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CHEMICAL SAFETY REPORT

Legal name of applicant(s):	SEBIA
Submitted by:	SEBIA
Substance:	4-Nonylphenol, branched and linear, ethoxylated (4-NPnEO) [Substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof]
Use title:	*Use-4:* Industrial use of 4-NPnEO for its detergent properties in the production of buffers and reagents in view of ensuