main manufacturers of mineral fertilizers in Europe (28 Member States + Norway)) to the Scientific Committee on Health and Environmental Risks (SCHER) for an assessment, in particular with regard to a potential health risk. In light of recent data, this study was an update of a previous publication by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, which later became the SCHER) dating from 2002⁶ on cadmium in mineral phosphate fertilizers. On 6 January 2016, following the plenary meeting of 27 November 2015, the SCHER published its final opinion on

² ANSES. (2011a). ANSES opinion and expert appraisal report on the second French Total Diet Study (TDS2) - Volume 1: Inorganic contaminants, minerals, persistent organic pollutants, mycotoxins and phyto-oestrogens, French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort.

³ ANSES. (2016). ANSES opinion and expert appraisal report on the Infant Total Diet Study (iTDS) - Volume 1: ANSES opinion & Summary and conclusions, French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort.

⁴ Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003 relating to fertilizers.

⁵ Revisiting and updating the effect of phosphate fertilizers to cadmium accumulation in European agricultural soils.

⁶ CSTEE, Scientific Committee on Toxicity, Ecotoxicity and the Environment. Brussels, C2/AST/csteeop/Cadmium in fertilizers 24092002/D(02), (2002). Opinion on "The Member State Assessments of the Risk to Health and the Environment from Cadmium in Fertilizers".

the analysis of the study by Fertilizers Europe on new conclusions regarding estimated future trends of cadmium accumulation in soils after adding cadmium to soils via phosphate fertilizers⁷.

In light of this information, ANSES was asked to issue an opinion regarding the following questions:

1. For local populations living near polluted sites and likely to be overexposed to cadmium:
 - a) What TRVs by ingestion (adults, children, etc.) should be used when carrying out quantitative health risk assessments?
 - b) What health benchmark values should be used for cadmium in biological media (blood, urine, etc.), according to age, for health management purposes?
2. For populations of workers in contact with fertilizers, products or processes involving cadmium, or working on polluted sites, and in light of information that may be obtained in the context of the formal request addressed to the InVS (National Institute for Public Health Surveillance, which became *Santé publique France* on 1 May 2016):
 - a) Are the risks associated with cadmium exposure in these occupational contexts adequately assessed under occupational health and safety regulations (using a sector survey, for example)?
 - b) What levels of contamination can be estimated for various occupational activities and situations?
 - c) What conclusions can be drawn in comparison with occupational exposure limits (OELs) and biological limit values (especially those recommended by ANSES)?
3. In all fertilizers and growing media, taking into account the aforementioned European studies and the specificity of these products, what cadmium levels would make it possible to control pollution of agricultural soils and contamination of crop production?

A conceptual framework summarising all of these questions can be found in Annex 1 of this opinion.

Following a progress report with the ministries that had signed the formal request, the Agency's experts agreed to focus Question 2 solely on the population of workers in contact with fertilizers or growing media, and not consider the issue of polluted sites and soils in their expert appraisal work. This agreement appears in the two amendments to the expert appraisal contract.

2. ORGANISATION OF THE EXPERT APPRAISAL

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

The collective expert appraisal initially fell within the sphere of competence of the Expert Committee on "Characterisation of substance hazards and toxicity reference values" (Substances Committee) which became the Expert Committee on "Health reference values" (HRV Committee) in September 2017. The methodological and scientific aspects of the work were presented to these Expert Committees.

ANSES entrusted the expert appraisal to expert rapporteurs from the Expert Committees on "Assessment of physical-chemical risks in food" (ERCA Committee), "Expert appraisal for setting exposure limits for chemical agents in occupational environments" (OEL Committee) and "Fertilizers and growing media" (MFSC Committee), as well as from the Expert Committees on Substances and the associated HRV Committee.

Regarding the first two questions (1a and 1b): the expert rapporteurs' work was presented to the ERCA and OEL Committees at their meetings on 12 October 2015 and 8 March 2016, respectively.

⁷ SCHER, Scientific Committee on Health and Environmental Risks (2015). Final Opinion on new conclusions regarding future trends of cadmium accumulation in EU arable soils. Adopted by the SCHER during its plenary meeting of 27 November 2015.

The collective expert appraisal report addressing these two questions was validated on 23 November 2017 by the HRV Committee. It should be noted that one expert from the HRV Committee expressed a dissenting opinion on the collective expert appraisal report for Question 1. His position is laid out in the “Dissenting Positions” section of the collective expert appraisal report.

Regarding Question 2: the expert rapporteurs’ work was presented to the Substances Committee at its meeting on 12 May 2016 and to the HRV Committee at its meetings on 16 October 2017, 18 October 2018 and 29 November 2018. The collective expert appraisal report dealing with Question 2 was validated on 29 November 2018 by the HRV Committee.

Regarding Question 3: the expert rapporteurs’ work was presented several times to the ERCA Committee, the Substances Committee, the HRV committee and the MFSC Committee between September 2016 and June 2018. The work related to this question and the collective expert appraisal report were validated by the ERCA Committee on 20 June 2018 and endorsed by the HRV committee on 22 June 2018.

This opinion is based, for the scientific aspects considered:

- for Question 1, on the report entitled “Exposure to cadmium. Proposals for toxicity reference values (TRVs) by ingestion and health benchmark values in biological media (blood, urine, etc.)” (November 2017);
- for Question 2, on the report entitled “Production and use of fertilizers and growing media: Assessment of occupational exposure to cadmium” (November 2018);
- for Question 3, on the report entitled “Exposure to cadmium. Proposals for cadmium levels in fertilizers and growing media that would control pollution of agricultural soils and contamination of crop production” (June 2018).

This opinion was validated by the HRV Committee on 29 November 2018. It should be noted that two experts from the HRV Committee abstained during the final validation of the opinion. Their abstentions were due to the fact that they had not participated in the work and discussions relating to Question 1 that led to bone effects being chosen as the critical effects for establishing the TRV by ingestion.

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 ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE EXPERT COMMITTEES

3.1. Question 1: Establishment of a toxicity reference value (TRV) by ingestion (adults, children, etc.) and choice of health reference values to be used for cadmium in biological media (blood, urine, etc.), according to age

3.1.1. What toxicity reference value by ingestion (adults, children, etc.) should be used when carrying out quantitative health risk assessments?

3.1.1.1. Foreword

A toxicity reference value, or TRV, is a toxicological indicator for qualifying or quantifying a risk to human health. It establishes the link between exposure to a toxic substance and the occurrence of an adverse health effect. TRVs are specific to a duration (acute, subchronic or chronic) and route (oral or respiratory) of exposure. The way TRVs are established differs depending on the knowledge or assumptions made about the substances' mechanisms of action. Currently, the default hypothesis is to consider a monotonic relationship between exposure (dose) and effect (response). In the current state of knowledge and by default, it is generally considered that for non-carcinogenic effects, toxicity is only expressed above a threshold dose (ANSES, 2017). In practice, the establishment of a TRV includes the following stages:

- choice of the critical effect;
- choice of a good quality scientific study generally enabling establishment of a dose-response relationship from among a series of studies of good quality;
- choice or establishment of a critical dose from experimental doses and/or epidemiological data;
- application of uncertainty factors to the critical dose to take uncertainties into account for threshold TRVs;
- conducting a linear extrapolation to the origin to determine an excess risk per unit for non-threshold TRVs.

TRVs are developed according to a highly structured and rigorous approach based on ad-hoc methodological expertise developed by ANSES (ANSES, 2017) in accordance with international standards.

3.1.1.2. Toxicological profile of cadmium

The absorption of cadmium after dietary exposure in humans is relatively low (3 to 5%); however, cadmium is efficiently retained in the kidneys and liver of humans, with a very long biological half-life ranging from 10 to 30 years.

Cadmium is primarily toxic to the kidneys, in particular the proximal tubular cells, where its accumulation can cause renal dysfunction. Cadmium can also have effects on bones, such as bone demineralisation, either directly by causing bone damage or indirectly further to renal dysfunction, resulting in an increased risk of fractures. After prolonged and/or high exposure, initially tubular lesions can be associated with a decrease in the glomerular filtration rate, likely to progress to kidney failure.

Cadmium also has reprotoxic effects. Several recent studies undertaken in pregnant women (Lin, 2011; Tian *et al.*, 2009; Kippler *et al.*, 2012; Gardner, 2013; Sun, 2014) reported a decrease in head circumference in newborns following maternal exposure to cadmium. These same studies also suggested a decrease in the children's height and weight, recorded during medical check-ups until the age of three or five years.

A few epidemiological studies have also suggested that discrete neurocognitive disorders have been induced by environmental and/or dietary exposure to cadmium. However, these studies remain insufficient in number to constitute a high level of epidemiological evidence.

Studies undertaken in adult populations of men and women have demonstrated a link between cadmium exposure and the development of atherosclerosis on the one hand, and an increase in the prevalence of vascular diseases associated with atherosclerosis on the other hand. These cardiovascular effects were observed at exposure doses similar to those associated with bone and kidney effects.

Orally, cadmium enters the gastro-intestinal tract via food or the ingestion of water. It can then bind to plasma proteins (e.g. albumin), erythrocytes and metallothioneins. From this blood compartment, cadmium is distributed in the liver, kidneys and other tissues. It is excreted via faeces and urine.

In 1993, the IARC classified cadmium as "carcinogenic to humans" (Group 1) due to its carcinogenic effects on the lungs of exposed workers (IARC, 1993). This classification was reviewed and confirmed as part of an update and re-assessment of all of the Group 1 compounds in the IARC Monographs (IARC, 2012).

According to the CLP Regulation⁸, cadmium is classified as carcinogenic (Category 1B), germ cell mutagenic (Category 2) and toxic for reproduction (Category 2).

3.1.1.3. Chronic oral TRV

3.1.1.3.1. Choice of the critical effect

The chronic toxicity of cadmium in humans has been widely studied in workplaces since the very first publications by Friberg in 1950 (EFSA, 2009a).

Epidemiological studies were conducted later on in the general population.

The toxicity of cadmium has been addressed in several summaries (WHO/IPCS, 1992; EC, 2007) and numerous scientific publications. Their conclusions were as follows: the critical effects of cadmium exposure primarily involve kidney function and bone tissue and can appear above threshold values for urinary cadmium (CdU) of 1 µg.g⁻¹ creatinine for renal effects and 0.5 µg.g⁻¹ creatinine for bone effects.

The threshold for the occurrence of cardiovascular effects has been estimated at 2 µg CdU.g⁻¹ creatinine. The data are not currently sufficient to determine thresholds for the occurrence of a reprotoxic effect or the neurodevelopmental effects that have been described experimentally and observed in epidemiological studies. The same is true for carcinogenic effects (hormone-dependent, testicular, prostatic, renal, etc.), which can affect individuals who are not occupationally exposed (IARC, 2012).

The CES chose bone effects, which are considered the strongest effects documented to date, as the critical effect.

⁸ The CLP (Classification, Labelling, Packaging) Regulation refers to Regulation (EC) No 1272/2008 of the European Parliament on classification, labelling and packaging of substances and mixtures.

3.1.1.3.2. Compilation and analysis of the existing TRVs

Several chronic oral TRVs, all based on renal effects, are currently available (EFSA, 2009a; JECFA, 2010; ATSDR, 2012) (see Table 1).

Table 1. Chronic oral TRVs proposed by JECFA (2010), EFSA (2009), and ATSDR (2012)

	JECFA (2010)	EFSA (2009)	ATSDR (2012)
Critical effects	Renal effects (renal tubular impairment)		
Key study	EFSA's pooled analysis (35 epidemiological studies)		Jarüp <i>et al.</i> , 2000
Assessment of tubular proteinuria and urinary cadmium	β2-microglobulin, Urinary cadmium (CdU) in µg.g ⁻¹ creatinine Exclusively population ≥ 50 years		Low-molecular-weight proteins
Critical CdU µg/g creatinine	5.24 (4.94-5.57) µg.g ⁻¹ creatinine (breakpoint)	4 (BMDL ₅) Adjustment factor of 3.9 1 µg.g ⁻¹ creatinine	0.5 µg.g ⁻¹ creatinine
Model for assessing dietary Cd	Amzal <i>et al.</i> , 2009 adapted (Cd half-life)	Amzal <i>et al.</i> , 2009	Kjellstrom and Nordberg, 1978
TRV (oral route)	Provisional tolerable monthly intake (PTMI): 25 µg.kg ⁻¹ bw.month ⁻¹ Provisional tolerable weekly intake (PTWI): 5.6 µg.kg ⁻¹ bw.week ⁻¹	Tolerable weekly intake (TWI): 2.5 µg.kg ⁻¹ bw.week ⁻¹ Tolerable daily intake (TDI): 0.36 µg.kg ⁻¹ bw.day ⁻¹	Minimal Risk Level (MRL): 0.1 µg.kg ⁻¹ bw.day ⁻¹

The HRV Committee did not select the existing TRVs because they were not based on the chosen critical effect; instead it chose to establish a new TRV.

3.1.1.3.3. Establishment of a new oral TRV

- Choice of critical effect and key study

The experts chose the epidemiological studies by Engström *et al.* (2011 and 2012) as the key studies. These studies found a correlation between exposure to cadmium and a decrease in bone density (possibly increasing the risk of osteoporosis or fractures) in Swedish women aged 56 to 69 (2688 individuals). This association was also demonstrated in men (age > 69) according to a recent study (Wallin *et al.*, 2016).

- Choice of critical concentration

The experts analysed the relationship between prolonged cadmium exposure and the risk of osteoporosis or bone fractures based on the articles by Engström *et al.* (2011 and 2012). The urinary cadmium concentration of $0.5 \mu\text{g.g}^{-1}$ creatinine corresponds to a NOAEL⁹ and was chosen as the critical concentration to derive the TRV.

- TRV calculation

Oral exposure from the ingestion of foodstuffs represents the main source of exposure to cadmium in non-smokers. That is why the experts chose to establish an oral TRV using the physiologically based pharmacokinetic (PBPK) model of Kjellström and Nordberg (Kjellström and Norberg, 1978) (see Annex 8 of the report), enabling a connection to be made between urinary cadmium concentrations and oral exposure values.

This PBPK model can be used to simulate the absorption, accumulation and excretion of cadmium through eight compartments including the lungs, gastro-intestinal tract, blood (which itself is divided into three compartments: plasma, erythrocytes and metallothionein), liver, kidneys and “other tissues”.

It can also be used to estimate changes in the maximum urinary concentration of cadmium (in $\mu\text{g.g}^{-1}$ creatinine according to age) not to be exceeded, to avoid exceeding the chosen critical concentration ($0.5 \mu\text{g.g}^{-1}$ creatinine at the age of 60) (see Annex 7 - Figure 3). The predictive capacity of PBPK modelling was previously covered by expert appraisals published by ATSDR (ATSDR, 2012) and ANSES (ANSES, 2012).

In light of the study by Chaumont *et al.* (2013) relating to the Belgian population, it should be noted that in the absence of external exposure data for Belgium, it was not possible to verify the predictive capacity of this PBPK model, i.e. the connection between external exposure (food) and internal doses (urinary cadmium), for this population.

Since the establishment of the oral TRV for cadmium relied on epidemiological studies undertaken in the general population, the experts decided not to apply an additional uncertainty factor.

- Proposed chronic oral TRV

An oral TRV was derived from the aforementioned PBPK model.

An oral **tolerable daily intake (TDI)** of $0.35 \mu\text{g Cd.kg bw}^{-1}.\text{day}^{-1}$ or an oral **tolerable weekly intake (TWI)** of $2.45 \mu\text{g Cd.kg bw}^{-1}.\text{week}^{-1}$ is compatible with a **urinary cadmium concentration not exceeding $0.5 \mu\text{g.g}^{-1}$ creatinine, in a 60-year-old adult**, assuming that ingestion is the only source of exposure to cadmium.

⁹ No Observed Adverse Effect Level

Table 2. Chronic oral TRV based on bone effects

Critical effect	Critical concentration	TRV
<p>Risk of osteoporosis or bone fractures</p> <p>Engström <i>et al.</i> (2011 and 2012)</p>	<p>Urinary cadmium = 0.5 µg.g⁻¹ creatinine at the age of 60 <u>PBPK modelling</u></p>	<p>TRV = 0.35 µg Cd.kg⁻¹.day⁻¹</p>

- Confidence level

The overall confidence level was assigned to this TRV based on the following criteria:

- Level of confidence in the database: high
- Level of confidence in the choice of the critical effect and the mode of action: moderate

Cadmium's toxicity to bones is established but still poorly documented. The mode of action at low doses has not been fully elucidated.

- Level of confidence in the choice of the key study: high

The epidemiological studies by Engström *et al.* (2011 and 2012) are very detailed and well argued. They were considered robust by the experts.

- Level of confidence in the choice of the critical concentration: moderate

Without access to individual data, it was not possible to derive a BMD from the epidemiological studies by Engström *et al.* (2011 and 2012).

A moderate-high overall confidence level was assigned to this TRV.

3.1.2. What health reference values should be used for cadmium in biological media (blood, urine, etc.), according to age, for health management purposes?

The PBPK model (Kjellström & Norberg, 1978) was also used to estimate changes in the maximum urinary concentration of cadmium not to be exceeded, from birth, to avoid exceeding the internal TRV (0.5 µg.g⁻¹ creatinine) at the age of 60.

Figure 3 and Table 13 of the report (see Annex 7 of the expert appraisal report) correspond to estimated urinary cadmium concentrations (in µg/g creatinine) according to age. The reported values (not to be exceeded to comply with the TRV of 0.5 µg.g⁻¹ creatinine at the age of 60) (see Table 13) are given for information purposes and should be interpreted in light of the estimated body weight values and the estimated values for daily urinary creatinine excretion.

3.1.3. Conclusions and recommendations of the Expert Committees regarding Question 1

The HRV Committee recommends:

- health reference values for urinary cadmium (in $\mu\text{g.g}^{-1}$ creatinine according to age) not to be exceeded to comply with the internal TRV of $0.5 \mu\text{g.g}^{-1}$ creatinine at the age of 60 (see Annex 2);
- a chronic TRV by ingestion for cadmium of $0.35 \mu\text{g Cd.kg bw}^{-1}.\text{day}^{-1}$ (equivalent to a TWI of $2.45 \mu\text{g Cd.kg bw}^{-1}.\text{week}^{-1}$). By definition, the TRVs apply to the entire population, including susceptible groups (ANSES, 2017¹⁰).

Table 3. Chronic oral TRV based on bone effects

Critical effect	Critical concentration	TRV
Risk of osteoporosis or bone fractures Engström <i>et al.</i> (2011 and 2012)	Urinary cadmium = $0.5 \mu\text{g.g}^{-1}$ creatinine at the age of 60 <u>PBPK modelling</u>	TRV = $0.35 \mu\text{g Cd.kg}^{-1}.\text{day}^{-1}$ Confidence level Moderate-High

¹⁰ Toxicity reference values (TRVs) - ANSES's TRV Development Guide - Permanent mission - Request No 2017-SA-0016. Third edition.

3.2. Question 2: Exposure of populations of workers in contact with fertilizers and growing media, potentially contaminated by cadmium

The population of workers in contact with fertilizers and growing media corresponds to professionals in industry sectors producing or using these products. The fertilizers taken into account in the expert appraisal work include organic, inorganic and organo-mineral fertilizers intended to ensure or improve plant nutrition, and organic, inorganic and organo-mineral soil conditioners that improve the physical, chemical and biological properties of soils (see Annex 3). Cadmium is a natural contaminant found in the phosphate rocks used to produce phosphate fertilizers.

Cadmium can also be quantified in leaching water and in wastewater for retreating. Therefore, it can ultimately be found in sewage treatment plant (STP) sludge. Following soil-plant transfers, cadmium can also be identified in compost.

3.2.1. Q2a: Are the risks associated with cadmium exposure in the sector of fertilizers and growing media adequately assessed under occupational health and safety regulations (using a sector survey, for example)?

A sector study on workers in contact with fertilizers and growing media was conducted, taking the following into account: an analysis of the scientific literature, hearings, stakeholder consultations, the INRS¹¹ COLCHIC database (chemical exposure data collection system of the laboratories of the regional health insurance funds), questionnaire-based surveys and site visits possibly including the taking of measurements.

This sector study found that the chemical risks taken into account for these professionals are those associated with exposure to dust in general but not to cadmium in particular. These professionals are exposed indirectly, as cadmium is found in various fertilizers and growing media as a contaminant/impurity. Thus, in view of the low cadmium content, the safety data sheets (SDSs) providing information about the chemical composition of phosphate fertilizers are not required to mention the presence of cadmium (since the cadmium concentration is below 0.1%). However, since some fertilizers and growing media are hazardous chemicals, the general rules for the prevention of chemical risks in the workplace apply¹². Nonetheless, due to the low cadmium content of fertilizers, they are not subject to the regulatory provisions relating to carcinogenic, mutagenic and reprotoxic substances, and the French Labour Code does not require any specific reinforced individual monitoring of these workers with regard to cadmium.

3.2.2. Q2b: Regarding workers, what levels of contamination can be estimated for different occupational activities and situations?

The sector study on fertilizers and growing media suggested that the industries included in the sector of fertilizers and growing media, and in which workers are likely to be exposed to cadmium, are as follows:

- the sector of phosphate fertilizers (from the unloading of imported raw materials (phosphate rocks) to the marketing and distribution of finished products (fertilizers));
- industries generating and applying fertilizers of waste origin (FWOs) (workers in contact with STP sludge, workers spreading FWOs, farms, etc.);

¹¹ National Research and Safety Institute

¹² Decree no. 2003-1254 of 23 December 2003 relating to the prevention of chemical risks (R. 231-54 to R. 231-54-17)

- users of fertilizers and growing media (farmers, workers in charge of maintaining green spaces, etc.).

3.2.2.1. Methodology used to estimate worker contamination levels

Workers can be exposed to cadmium and its compounds by the respiratory tract or via the accidental ingestion of dust from contaminated hands and food¹³. Since cadmium can have systemic effects (carcinogenic and renal in particular) and occupational exposure to cadmium can involve routes of exposure other than inhalation, biological monitoring of exposure should be the preferred method for assessing exposure, because it enables the internal dose of cadmium actually absorbed to be assessed. This is all the more important because cadmium is a cumulative toxin, whose toxicity is thus related to the cumulative dose over time¹⁴.

No biometrological monitoring data were found during this expert appraisal work. Therefore, in the absence of such data, atmospheric concentration data for cadmium, when available, were used by default to estimate occupational exposure to cadmium, keeping in mind uncertainties as to other possible routes of exposure. In some cases, levels of atmospheric exposure to cadmium were also estimated based on those for inhalable dust, since most of the time only these data were available. Atmospheric cadmium concentrations were thus indirectly estimated considering the expected maximum levels for the various types of fertilizers and growing media in question. In some cases, when they thought it was possible, in the absence of quantified data relating to atmospheric concentrations of inhalable dust, the experts also relied on expert judgement to assess levels of atmospheric exposure to inhalable dust during their few on-site visits.

3.2.2.2. Contamination levels estimated from the various types of data available for workers in contact with fertilizers and growing media potentially contaminated by cadmium

Workers involved in the production of phosphate fertilizers

To corroborate the few atmospheric data found in the scientific literature (Heederick, 1994), ANSES asked the INRS to extract data from the COLCHIC database. The results had been obtained from measurements taken by the eight inter-regional laboratories of the CARSAT/CRAMIF¹⁵ and the INRS from 1987 to 2017. The data analysed related to the sector for manufacture of fertilizers and nitrogen compounds (NAF 2015Z), and specifically to fertilizer dust (superphosphate) (CAPROEX POU 107). Statistical processing was based on raw results corresponding to the duration of sampling not weighted over eight hours and not corrected by a protective factor. The analyses (see Annex 8 of the Q2 report) were undertaken by grouping together exposure measurements (individual samples – QTI) and ambient measurements (fixed-station samples – QTA). This processing focused on sampling with a duration of more than 60 minutes stratified by task code for inhalable dust and more broadly for cadmium given the small number of measurements. Atmospheric cadmium

¹³ HAS, 2015 - Decision no. 2015.0236/DC/SBPP. Good practice recommendation "Occupational health monitoring of workers who are or have been exposed to pulmonary carcinogens" prepared by the French Society for Occupational Medicine.

¹⁴ French Society for Occupational Medicine. Biological monitoring of occupational exposure to chemicals. TM37 good practice recommendations. *Références en Santé au Travail* 2016(146):29.

¹⁵ CARSAT: *Caisse d'assurance retraite et de la santé au travail* – Occupational health and pension insurance fund; CRAMIF: *Caisse régionale d'assurance maladie d'Île-de-France* – Île-de-France regional health insurance fund

concentrations in inhalable dust, for the 1987-2017 period and the sector for manufacture of fertilizers and nitrogen compounds, ranged from 0.10 to 3.8 mg/m³ (COLCHIC data).

In 2018, as part of this study, ANSES called on the Nord Picardie CARSAT to take samples of dust during the production and packaging of superphosphate fertilizers in a company operating in the field of mineral fertilizers and specialist products. The analysis of these dust samples showed cadmium concentrations below the limits of quantification (below 0.1 µg.m⁻³) for the population of workers likely to be exposed to cadmium.

Workers involved in the distribution of phosphate fertilizers

Since no atmospheric contamination data for cadmium were found in the phosphate fertilizer distribution sector, a phosphate fertilizer storage silo was visited in November 2017. The visited facility is located in the Meurthe-et-Moselle *département*, in a rural environment; it stores harvested cereals as well as fertilizers intended for around 100 farmers. The fertilizer of this facility is transported by barge to a river port and then by lorry to the agricultural cooperative's silo. In general, the barges are directly unloaded using power shovels. Port-to-silo deliveries usually take place between June and August over a period that can last several days. Once they have reached the cooperative, the lorries are unloaded using a conveyor belt that discharges to a wooden box. This lorry unloading operation with a conveyor belt lasts around 10 minutes for a 28-tonne lorry. According to the site's manager, this operation releases significant quantities of dust that can require the wearing of respiratory personal protective equipment (PPE).

In these conditions, the HRV Committee was only able to roughly estimate contamination levels in ambient air for cadmium, since no atmospheric concentration data were available for these workstations. Taking into account the information provided, the experts estimated a duration of exposure during lorry unloading of around three to four hours per year, with levels of atmospheric exposure to total dust that may be above 10 mg.m⁻³ (especially when the operator enters the box to move the conveyor belt).

Workers in contact with STP sludge

As part of this request, ANSES organised three visits to sewage treatment plants (STPs) between November 2017 and January 2018.

At one of these STPs, the INRS had measured exposure to bioaerosols in 2016 as part of a national study. These measurements showed ambient concentrations of inhalable dust of around 0.08 to 0.53 mg.m⁻³. They were taken at various sludge treatment workstations, including the centrifugation and dryer-granulator zone. In these zones, assuming maximum authorised levels of cadmium in STP sludge of 10 mg Cd.kg⁻¹ dry matter¹⁶ (DM), the fixed-station ambient measurements led to cadmium concentrations not exceeding 5.3·10⁻³ µg.m⁻³.

At the second visited STP, measurements of atmospheric exposure to inhalable dust and cadmium had been taken in 2007 in the drying unit. These measurements showed ambient concentrations of inhalable dust of 0.53 to 5.90 mg.m⁻³ whereas operators were exposed to a concentration of 20 mg.m⁻³ over an eight-hour period. Cadmium measurements taken with these dust samples gave concentrations ranging from 0.79 to 0.93 µg.m⁻³.

¹⁶ Ministerial Order of 08/01/1998 laying down the technical requirements applicable to the spreading of sludge on agricultural soil pursuant to Decree No 97-1133 of 08/12/1997 on the spreading of sludge resulting from wastewater treatment

Although these results were not representative (limited number of measurements), they showed that there is potential for cadmium exposure in this type of unit and for workers assigned to pellet transport, whether within the site or to reclamation sites (spreading, energy recovery). At this STP, in agreement with the occupational physician, urinary cadmium analyses were undertaken in May 2018 for the seven technicians at the sludge dryer station. Only six samples could be used. The analysis results showed urinary cadmium levels between 0.12 and 0.26 $\mu\text{g}\cdot\text{g}^{-1}$ creatinine.

Workers in companies specialising in agricultural work, in charge of spreading FWOs (STP sludge, livestock manure, etc.)

Field application operations can release large quantities of dust, especially during the spreading of dried sludge. However, no atmospheric measurements were identified.

It should nonetheless be noted that:

- operators are usually isolated in a Category-4 cabin according to the NF ISO 15695 standard (pressurised cabin);
- the modern tools used reduce aerosol emissions (ground-level dispersal using a self-propelled drop hose for example, with or without an incorporator);
- the applied products usually contain low levels of cadmium.

Regarding operations involving the unloading-loading of dry sludge, in light of the wide variety of tools potentially used (power shovel or tractor without or without a cabin) and the configuration of the work zones (storage of large quantities in the same location, in open air, etc.), the experts considered that these operations could lead to non-negligible exposure. However, they were unable to quantify this exposure because no measurements were available.

Agricultural workers

No data on atmospheric concentrations of cadmium were found for the sector of agricultural workers.

Nevertheless, the HRV Committee underlines that:

- operations involving the spreading of STP sludge or the loading of phosphate fertilizers are generally performed by employees of specialist spreading companies (sludge) or agricultural cooperatives (phosphate fertilizers). When phosphate fertilizers are supplied via a 'big bag'¹⁷, farmers may be exposed to dust when opening it;
- phosphate fertilizers are applied once a year, over a period of a few days, generally in the autumn;
- the literature reports extremely vague knowledge with regard to the FWOs (sludge, manure, etc.) produced (type and quantity) and their spreading, as well as a heterogeneous distribution of production between regions, for livestock manure in particular. Therefore, it appears it is not possible to determine a realistic exposure scenario for fertilizers and growing media for all agricultural workers in France.

¹⁷ A 'big bag' is a large soft bag enabling large quantities of miscellaneous non-hazardous dry materials (fertilizer, sand, rubble, etc.) to be transported in bulk.

Workers in the gardening sector using fertilizers and growing media

This paragraph applies to professionals in contact with smaller amounts of fertilizers and growing media (garden centre employees, park maintenance agents, etc.). In the current state of knowledge, it is not possible to rule on the exposure of these professionals, due to a lack of available data.

3.2.3. Q2c: What conclusions can be drawn in comparison with occupational exposure limits (OELs) and biological limit values (especially those recommended by ANSES)?

As stated above and since biological monitoring of exposure is the method that should be used to assess cadmium exposure, no accurate and representative assessment of exposure could be undertaken for populations of workers in contact with fertilizers and growing media potentially contaminated by cadmium, due to a lack of biometrological data and the small number of measurements available, including in terms of atmospheric exposure levels.

It is also important to stress that the estimates obtained during this work rely largely on respiratory exposure to cadmium, and that as a result, they may not reflect the actual cadmium exposure of professionals in contact with fertilizers and growing media.

Regarding the available reference values that can be used in comparison with the estimated levels of occupational exposure, ANSES recommended the following in 2018¹⁸ as part of its expert appraisal work aiming to assess chronic occupational exposure to cadmium:

- a pragmatic biological limit value¹⁹ (BLV) of 5 µg.g⁻¹ creatinine for urinary cadmium;
- biological reference values of 0.8 µg.g⁻¹ creatinine (for non-smokers) and 1.0 µg.g⁻¹ creatinine (for smokers) corresponding to the 95th percentile of the values found in the general population of adults from the National Nutrition and Health Study (ENNS) (Fréry *et al.*, 2009);
- a pragmatic 8-hour OEL¹⁵ of 3 µg.m⁻³ (sampling of the inhalable fraction) for cadmium and its compounds, considering impairment of renal function as the critical effect.

Moreover, in 2017, the SCOEL²⁰ recommended an 8h-OEL of 1 µg.m⁻³ for the inhalable fraction for cadmium and its compounds.

Workers involved in the production of phosphate fertilizers

Based on the results of the COLCHIC database extraction, it can be said that the OELs recommended by ANSES (3 µg.m⁻³) and the SCOEL (1 µg.m⁻³) are likely to be exceeded in these industry sectors (see Table 4 below). The analysis of the COLCHIC data showed average cadmium exposure of around 1.1 µg.m⁻³ with a maximum value of 3.8 µg.m⁻³.

The most exposed workstations appear to correspond to raw material grinding activities.

¹⁸ ANSES (2018). Occupational exposure limits for chemical agents. Assessing the health effects and methods for measuring occupational exposure for cadmium and its compounds. Maisons-Alfort 134 p.

¹⁹ In light of the available data, it was not possible to establish limit values based on the carcinogenicity of cadmium. Thus, renal effects were used to establish limit values for cadmium and its compounds.

²⁰ Scientific Committee on Occupational Exposure Limits;

SCOEL (2017). SCOEL/OPIN/336 Opinion from the Scientific Committee on Occupational Exposure Limits for cadmium and its inorganic compounds. European Commission. 52p

Workers in contact with STP sludge

In this industry sector, assuming compliance with the maximum authorised levels of cadmium in STP sludge (10 mg Cd.kg⁻¹ dry matter (DM)), the fixed-station ambient measurements taken²¹ by the INRS in 2016 tend to suggest cadmium concentrations of around 1 ng.m⁻³ of air.

This led the experts to consider that the atmospheric cadmium exposure of workers in STPs is low in relation to the 8h-OEL of 3 µg.m⁻³ recommended by ANSES.

This estimate was corroborated by the urinary cadmium analyses performed for seven technicians working at the sludge dryer station at one of the STPs visited (see above). For the six workers (smokers and non-smokers) whose urinary cadmium measurements were usable, the analysis results showed urinary cadmium levels between 0.12 and 0.26 µg.g⁻¹ creatinine. These values were below 0.8 µg.g⁻¹ creatinine, which is the biological reference value (BRV) recommended for non-smokers and corresponds to the 95th percentile of the values found in the general population of adults from the French ENNS study (Fréry *et al.*, 2009).

Workers in contact with fertilizers and growing media for which ANSES did not have atmospheric contamination data for cadmium

An analysis was undertaken, based on an estimate of the exposure frequency and the assumed atmospheric exposure levels for dust and using the data from the literature, to estimate atmospheric exposure levels for cadmium (for example, from the threshold concentration of cadmium in fertilizers).

Based on these estimates, the OEL for dust deemed “without specific effects” of 10 mg.m⁻³ may be exceeded, especially in employees of agricultural cooperatives, whether working in storage silos for phosphate fertilizers, carrying out FWO unloading-loading operations, or performing maintenance operations.

For workers in agricultural cooperatives, assuming an atmospheric concentration of inhalable dust of 10 mg.m⁻³ and Cd concentrations ranging from 60 mg to 90 mg/kg P₂O₅, the estimated atmospheric concentrations of cadmium are between 0.6 µg.m⁻³ and 0.9 µg.m⁻³ (see Table 4). Exposure during the loading of spreaders (delivery to farmers) appears to be of the same order of magnitude regarding the duration of exposure, but with lower estimated atmospheric concentrations (expert opinion assuming an unconfined space, loading in open air, etc.).

Regarding the sector of FWO transport and spreading, field application operations can release dust, especially during the spreading of dried sludge. For these spreading operations, no data on dust were identified. However, considering that:

- operators are usually isolated in a Category-4 cabin according to the NF ISO 15695 standard (pressurised cabin);
- the modern tools used reduce aerosol emissions (ground-level dispersal using a self-propelled drop hose for example, with or without an incorporator);

²¹ As a reminder, the ambient concentrations of inhalable dust were around 0.08 to 0.53 mg/m³.

- the applied products usually contain low levels of cadmium (between 0.02 and 50 mg.kg⁻¹ DM) (see Chap. 3 of the collective expert appraisal report - Cd concentrations identified in the study by Belon, 2012);

the exposure by inhalation of operators to dust-aerosols can be considered low, and atmospheric exposure to cadmium during these operations can thus be considered negligible in relation to the pragmatic 8h-OEL of 3 µg.m⁻³ recommended by ANSES.

Concerning operations involving the unloading-loading of dry sludge, in light of the wide variety of tools potentially used (power shovel or tractor with or without a cabin) and the configuration of the work zones (storage of large quantities in the same location, in open air, etc.), the experts considered that these operations could lead to non-negligible atmospheric exposure to dust. However, this could not be quantified because no measurements were available.

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Table 4. Summary of estimated atmospheric cadmium concentrations for workers in the sector of fertilizers and growing media

Type of fertilizer or growing medium	Sector/activity	Source	[Cd] µg/m ³	Ratio (Measured or estimated atmospheric concentration/OEL recommended by ANSES or the SCOEL)		Expert comments and observations
				ANSES (3 µg/m ³)	SCOEL (1 µg/m ³)	
STP sludge	Sludge production	Urinary cadmium measurement campaign conducted as part of this expert appraisal	Occupational exposure considered negligible since the measured urinary cadmium values were below the BRV of 0.8 µg.g ⁻¹ creatinine recommended by ANSES for non-smokers			Since the measured urinary cadmium levels were below the BRV recommended by ANSES, occupational exposure to cadmium can be considered negligible. However, as these measurements were taken at a single STP, these conclusions for a limited number of workers cannot be considered as representative of all STPs.
Phosphate fertilizers	Loading/unloading	Heederick (1994) (**)	0.02-4.8 µg/m ³	0.006- 1.6	0.02-4.8	The highest dust levels appear to correspond to raw material grinding activities and phosphate rock unloading operations.
	Production-grinding	COLCHIC (*) (1987-2017)	Mean: 1.1 Max 3.8 µg/m ³	0.36 1.27	1.1 3.8	
	Formulation	Measurement campaign (*) (2018)	<0.1 µg/m ³	<0.03	< 0.1	
	Distribution			< 0.33		The site visits and worker interviews suggested that this work stage is

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	- Agricultural cooperative	Expert judgement (***)	<1.0 µg/m ³			likely to induce exposure to atmospheric concentrations of inhalable dust probably exceeding 10 mg/m ³ .
FWOs	Spreading	Expert judgement (***)		Negligible		No available data on dust
All types	Agricultural workers	Expert judgement (***)		Negligible		No available data on dust
	Gardening professionals	In the current state of knowledge, it is not possible to rule for this industry sector, in the absence of available data on the types of fertilizers and growing media used, their quantities and frequency of use, the types of tools used and exposure scenarios.				

* Atmospheric concentrations of Cd actually measured

** Atmospheric concentrations of Cd estimated from atmospheric concentrations of inhalable dust

*** Based on rough estimates of atmospheric concentrations of dust as evaluated by industrial hygiene experts

3.2.4. Conclusions and recommendations of the Expert Committees regarding Question 2

Conclusions of the HRV Committee:

The sector study on the main fertilizers and growing media showed that the industry sectors in which workers are likely be exposed to cadmium are as follows:

- the sector of phosphate fertilizers, from the unloading of phosphate rocks to the marketing and distribution of finished products, in particular raw material grinding activities;
- industries generating and applying fertilizers of waste origin (FWOs);
- users of fertilizers and growing media (farmers, workers in charge of maintaining green spaces, etc.).

The sector study also highlighted the following points:

- there are no biological measurement results for assessing exposure to cadmium;
- exposure, which is essentially taken into account by companies when assessing risks, is that associated with dust and not with cadmium;
- a limited number of atmospheric measurements (concentrations of inhalable dust and cadmium) were identified from literature data, the COLCHIC database extraction and measurement campaigns in sectors producing phosphate fertilizers and STP sludge. In light of this small number, the identified data cannot be considered representative of the cadmium exposure of workers in these sectors or that of fertilizers and growing media;
- regarding professionals in the sectors of phosphate fertilizers distribution and the application of fertilizers and growing media, and the population of farmers, no exposure data were identified.

Therefore, in light of these observations, the cadmium exposure of workers in the sector of fertilizers and growing media, from producers to end users, could only be roughly estimated.

The very few atmospheric concentration data for cadmium were compared with the OELs recently recommended by ANSES ($3 \mu\text{g}\cdot\text{m}^{-3}$, 2018) and the SCOEL ($1 \mu\text{g}\cdot\text{m}^{-3}$, 2017). Based on the data from the COLCHIC database, these thresholds were found to be exceeded in particular for workers from the sector of phosphate fertilizer production (see Table 4).

For workers in other sectors (distribution-use of fertilizers and growing media, spreading, farmers, etc.), in the absence of atmospheric concentration data for inhalable dust, the experts cannot formally rule on these workers' atmospheric exposure to cadmium. This exposure could only be estimated, based on the judgement of industrial hygiene experts (see Table 4).

Recommendations of the HRV Committee:

Regarding the cadmium exposure of farmers, the HRV Committee recommends including cadmium in the list of substances to be assayed in the "Family Farm" research project on the exposure of French farmers and their families to pesticides, implemented by the French Ministry of Agriculture.



The HRV Committee also recommends undertaking surveys of farmers and sellers of fertilizers and growing media to collect precise information about the quantities and types of fertilizers and growing media applied. Collecting this information would help improve the robustness of exposure scenarios.

3.3. Question 3: In all fertilizers and growing media, taking into account the aforementioned European studies and the specificity of these products, what cadmium levels would make it possible to control pollution of agricultural soils and contamination of crop production?

3.3.1. Foreword

Apart from smoking, the main source of exposure to cadmium in the general population is food (EFSA, 2009²², 2012²³). According to the second Total Diet Study (TDS2, ANSES, 2011a)²⁴, the TRV for cadmium defined by EFSA in 2009 was exceeded in 0.6% of adults and 15% of children. This indicates that a health risk cannot be ruled out. The main foods identified as contributing to exposure to cadmium were bread and dried bread products as well as potatoes and related products (ANSES, 2011a, b). Moreover, in 2011, after EFSA (2009) lowered the TRV by a factor of 3, a revision of the maximum levels for cadmium in foodstuffs was initiated in the European Union.

In this context, ANSES was asked to determine the impact of lowering the maximum content in foodstuffs on the French population's levels of exposure to cadmium²⁵ (ANSES, 2011b). The simulations performed, especially regarding the main contributors to cadmium exposure, showed that lowering the maximum levels had a moderate impact on consumer exposure due to the ubiquitous nature of cadmium and the regulations that had been in place for several years (Regulation (EC) No 1881/2006²⁶). Therefore, to reduce population exposure, ANSES recommended acting on the level of contamination of environmental sources, particularly regarding the inputs (contaminated fertilizers, spreading of sewage sludge, etc.) partly responsible for soil and food contamination.

More recently, the conclusions of the Infant Total Diet Study (iTDS) published in September 2016 (ANSES, 2016)²⁷ confirmed those of the TDS2, i.e. that the health risk associated with cadmium cannot be ruled out for children under the age of three years. In the iTDS, the main contributors to cadmium exposure for children over the age of five months were the same as those identified for the general population. ANSES had concluded that the recommendations issued to reduce the dietary exposure of the general population were also relevant for children less than three years old, to limit the accumulation of cadmium from a very early age. The strengthening of management measures aimed at limiting levels of exposure to cadmium therefore appears necessary.

Fertilizers (see Annex 3) are one of the sources of cadmium in agricultural soils, and one of the points at which it enters the food chain (see Annex 1). Mineral phosphate fertilizers on the market have been identified as the main source of cadmium in agricultural soils. They are made from natural

²² European Food Safety Authority, EFSA. (2009). Cadmium in food. Scientific Opinion of the Panel on Contaminants in the Food Chain. The EFSA Journal 980, 1-139.

²³ European Food Safety Authority, EFSA. (2012). Cadmium dietary exposure in the European population. EFSA Journal 2012;10(1):2551. [37 pp.] doi:10.2903/j.efsa.2012.2551.

²⁴ ANSES. (2011a). ANSES opinion and expert appraisal report on the second French Total Diet Study (TDS2) - Volume 1: Inorganic contaminants, minerals, persistent organic pollutants, mycotoxins and phyto-oestrogens, French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort.

²⁵ ANSES (2011b). ANSES opinion on the revision of maximum content for cadmium in foodstuffs intended for human consumption.

²⁶ Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs.

²⁷ ANSES. (2016). ANSES opinion and expert appraisal report on the Infant Total Diet Study (iTDS) - Volume 1: ANSES opinion & Summary and conclusions, French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort.

phosphate rocks that can contain cadmium in high concentrations depending on the geographical area from which the rock is extracted. Phosphate fertilisation is adjusted according to the plants' phosphorus needs and the availability of phosphorus in the soil. Belon *et al.* (2012)²⁸ showed that cadmium inputs to the soil in France attributable to fertilizers are closely related to the mineral phosphate fertilizers used in arable-farming *départements*. This can be explained by their cadmium content and the amounts of fertilizer used. Moreover, livestock manure makes a significant contribution to soil inputs in livestock-farming regions (Brittany for example). The ADEME-SOGREAH report (2007)²⁹ corroborates the fact that mineral phosphate fertilizers account for more than half of cadmium inputs to the soil, while animal manure accounts for 25%.

The desire to control cadmium inputs from fertilizers is not new and is reflected in French regulations by the safety criteria defined for marketing authorisations for fertilizers and growing media, which have been included in standards relating to specific fertilizers and growing media such as organic soil amendments (NF U 44-051), mineral soil amendments (NF U 44-001), etc. Inorganic mineral fertilizers are defined at European level by Regulation (EC) No 2003/2003³⁰, which does not however set a cadmium limit in CE-marked fertilizers. The French standard NF U 42-001-1 currently sets a regulatory maximum cadmium content for these mineral fertilizers of 90 mg Cd.kg⁻¹ by mass of phosphoric anhydride (P₂O₅) equivalent.

The European Commission's work to revise the regulations relating to fertilizers aims to set new limit values for contaminants in all fertilizers, taking into account the adverse effects of cadmium on humans and the environment. In particular, in the case of a CE-marked organo-mineral fertilizer, there are plans to set the cadmium content for a phosphorus (P) content by mass of phosphoric anhydride (P₂O₅) equivalent ("phosphate fertilizer") to the value of 60 mg Cd.kg P₂O₅⁻¹, and then three years later to 40 mg Cd.kg P₂O₅⁻¹, and lastly, 12 years later, to 20 mg Cd.kg P₂O₅⁻¹. This proposal also suggests a cadmium threshold value of 3 mg.kg⁻¹ DM for CE-marked alkaline and organic mineral soil amendments and a cadmium threshold value of 1.5 mg.kg⁻¹ DM³¹ for inorganic soil amendments. During the inter-institutional discussions, the Council of Europe proposed a cadmium content of 60 mg Cd.kg P₂O₅⁻¹ ³² in CE-marked organo-mineral fertilizers.

In view of the agronomic benefits of applying fertilizers to agricultural soils on the one hand, and the identification of these fertilizers as a source of both environmental contamination and addition of cadmium to the food chain on the other, ANSES was commissioned to propose cadmium levels in fertilizers that would reduce pollution of agricultural soils and contamination of crop production, thereby reducing the dietary exposure of consumers (see Annex 1).

3.3.2. Methodology used to propose cadmium levels in fertilizers that would control pollution of French agricultural soils, contamination of crop production and dietary exposure

The aim was to reduce cadmium contamination in French agricultural soils and crops and protect consumer health in view of the consumption and toxicity of this chemical contaminant.

²⁸ Belon E., Boisson M., Déportes IZ., Eglin TK., Feix I., Bispo AO., Galsomies L., Leblond S., Guellier C. R. (2012). An inventory of trace elements inputs to French agricultural soils. *Science of The Total Environment* 439:87-95.

²⁹ ADEME/SOGREAH. (2007). Bilan des Flux de Contaminants Entrant sur les Sols Agricoles de France Métropolitaine. Final report, pp. 330.

³⁰ Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003, as amended by Commission Regulation (EU) No 463/2013 of 17 May 2013

³¹ European Commission (2016). Limits for cadmium in phosphate fertilizers. Accompanying the document Proposal for a Regulation of the European Parliament and of the Council laying down rules on the making available on the market of CE marked fertilising products and amending Regulations (EC) No 1069/2009 and (EC) No 1107/2009

³² Council of the European Union. (2017). Working document from the Presidency to the Working Party on Technical Harmonisation (Dangerous Substances - Fertilizers) - Compromise for cadmium limits in phosphate fertilizers

To propose cadmium levels in fertilizers that would control pollution of French agricultural soils, contamination of crop production and therefore the dietary exposure of consumers, a mathematical model was built.

This choice was based on a literature review that consisted firstly in carrying out a critical analysis of existing European work on the subject, and secondly in producing an up-to-date review of cadmium transfer from environmental sources of cadmium to agricultural soils through to consumer exposure.

3.3.2.1. Critical analysis of European work on limit values for cadmium in fertilizers

The analysis of European work (Swedish Chemicals Agency (KEMI), 2011³³; Smolders and Six (Fertilizers Europe), 2013³⁴; SCHER, 2016³⁵) showed that the results of this work cannot be directly transposed to the situation in France as a whole (mean application of mineral fertilizers, soil characteristics such as Cd content, pH, etc.) (see collective expert appraisal report for Question 3). However, this analysis stressed that it is preferable to limit cadmium inputs to the soil from commercial phosphate fertilizers. In this work, the effect of mineral phosphate fertilizers on cadmium accumulation in agricultural soils was studied using a mass-balance approach that consisted in modelling cadmium concentrations in soils over a period of 99 years given cadmium's persistence in soil. The quality of mineral phosphate fertilizers can be controlled more effectively than that of more complex and less documented livestock manure, which should nevertheless be the focus of sustained attention.

3.3.2.2. Up-to-date review of cadmium transfer, from inputs to agricultural soils through to consumer exposure

Relevant parameters in terms of cadmium transfer from environmental sources of input to agricultural soils through to consumer exposure were reviewed before the model was built (see collective expert appraisal report dealing with Question 3). Figure 1 shows the transfer of cadmium throughout the food chain, from the source (fertilizers) to the targets covered by the question (soil, agricultural production, consumers) and highlights key parameters related to this transfer. The elements identified in this work that play a role in cadmium exposure are as follows:

- the pedo-geochemical background associated with the cadmium content naturally found in soils;
- soil pH, which is a key parameter for the phytoavailability of cadmium;
- cadmium input to soils from fertilizers and the associated agricultural practices;
- cadmium input to soils from atmospheric deposition;
- cadmium input to soils through irrigation water;
- cadmium transfer from soil by leaching;
- cadmium transfer from the soil to the plant, associated with the concept of phytoavailability;

³³ "Kadmiumhalten måste minska– för folkhälsans skull En riskbedömning av kadmium med mineralgödsel i fokusRapport från ett regeringsuppdrag. 2011".

³⁴ Revisiting and updating the effect of phosphate fertilizers to cadmium accumulation in European agricultural soils.

³⁵ SCHER, Scientific Committee on Health and Environmental Risks (2015). Final Opinion on new conclusions regarding future trends of cadmium accumulation in EU arable soils. Adopted by the SCHER during its plenary meeting of 27 November 2015.

- cadmium transfer through soil consumption by animals.

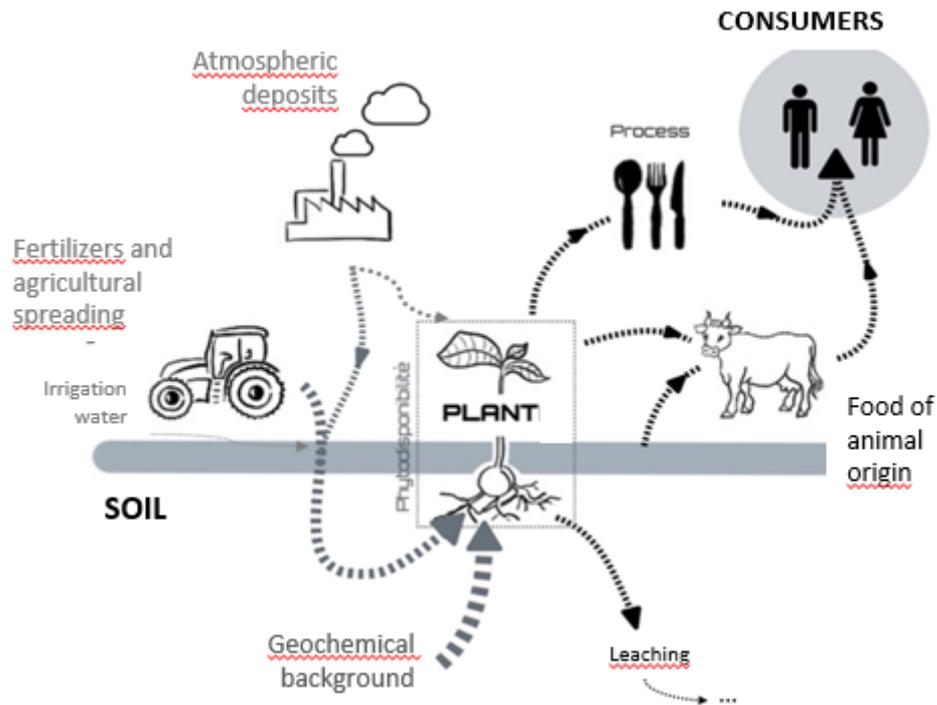


Figure 1. Conceptual diagram of cadmium transfer from environmental sources to end consumers of foodstuffs contaminated by cadmium

3.3.2.3. Construction of a cadmium transfer model for assessing cadmium levels in fertilizers that would reduce agricultural soil pollution, crop contamination and consumer exposure

A mathematical model was developed for assessing cadmium transfer from the application of fertilizer to the soil through to the plant following an action at the source. It took into account all of cadmium's input pathways to the soil (fertilizers, atmospheric deposition, irrigation water) and output pathways from the soil (food-crop cultivation, leaching) as well as variability throughout this transfer (see Figure 1). According to the fertilisation plans associated with the use of fertilizers, the modelled changes in cadmium contamination levels in crops were applied to the associated dietary exposure in order to assess the health risk. The proposed threshold value for cadmium in fertilizers is based on the results obtained with this model (according to realistic cadmium input scenarios tested for the assessment of risks, associated with representative and protective fertilisation scenarios for the contamination of French agricultural soils by fertilizers). The assessment process is shown in Figure 2.

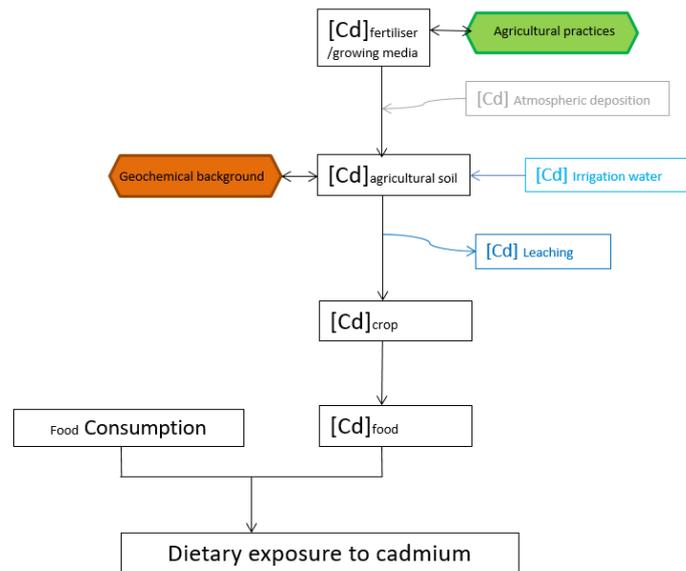


Figure 2. Schematic overview of the modelling of cadmium transfer from the input of cadmium to agricultural soils via fertilizers through to the consumer via crop production

The mathematical model was developed based on the use of a mineral phosphate fertilizer, identified as the main source of cadmium inputs to French agricultural soils. This choice also resulted from the availability of controlled data for phosphate fertilizers and the option of testing different cadmium levels in phosphate fertilizers. The model incorporating input data relating to cadmium inflows was then broadened, with the aim of comparing flows, to include the use of other fertilizers (livestock manure, STP sludge, etc.). This is because these other fertilizers are also likely to add cadmium to the soil.

To build the model, soil parameters modulating cadmium transfer from the application of fertilizers were selected. These first included pH, a determining factor in cadmium mobility, followed by parameters such as organic matter, clay and carbon content related to cadmium transfer. The geochemical background was also a parameter to be taken into account in the modelling, given its importance for the stock of soil cadmium.

Since the application of fertilizer to all crops could not be fully taken into account when building the mathematical model, it was limited to the application of phosphate fertilizer to two crops identified as the sources of the main foods contributing to consumer exposure to cadmium (ANSES, 2011a, 2011b, 2016). These crops, respectively with low and high phosphorus demand, are wheat and potatoes. Regarding phosphate fertilisation plans, common agricultural practices associated with wheat and potato crops were considered. The model was based on agricultural use in wheat monoculture or in potato/wheat/wheat rotation according to annual application or application with an unfertilised period of two years (i.e. with only one application of mineral phosphate fertilizer over a three-year period).

The model was built in two phases:

- Modelling of cadmium transfer from its input to agricultural soils through to cultivation: construction of the mathematical model on the basis of a “mass-balance” approach

Initially, the transfer of cadmium from its input to agricultural soils via fertilizers through to crop production (potatoes and wheat (grain)) was modelled. This part of the model was built using a mass-

balance approach that consisted in calculating the balance between the inflow and outflow pathways of cadmium in agricultural soil, taking into account:

- 1) all cadmium pathways into soil (fertilizers, atmospheric deposition and the model's particular characteristic of considering irrigation water);
- 2) cadmium output pathways from agricultural soil (crop cultivation, leaching).

In this first phase of the model, modelled cadmium concentrations in soil (surface horizons), wheat (grain), potato and leaching water were generated over 99 years using Monte Carlo simulations. For a given fertilisation plan, 10,000 plots were simulated. The simulations took into account the diversity of plots found in France, in particular through the use of data from the Soil Quality Measurement Network (RMQS, www.gissol.fr). In addition, each plot was defined by a vector containing the cadmium concentration related to the geochemical background, concentrations of organic matter, clay and carbon, and soil pH. The correlations observed between these parameters in the French plots were therefore taken into account. Variations in cadmium concentrations were then calculated according to the modelling period (example: 10, 20, 60 and 99 years) for the 10,000 plots. Some parameters, such as rainwater, yields and irrigation water quantity, varied from plot to plot and from year to year. The variability of these parameters was taken into account by randomly drawing a different value per plot and per year directly from the distributions fitted to the data. Modelling of cadmium output pathways from agricultural soil to crops (wheat grain and potato) and leachate was based on the integration of transfer equations selected in this work following a literature search (Franz *et al.*, 2008³⁶, De Vries *et al.*, 2011³⁷ and 2013³⁸, Ran *et al.*, 2016³⁹).

The algorithm was programmed using R software (version 3.4.0, 21-04-2017) and an application was developed in R-Shiny enabling the user to select the plan to be simulated.

Because of the difficulty of estimating the actual proportion of bioavailable cadmium relative to the application of fertilizer, the modelling assumed that total cadmium was fully bioavailable (a situation considered protective from a health standpoint). Cadmium speciation in agricultural inputs could obviously not be taken into account directly, but were taken into account indirectly through soil characteristics (pH, carbonates, etc.) by the transfer equations.

A table of the input parameters (values and equations relating to calcium inflows and cadmium outflows from the soil) was developed in connection with the probabilistic model built using the mass-balance approach and describing how variability was integrated and how uncertainty was dealt with. This is presented in the collective expert appraisal report addressing Question 3 of this formal request (see Table 19).

The means and percentiles of cadmium concentrations in soil, the plant (wheat (grain) and potato) and leaching water for all plots were ultimately presented in the form of tables and graphs. An analysis according to soil type (geochemical background concentration, organic matter, clay, carbon and pH) as well as input parameters (rainwater quantity, cadmium concentration in irrigation water, etc.) was provided.

³⁶ Franz E, Römkens P, van Raamsdonk L, Fels-Klerx Vd. (2008). A chain modeling approach to estimate the impact of soil cadmium pollution on human dietary exposure. *Journal of Food Protection* 2008; 71: 2504-2513.

³⁷ De Vries, McLaughlin, Groenenberg. (2011). Transfer functions for solid-solution partitioning of cadmium for Australian soils. *Environmental Pollution* 159 (2011) 3583-3594.

³⁸ De Vries, McLaughlin. (2013). Modeling the cadmium balance in Australian agricultural systems in view of potential impacts on food and water quality. *Science of the Total Environment* 461-462 (2013) 240-257.

³⁹ Ran J., Wang D., Wang C., Zhang G., Zhang H. (2016). Heavy metal contents, distribution, and prediction in a regional soil-wheat system. *Science of The Total Environment* 2016; 544: 422-431.

- Modelling of consumer exposure

Secondly, cadmium transfer from crop production through to consumers via food was modelled to estimate consumer exposure. This second part of the model drew on an existing model used by ANSES in the context of the request for an opinion on the revision of maximum content for cadmium in foodstuffs, under Request No 2011-SA-0194 (ANSES, 2011b). Simulations carried out with the model were used to obtain variations in cadmium concentrations (decrease or increase) in wheat grains and potatoes according to the fertilisation scenario. The variations (expressed as a mean percentage) in cadmium concentrations obtained in plants according to the fertilisation scenario were applied to the mean cadmium contamination of wheat- and potato-based foods and ingredients (ANSES, 2011a). This approach enabled the impact on consumer exposure to cadmium to be estimated.

The model's output data were ultimately used to deduce the mean chronic exposure, as well as that at the 95th percentile of adult and child consumers, according to the modelled projection time (10, 20, 60, 99 years), in correlation with the study of the change in cadmium contamination in crops (wheat and potato) associated with the fertilisation scenarios entered in the model.

3.3.3. Selection of cadmium fluxes from fertilizers tested in the model in order to derive cadmium levels in fertilizers that would reduce contamination of French agricultural soils and crops through to consumer exposure

The model was initially used for phosphate fertilisation plans as part of agricultural use in wheat monoculture or in potato/wheat/wheat rotation.

The use of phosphate fertilizers depends on the phosphorus demand of the crop and the phosphorus supply in the soil in France (poor, moderate, rich). The experts therefore considered the fertilisation plans with the highest demand for mineral phosphate fertilizers added to agricultural soils and associated with soils low in phosphorus in relation to the phosphorus demands of the plants. This maximalist situation requiring the highest application of phosphate fertilizers covers one third of the agricultural soils (crops and meadows) in France (RMQS – GIS SOL). The application doses associated with the fertilisation plans considered in the model relied on the agronomic recommendations and coefficient grids of the Arvalis-Plant Institute and the COMIFER on phosphate fertilisation.

The fertilisation plans considered for the model were as follows:

- Wheat monoculture:
 - Annual application of 80 kg P₂O₅.ha⁻¹.year⁻¹;
 - And application of 100 kg P₂O₅.ha⁻¹.year⁻¹ with an unfertilised period of two years.
- Potato/wheat/wheat rotation:
 - Annual application of 100 kg P₂O₅.ha⁻¹.year⁻¹;
 - And application of 180 kg P₂O₅.ha⁻¹.year⁻¹ with an unfertilised period of two years.

The phosphate application doses were then cross-referenced with the cadmium concentrations in the fertilizer to obtain the cadmium fluxes to agricultural soils via phosphate fertilizer.

For the cadmium concentration in the mineral phosphate fertilizer entered in the model, the starting assumption considered was the current standardised regulatory threshold in France in phosphate fertilizers of 90 mg Cd.kg P₂O₅⁻¹, as well as the reduced thresholds proposed in the European

Commission's draft revision of the regulation on CE-labelled fertilizers, of 60, 40 and 20 mg Cd.kg P₂O₅⁻¹. These thresholds were considered to be fixed or degressive (in accordance with a proposal in the draft revision of the regulation) throughout the modelling process, as summarised in the table below. The model was adapted according to the constant or degressive cadmium thresholds in the phosphate fertilizer applied to the agricultural soil during the projection time.

Table 5. Cadmium concentration threshold assumptions in phosphate fertilizers tested in the probabilistic model

Cadmium concentration in phosphate fertilizer	Fixed thresholds during modelling (mg Cd.kg P ₂ O ₅ ⁻¹)	Projection period: 1 to 99 years			
		90	60	40	20
	Degressive thresholds during modelling (mg Cd.kg P ₂ O ₅ ⁻¹)	Years 1 to 3	Years 4 to 15	Years 16 to 99	
	60	40	20		

Coupling the application doses with the cadmium content to be tested according to the fertilisation plans (wheat monoculture or rotation) resulted in 20 fertilisation plan scenarios associated with the use of mineral phosphate fertilizers that were tested.

This modelling was accompanied by simulations comparing cadmium fluxes according to the type of fertilizer (organic/inorganic), in order to more broadly discuss phenomena of cadmium accumulation in various compartments. Cadmium fluxes (expressed in g.ha⁻¹ and per year) depend on the quantities added to soils and the measured concentrations in fertilizers. In addition to testing cadmium content in fertilizer (especially for mineral phosphate fertilizers with controlled data), the consideration of fluxes has benefits for users. Regardless of the fertilizer used, this enables the addition of an element to be modulated in quantitative and temporal terms with a view to the sustainable management of cadmium inflows to agricultural soils and crops.

The 20 fertilisation plan scenarios associated with the use of phosphate fertilizers correspond to estimated cadmium fluxes of 0.67 to 9.00 g Cd.ha⁻¹.year⁻¹ depending on the scenario.

Cadmium fluxes to the soil from mineral phosphate fertilizers were compared with those from organic fertilizers. Calcium and magnesium soil amendments were not taken into account in the model due to their very low cadmium content. Cadmium fluxes to agricultural soils were derived for organic fertilizers for which data were available.

The model was used to simulate cadmium fluxes relative to:

- anaerobic digestates with a derived annual flux of 1.75 g Cd.ha⁻¹.year⁻¹ based on the mean cadmium concentration of 7.50 g Cd.ha⁻¹.year⁻¹ identified in fertilizer considering the regulatory threshold for cadmium in digestates⁴⁰;
- cattle manure with a derived annual flux of 2.55 g Cd.ha⁻¹.year⁻¹;
- STP sludge with a derived annual flux of 4.80 g Cd.ha⁻¹.year⁻¹.

⁴⁰ Ministerial Order of 13 June 2017 approving specifications for the placing on the market and use of agricultural anaerobic digestates as fertilizers

Cadmium fluxes were derived for organic fertilizers considering the mean cadmium concentration identified in these fertilizers (Plateau (2001)⁴¹, Chambre d'Agriculture Bretagne *et al.* (2007)⁴², Irstea and SOLAGRO (2012)⁴³, Benoît *et al.* (2014)⁴⁴, Wolf Environnement (2001)⁴⁵), except that the regulatory threshold was used for anaerobic digestates. The applied quantities of organic fertilizer considered in the model correspond to possible practices.

For livestock manure and digestates from anaerobic digestion on farms, these amounts were calculated on the basis of a nitrogen input corresponding to the maximum threshold of the Nitrate Directive⁴⁶, which lays down a nitrogen input of 170 kg of nitrogen.ha⁻¹.year⁻¹. For STP sludge, the maximum threshold authorised by the regulations was used, as the amounts of nitrogen and the physical nature of the sludge (liquid, paste or solid) can vary. The maximum application threshold authorised by the regulations was selected as the starting point (3 tonnes DM.ha⁻¹.year⁻¹)⁴⁷.

The mathematical model built was therefore adapted for all the simulations, enabling the cadmium fluxes to be varied according to the agronomic practices and projection time.

3.3.4. Results

The results of the simulations were analysed with regard to both the health risk and the characteristics of the receiving agricultural soils.

The predictive relevance of the model was assessed with regard to the modelled cadmium concentrations in soil, wheat, potatoes and leachate. The model developed is a consistent predictive tool for estimating the change in the proportion of leached cadmium and in cadmium contamination levels in agricultural soils, plants (wheat and potatoes) and the related final food products.

The results of the simulations, initially tested in the model with fertilisation plans associated with the use of mineral phosphate fertilizers with various cadmium levels (with regard to the soil-plant (wheat grain, potato)-leachate matrices), showed, over the model's simulation time (projection from 0 up to 99 years), the beginning of stabilisation and a reduction in cadmium accumulation in soils (and in its transfer to plants), from a cadmium content of 40 mg Cd.kg P₂O₅⁻¹ in phosphate fertilizers (according to fertilisation plans when there was an unfertilised period of two years).

This reduction in cadmium accumulation in soils and in its transfer to crops was far more marked for a cadmium content of 20 mg Cd.kg P₂O₅⁻¹ in phosphate fertilizers in all the simulations, with or without an unfertilised period. However, at the two highest cadmium concentrations in mineral phosphate fertilizer tested in the model (i.e. 60 and 90 mg Cd.kg P₂O₅⁻¹), cadmium accumulation in the soil and a significant transfer of cadmium to crops and leaching water were observed, regardless

⁴¹ Plateau A (2001). Effluents d'élevage - Elaboration d'un référentiel national, Paramètres agronomiques classiques et éléments traces métalliques des effluents d'élevage bovin, ovin et caprin. Engineering internship report, Angers Higher School for Agriculture; 2001.

⁴² Chambre d'Agriculture Bretagne, SNCVA, Cemagref. (2007). Les bonnes pratiques d'épandage du fumier. 2007: 29 pages. Available guide: [http://www.synagri.com/ca1/PJ.nsf/TECHPJPARCLEF/08890/\\$File/bonnes%20pratiques%20epandage%20FUMIER.pdf?OpenElement](http://www.synagri.com/ca1/PJ.nsf/TECHPJPARCLEF/08890/$File/bonnes%20pratiques%20epandage%20FUMIER.pdf?OpenElement).

⁴³ Irstea, SOLAGRO. (2012). Etat de l'art des digestats et leurs procédés de post traitement (DIVA project). ANR project - 10 - BIOE - 007 2012; Deliverables 2.1, 2.2, 2.3, 3.1: 76pp. Available: <https://diva.irstea.fr/livrables/>.

⁴⁴ Benoît P., Brugère H., Casellas M., Dabert P., Fuchs J., Giamberini L., et al. (2014). ESCo "Matières fertilisantes d'origine résiduaire". Caractéristiques physico-chimiques et biologiques des Mafor. Rapport final de l'expertise collective. Chapter 2. 2014: 212.

⁴⁵ Wolf Environnement S, SAS. (2001). Bilan entre micropolluants organiques, éléments traces métalliques, paramètres agronomiques, pH et matière sèche des boues de station d'épuration d'effluents urbains (données de Janvier 1998 à avril 2000). In: 2001. CA-j, editor, 2001.

⁴⁶ Council Directive 91/676/EEC of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources on EUR-Lex, Official Journal No L 375 of 31/12/1991 p. 0001 - 0008 (viewed on 3 May 2018)

⁴⁷ Ministerial Order of 8 January 1998 laying down the technical requirements applicable to the spreading of sludge on agricultural soil pursuant to Decree No 97-1133 of 8 December 1997 on the spreading of sludge resulting from wastewater treatment

of the fertilisation plan in wheat monoculture or potato/wheat/wheat rotation, with or without a two-year unfertilised period.

During the analysis of the mass balances between the compartments following the simulations, it appeared that cadmium was transferred into leaching water more than into the soil and crop matrices. Although the study of the change in leached cadmium according to the fertilisation plans exceeds the strict scope of the formal request, the ERCA Committee notes that these transfers to ground water and surface water contribute to environmental contamination and should be limited as far as possible because of the resulting environmental and health impacts. In addition, this water may subsequently be used for crop irrigation.

A reduction over time in cadmium transfer to the plant and leaching water with soils ultimately having lower contamination was observed with the realistic scenarios tested in the model associated with the use of degressive thresholds for cadmium in mineral phosphate fertilizers. These scenarios aim to reduce the cadmium concentration in mineral phosphate fertilizers to 20 mg Cd.kg P₂O₅⁻¹ within the next 15 years.

With regard to protecting consumer health, although a level exceeding the oral TRV for cadmium in adults and children derived in this request (0.35 µg Cd.kg bw⁻¹.day⁻¹) was still observed after action to reduce levels at the source in mineral phosphate fertilizer applied to agricultural soils, the results obtained showed that if no action is taken to reduce the cadmium content in mineral phosphate fertilizers (maintaining the current standardised regulatory threshold in France in phosphate fertilizers of 90 mg Cd.kg P₂O₅⁻¹), there will be a significant negative impact for the consumer, with a significant increase observed in the percentage of cases exceeding the TRV for adults as well as for children. In this situation (maintaining the current standardised regulatory threshold in France in phosphate fertilizers of 90 mg Cd.kg P₂O₅⁻¹), the percentage of children in which the TRV is exceeded would double after 99 years of projection, while in one third or more of children, it would not be possible to rule out a risk.

With fertilisation plans associated with a cadmium content of 20 mg Cd.kg P₂O₅⁻¹ in mineral phosphate fertilizers (fertilisation scenarios with constant or degressive cadmium thresholds over time), with a projection time of 99 years, a significant reduction in the percentage of the population exceeding the TRV was observed (see Tables 23 and 24 and Figures 25, 26, 27 and 28 of the collective expert appraisal report dedicated to Question 3).

Cadmium inputs to agricultural soils via mineral phosphate fertilizers can potentially be regulated at the source by choosing phosphate sources that are naturally low in cadmium or by using cadmium-removal techniques. However, organic fertilizers (STP sludge, livestock manure, etc.) are cadmium sources whose concentrations are associated with widespread and ubiquitous environmental contamination (animal feed, domestic waste, industrial waste, transport, atmospheric deposition, etc.) (see Annexes 1 and 2).

The modelling results on cadmium transfers associated with the use of mineral phosphate fertilizers were compared with those of the modelling associated with inflows to soils from organic fertilizers. This comparison showed that cadmium inputs to soils from applications of organic fertilizer were related not to a high concentration of cadmium in the materials but essentially to the amount applied. Using input data on fluxes of organic fertilizers and mineral phosphate fertilizers and based on a wheat monoculture plan, a decrease was observed in cadmium accumulation in the soil and its transfer to wheat grain following an annual tested flux of between 0.67 and 1.75 g Cd.ha⁻¹.year⁻¹. These fluxes are representative of the scenarios using farm anaerobic digestates with a mean cadmium concentration of 0.7 mg.kg⁻¹ DM and with phosphate fertilizers having a cadmium content of 20 mg Cd.kg P₂O₅⁻¹. Based on a flux of 2.55 g Cd.ha⁻¹.year⁻¹, cadmium accumulation in soil and its transfer to the crop were observed.

A comparison of the modelling results for fertilisation by mineral phosphate fertilizers on the one hand and by organic fertilizers on the other showed that irrespective of the type of fertilizer and fertilisation plans tested, a cadmium flux of less than $2 \text{ g Cd}\cdot\text{ha}^{-1}\cdot\text{year}^{-1}$ led to a decrease in cadmium accumulation in agricultural soil and in its transfer to the environment.

The influence of agricultural soil characteristics on cadmium transfer was studied. Following simulations of the application of mineral phosphate fertilizers, a risk of cadmium accumulation was observed in the case of agricultural soils that are already rich in cadmium (which may be related to their composition and properties) and/or that have a $\text{pH} > 7.5$, as well as a risk of cadmium transfer to crops in the presence of acid soils ($\text{pH} < 6.5$). With the exception of mineral phosphate fertilizers with content equal to or less than $40 \text{ mg Cd}\cdot\text{kg P}_2\text{O}_5^{-1}$, it seems necessary to restrict the use of these fertilizers according to the typology of the receiving agricultural soil, especially in the presence of:

- cadmium-rich soil ($> 0.7 \text{ mg kg}^{-1}$; this covers 7.1% of the agricultural soils supporting crops and meadows in France);
- soil with a $\text{pH} < 6.5$ (this covers 50% of the agricultural soils in France);
- and soil with a $\text{pH} > 7.5$ (this covers 30% of the agricultural soils in France).

However, it should be noted that in alkaline soils, cadmium is immobilised by precipitation regardless of the cadmium content of the mineral phosphate fertilizers.

Following a reduction in cadmium content in mineral phosphate fertilizers, the effect on the bioavailability of cadmium was clearly distinguishable on acid soils, in which a significant decrease in cadmium transfer was observed. Therefore, the ERCA Committee notes the benefit of reducing cadmium concentrations in mineral phosphate fertilizers, particularly with regard to acid soils that promote the solubility of this element. It was noted that cadmium can be immobilised in acid soils when their pH is increased by liming or by adding alkaline soil amendments. However, doubts were raised on this point according to the cadmium inputs to the soil: since the transfer of cadmium to crops is limited, this ultimately results in cadmium accumulating in soils.

These techniques are not sustainable alternatives for avoiding cadmium transfers to food: it is important to note that such liming practices, however beneficial they may be in the short term, represent a medium- and long-term hazard, since there is no guarantee that the pH increase will be sustainable.

On the contrary, the soil processes at work will tend to restore the original physico-chemical balances and lower the pH , which in the long term could promote transfers from soil to crops and leaching water.

3.3.5. Conclusions and recommendations of the Expert Committees regarding Question 3

Modelling the change in cadmium concentrations over time under different fertilizer application scenarios showed that it is possible to significantly reduce cadmium concentrations in soils and its transfer to plants and leaching water if inflows are strictly controlled. This would lead to a reduction in consumer exposure to cadmium.

In order to control pollution of agricultural soils, contamination of agricultural production and consequently the associated dietary exposure, the ERCA Committee recommends not to exceed an annual cadmium flux of $2 \text{ g Cd}\cdot\text{ha}^{-1}\cdot\text{year}^{-1}$ regardless of the type (fertilizer/soil amendment, organic/mineral origin, etc.) and total quantity of fertilizer(s) added to agricultural soil.

A cadmium content equal to or less than 20 mg Cd.kg P₂O₅⁻¹ in mineral phosphate fertilizer products that can be regulated at the source would ensure that this annual flux of 2 g Cd.ha⁻¹.year⁻¹ is not exceeded.

Furthermore, the results showed that a cadmium content below 1 mg Cd.kg⁻¹ dry matter in organic fertilizers would comply with this flux. In view of the difficulty of controlling cadmium concentrations in organic fertilizers, recommending a cadmium limit in this type of input could lead to their agricultural reuse being limited and their redirection encouraged towards other disposal or reuse methods (landfilling in storage centres, incineration, anaerobic digestion, etc.), which could also constitute sources of pollution that need to be controlled.

The ERCA Committee also recommends that information on cadmium content be provided for all fertilizers before application.

Furthermore, the use of agricultural practices that can trap cadmium in the short term, such as liming or addition of organic matter, or remediation techniques such as phytoremediation, is not a sustainable solution. Indeed, these techniques can only trap cadmium temporarily and, depending on the contaminant inputs, do not guarantee that this adsorption will continue in the medium and long term without repeated human intervention. They cannot therefore replace an active policy of reducing cadmium inputs to agricultural soils.

Cadmium-removal techniques can be used to reduce cadmium content in mineral phosphate fertilizers. Currently, the efficiency and cost of cadmium-removal processes to improve the quality of mineral phosphate fertilizers are not yet optimised. The ERCA Committee recommends that research be developed in order to optimise and develop these processes. It also notes that organic fertilizers have been little studied and their contaminant composition varies widely. Here too, research should be developed on the characterisation of these agronomic inputs.

The investigation of this third question of the request enabled avenues of research to be identified. Based in particular on the uncertainties addressed during this work, the need to produce additional information and data was also identified with the aim of continuous improvement, particularly on subjects related to phytoavailability, cadmium speciation, transfers between soil-plant-animal-food of animal origin, etc. Surveys of farmers and fertilizer/growing media sellers and producers would also help improve precision regarding the quantities of phosphate fertilizer applied.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

Cadmium is a ubiquitous trace metal element found in various environmental compartments due to its natural presence in the Earth's crust and to anthropogenic inputs related to industrial and agricultural activities. Its characteristics allow it to easily enter the food chain via plants that absorb it through their roots. The toxicity of cadmium metal is proven (classified by the IARC as carcinogenic to humans (Group 1) in 2012; classified as Category 1B carcinogenic and Category 2 toxic for reproduction according to the European CLP Regulation).

These combined hazard and exposure characteristics support the importance of health assessment work on exposure to this substance. The Agency's opinion following its Infant Total Diet Study (ANSES, 2016) recommended reducing exposure, by acting in particular on the level of environmental contamination and especially on inputs (mineral fertilizers, organic fertilizers and soil conditioners, etc.).

As part of this current opinion, the collective expert appraisal on the health risks associated with cadmium undertaken in various domains (toxicity to the general population, occupational exposure,

overall environmental cycle) provided evidence supporting management and decision-making by the public authorities.

Although it was not based on a quantitative health risk assessment, the expert appraisal on human exposure to cadmium provided an opportunity to:

- i. update the state of knowledge on the toxicological effects of cadmium on human health and propose a new toxicity reference value (TRV) by ingestion;
- ii. study the professional sector of fertilizers and the associated sources of cadmium exposure;
- iii. analyse, using a “from farm to fork” mathematical model, the change in cadmium contamination levels from the addition of fertilizers to soils through to the consumed food. This analysis determined cadmium levels that would control and reduce pollution of agricultural soils, contamination of crop production and dietary cadmium exposure in consumers, as well as occupational exposure, albeit indirectly.

These three aspects (establishing a TRV, knowledge of the sector of fertilizers and growing media, and cadmium contamination levels in fertilizers), which mutually interact, enable a better understanding of human exposure to cadmium (see Annex 1, Figure 3).

4.1. ANSES conclusions

ANSES endorses the conclusions of the HRV Committee and ERCA Committee, and reiterates the following conclusions:

- Proposals for TRVs by ingestion and health reference values in biological media:
 - i. The critical health effect of cadmium, selected by the experts based on epidemiological studies by Engström *et al.* (2011 and 2012), targets bone effects (especially bone demineralisation);
 - ii. The urinary cadmium concentration of $0.5 \mu\text{g}\cdot\text{g}^{-1}$ creatinine was selected as the critical concentration in biological media for a 60-year-old adult, assuming that ingestion is the only source of exposure to cadmium (excluding exposure from smoking);
 - iii. Considering a urinary cadmium concentration of $0.5 \mu\text{g}\cdot\text{g}^{-1}$ creatinine, and after toxicokinetic modelling (PBPK model), the TRV derived for cadmium is a tolerable daily intake (TDI) of $0.35 \mu\text{g Cd}\cdot\text{kg bw}^{-1}\cdot\text{day}^{-1}$ (equivalent to a tolerable weekly intake (TWI) of $2.45 \mu\text{g Cd}\cdot\text{kg bw}^{-1}\cdot\text{week}^{-1}$).
- Assessment of occupational exposure to cadmium in the sector of fertilizers and growing media:
 - iv. Few data are available concerning biological monitoring or cadmium exposure by inhalation of workers in the sector of fertilizers and growing media;
 - v. The sector study highlighted, on the basis of very incomplete data, cases of the OELs recommended by ANSES ($3 \mu\text{g}/\text{m}^3$) and the SCOEL ($1 \mu\text{g}/\text{m}^3$) being exceeded, especially for workers from the phosphate fertilizer production sector;
 - vi. Aside from in two targeted sectors for which very few data are available, no biological measurements have been taken for workers, which means that occupational exposure to cadmium cannot be rigorously assessed.
- Regarding the question on proposals for cadmium levels in fertilizers that would control pollution of agricultural soils and contamination of crop production:

- vii. An annual cadmium flux via fertilizers not exceeding $2 \text{ g Cd}\cdot\text{ha}^{-1}\cdot\text{year}^{-1}$ regardless of the type (fertilizer/soil amendment, organic/mineral origin, etc.) and total quantity of fertilizer added to agricultural soil is the recommended maximum limit, which would control pollution of French agricultural soils, contamination of crop production and therefore the associated dietary exposure;
- viii. With regard to the fertilisation plans tested, a cadmium content equal to or less than $20 \text{ mg Cd}\cdot\text{kg P}_2\text{O}_5^{-1}$ in mineral phosphate fertilizer products that can be regulated at the source would ensure that this annual flux of $2 \text{ g Cd}\cdot\text{ha}^{-1}\cdot\text{year}^{-1}$ is not exceeded.

4.2. ANSES recommendations

ANSES endorses the recommendations of the HRV Committee and ERCA Committee, and stresses the following points in particular:

Regarding occupational exposure

In light of the poor data that are available for assessing the occupational exposure to cadmium of workers in contact with fertilizers containing it, ANSES reminds employers of their health and safety obligations to their employees, according to Article L.4121-1 and following of the French Labour Code. In this context, they should first assess risks that cannot be avoided, to be able to implement measures for the prevention of occupational risks as well as information and training measures and establish a suitable organisational structure and resources. In this regard, ANSES stresses the importance of the recommendation on providing clear information about the cadmium content of fertilizers (regardless of their origin). Furthermore, since this work demonstrated that there are certain workstations with likely exposure to cadmium, ANSES recommends that exposure to cadmium via the use of fertilizers be assessed as part of primary prevention efforts. To that end, it reiterates that biometry is the method that should be used whenever possible to assess exposure to cadmium, which is a toxin whose toxicity is related to the cumulative dose over time.

Regarding long-term changes in the population's dietary exposure

Given the ubiquitous nature of cadmium and the need for action to reduce long-term dietary exposure to this element, the analysis of the contamination cycle (see Figure 3, Annex 1) demonstrated:

- the importance of controlling cadmium inputs in this cycle (regardless of the types of inputs);
- the potential benefits of reducing cadmium inflows from fertilizers in loops of the cycle.

In this regard, ANSES underlines the value established by the experts, corresponding to an annual flux limit of $2 \text{ g Cd}\cdot\text{ha}^{-1}\cdot\text{year}^{-1}$ (regardless of the type (fertilizer/soil amendment, organic/mineral origin, etc.) and total quantity of fertilizer added to agricultural soil), that would initiate a downward cycle for dietary exposure.

This threshold can be reached, assuming that mineral phosphate fertilizers are the only source of inputs, by a maximum value of $20 \text{ mg Cd}\cdot\text{kg}^{-1} \text{ P}_2\text{O}_5$. ANSES notes the compromise reached at

European level on 18 November 2018, setting an initial limit value for cadmium in mineral phosphate fertilizers of 60 mg Cd.kg⁻¹ P₂O₅, and affirms that this compromise does not promote a rapid reversal of the trend.

Furthermore, ANSES underlines that the use of organic fertilizers with a cadmium content below 1 mg Cd.kg⁻¹ dry matter is another pathway for ultimately reducing contamination in food products.

Thus, given the temporary effectiveness of trapping techniques (liming, phytoremediation, etc.), it particularly supports the experts' recommendations dealing with the following three pathways for change:

- continuing to lower the limit value below 60 mg Cd.kg⁻¹ P₂O₅ for mineral phosphate fertilizers and developing cadmium-removal techniques relative to their production;
- reducing the cycle of contamination associated with the application of all other types of inputs;
- making information available on the cadmium content of the products used.

Using appropriate drivers for action to implement these recommendations will ultimately reduce levels below the threshold of 2 g Cd.ha⁻¹.year⁻¹, which is essential to reverse the increase in the percentage of the population (adults and children) whose exposure exceeds the toxicity reference value for cadmium by dietary exposure only.

Dr Roger Genet

KEYWORDS

Cadmium, toxicity, toxicity reference value, reference health value, fertilizer, soil and crop contamination, dietary exposure

ANNEXES

Annex 1: Conceptual framework of the request

The objectives of the scientific expert appraisal are to:

- (i) Review the toxicological effects of cadmium on human health and the TRV by ingestion for cadmium;
- (ii) Study the professional sector of fertilizers and the associated sources of cadmium contamination;
- (iii) Ultimately recommend cadmium levels that would control and reduce pollution of agricultural soils, contamination of crop production and dietary exposure to cadmium in consumers.

These three aspects, which mutually interact, should enable a better understanding of human exposure to cadmium (Figure 3).

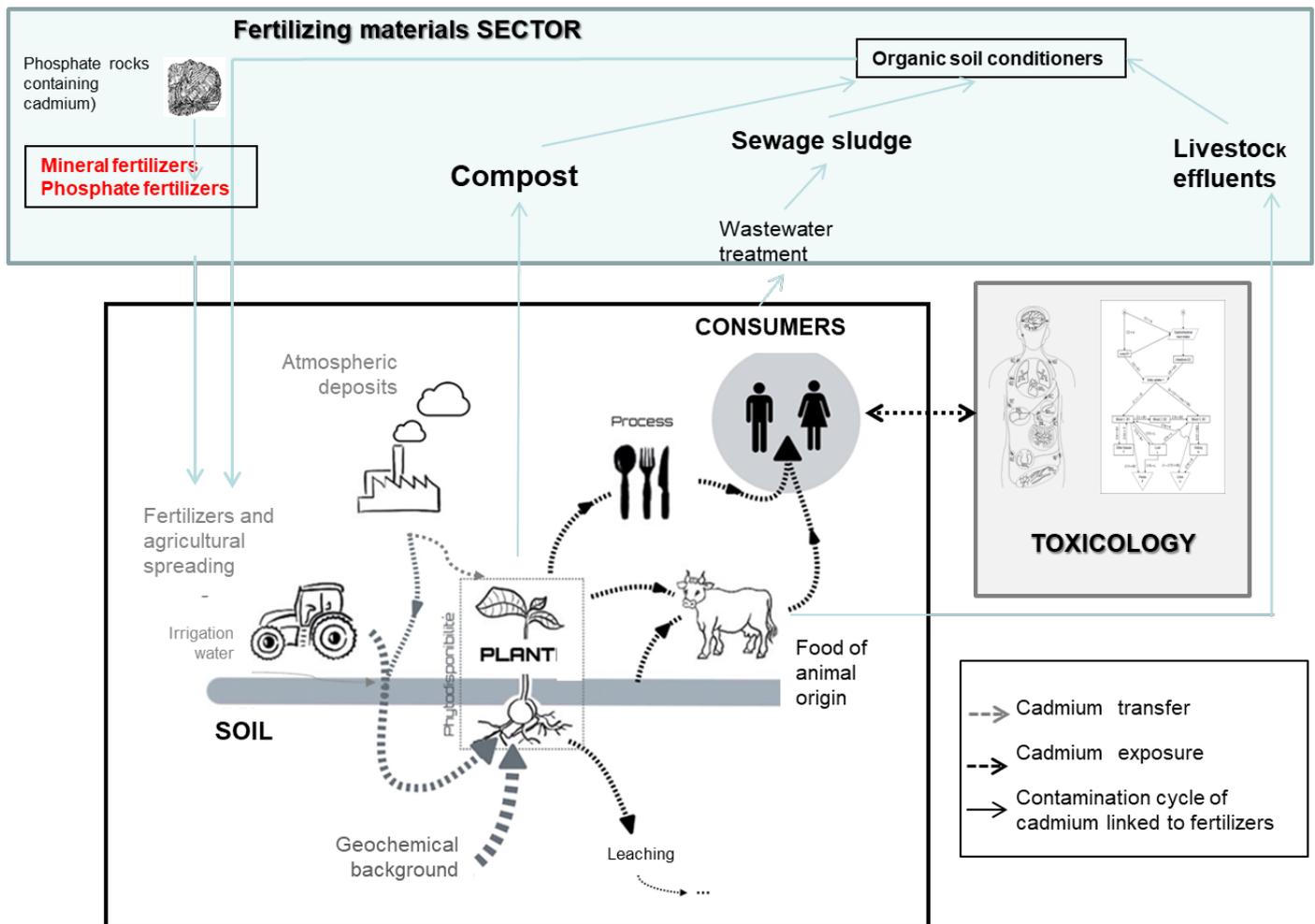


Figure 3: Human exposure to cadmium – from its sources in the environment, including the sector of fertilizers, through to consumer exposure

Annex 2: Median biological reference values for cadmium (in µg/g creatinine according to age)

Age (year)	Urinary Cd in µg/g creatinine	Estimated body weight (kg)	Age (year)	Urinary Cd in µg/g creatinine	Estimated body weight (kg)
0	0.00	4	33	0.20	72
1	0.02	8	34	0.21	72
2	0.03	12	35	0.22	72
3	0.04	16	36	0.23	73
4	0.04	20	37	0.25	73
5	0.05	24	38	0.26	73
6	0.05	27	39	0.28	73
7	0.06	31	40	0.29	73
8	0.06	34	41	0.31	73
9	0.06	37	42	0.32	73
10	0.06	40	43	0.34	72
11	0.07	42	44	0.36	72
12	0.07	45	45	0.37	72
13	0.07	47	46	0.39	72
14	0.08	50	47	0.40	72
15	0.08	52	48	0.42	71
16	0.08	54	49	0.43	71
17	0.09	56	50	0.44	71
18	0.09	58	51	0.46	71
19	0.10	59	52	0.47	70
20	0.10	61	53	0.47	70
21	0.11	62	54	0.48	70
22	0.11	64	55	0.48	70
23	0.12	65	56	0.49	69
24	0.12	66	57	0.49	69
25	0.13	67	58	0.49	69
26	0.13	68	59	0.49	69
27	0.14	69	60	0.49	69
28	0.15	69	61	0.49	69
29	0.16	70	62	0.49	69
30	0.16	71	63	0.50	69
31	0.17	71	64	0.50	69
32	0.19	71	65	0.51	69

Annex 3: Summary of the various typologies of fertilizers and growing media

Article L.255-1 of the French Rural Code defines fertilizers and growing media.

The fertilizers taken into account in the expert appraisal work include organic, inorganic and organo-mineral fertilizers intended to ensure or improve plant nutrition, and organic, inorganic and organo-mineral soil amendments that improve the physical, chemical and biological properties of soils.

Fertilizers and growing media represent a vast category. Their composition differs widely; it can be clearly defined, as in the case of synthetic fertilizers, or consist of various mixtures, as with sludge from sewage treatment plants (STPs) likely to contain numerous contaminants.

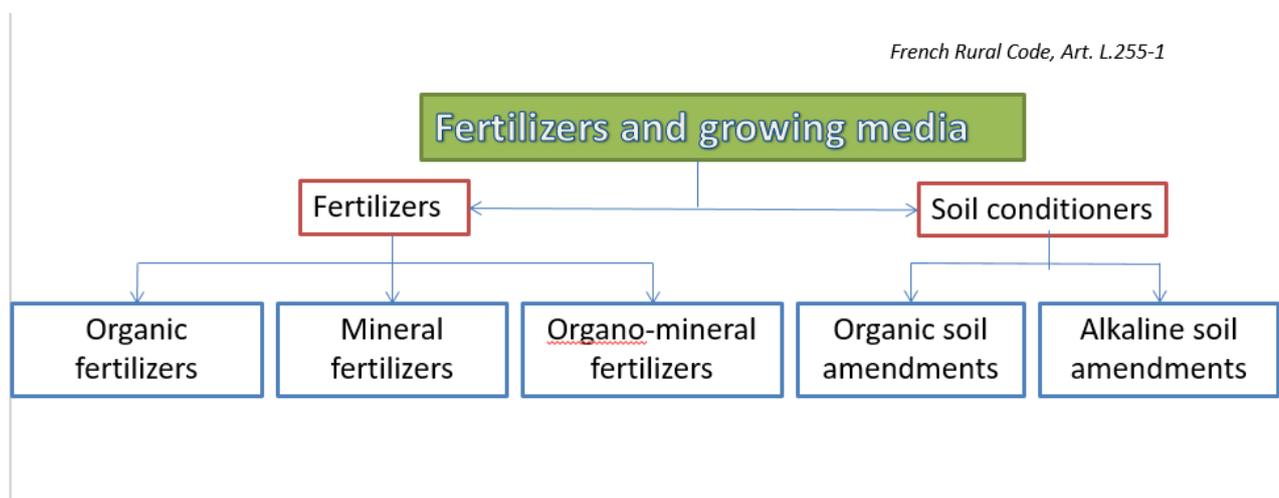


Figure 4: The various typologies of fertilizers and growing media

Fertilizers intended to supply plants with directly useful nutrients.

These may be primary or secondary nutrients or trace elements.

These nutrients are classified into three groups in order of importance for plants:

- o Primary nutrients: nitrogen, phosphorus and potassium;
- o Secondary nutrients: calcium, magnesium, sulphur and sodium;
- o Trace elements: although very small quantities of them are required, they are essential for plants (iron, manganese, chlorine, copper, zinc, etc.).

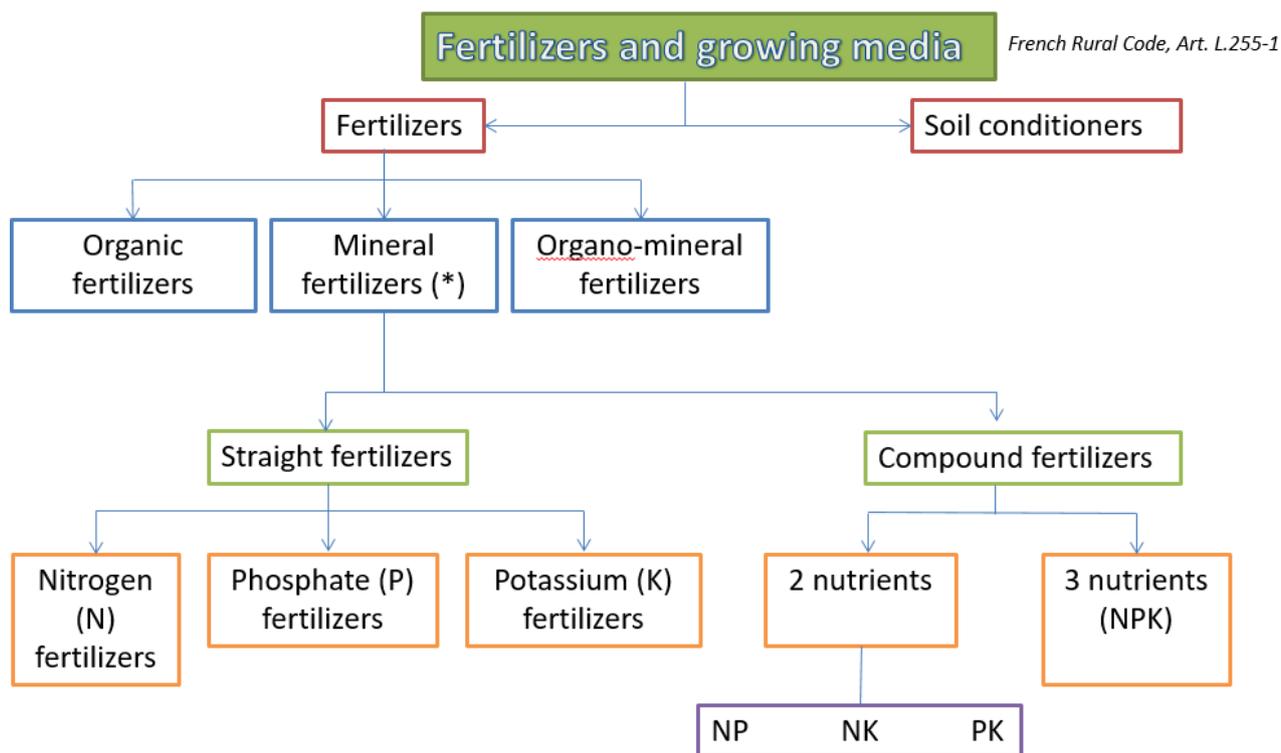


Figure 5: Positioning of phosphate fertilizers likely to be contaminated by cadmium

Fertilizers encompass all products containing more than 3% of one of the primary nutrients. They themselves are subdivided into three classes:

- o Organic fertilizers, which are either of animal or plant origin. They can also be synthesised;
- o Mineral fertilizers, whose declared nutrients take the form of mineral salts, obtained by extraction and/or by physical and/or chemical industrial processes;
- o Organo-mineral fertilizers, whose declared nutrients, of both organic and mineral origin, are obtained by the mixing and/or chemical combination of organic and mineral products or fertilizers.

Mineral nitrogen and potassium fertilizers contain very low levels of trace metal elements (TMEs) (including cadmium) (ADEME, 2007c). Therefore, they were not considered in the rest of this work. Concerning mineral phosphate fertilizers, natural calcium phosphate is used as a basic raw material for the production of these fertilizers. Natural deposits are primarily located in Morocco, the USA, Russia and the Middle East. All of these deposits contain varying levels of phosphates and naturally include other chemical elements. Therefore, the concentration of trace metal elements (including cadmium) in phosphate rocks may vary depending on the deposit. Thus, depending on the origin of the raw material and the specifications for the finished product (composition/formulation), some mineral phosphate fertilizers can also contain relatively high levels of natural cadmium.

In France, for the mineral phosphate fertilizers on the market containing more than 5% P_2O_5 , the authorised maximum threshold for cadmium established by the French standard NF U 42-001-1 of 2011 (AFNOR, 2011) is currently 90 mg Cd.kg $P_2O_5^{-1}$.

Soil conditioners used to modify or improve the physical, chemical or biological properties of soils. The role of soil conditioners, unlike that of fertilizers, is to modify the structure and acidity of soils, even though they sometimes also constitute a non-negligible source of nutrients. A distinction is made between:

- o Organic soil amendments: mainly containing fermented or fermentable carbon compounds of plant origin, they are used to maintain or reconstitute the stock of organic matter in the soil. The nitrogen, phosphorus and potassium content of unprocessed products must not exceed 3% for each element and their sum must be below 7%, otherwise the soil conditioner becomes a fertilizer. Fertilizers of waste origin (FWOs) belong to this class.
- o Alkaline soil amendments, also called calcium or mineral soil amendments: these contain calcium or magnesium, generally in the form of oxides, hydroxides or carbonates, but have no organic matter and no declarable levels of nitrogen, phosphorus, potassium or trace elements. These soil amendments are mainly used to maintain or increase the soil's pH.

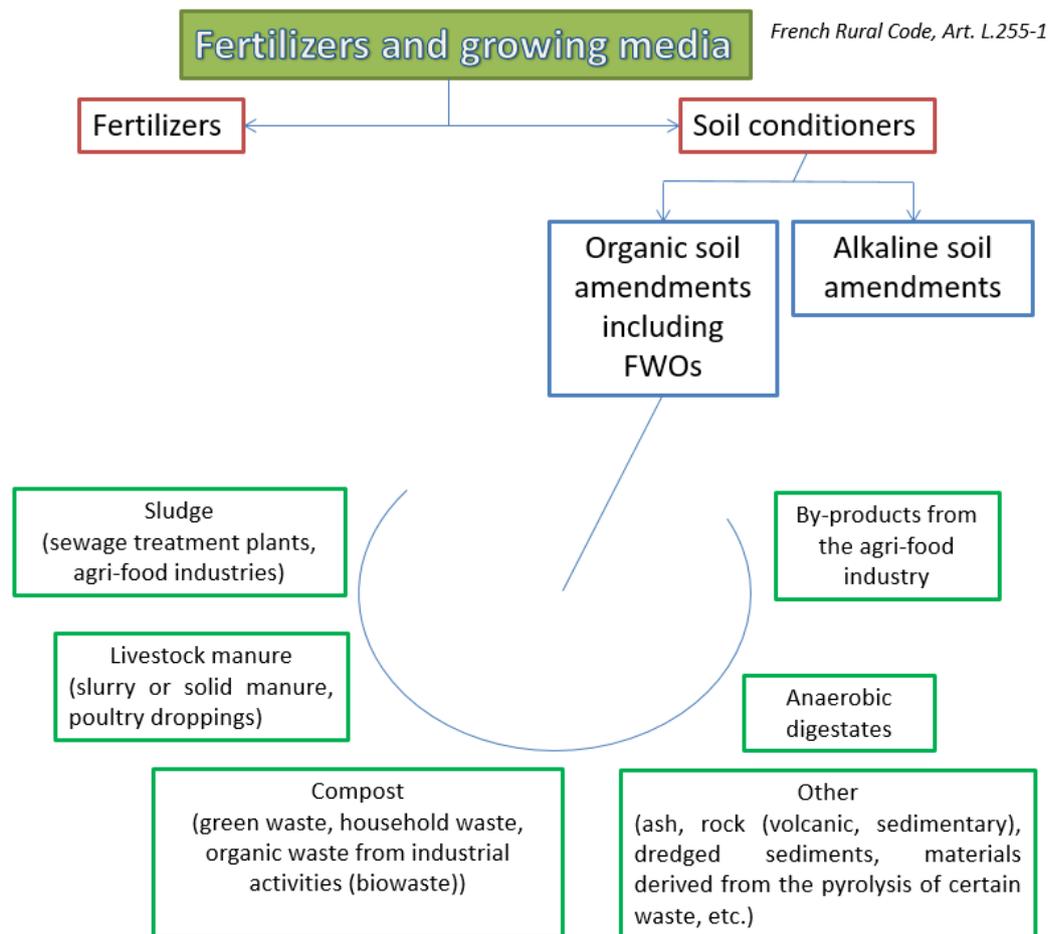


Figure 6: Classification of soil amendments and description of FWOs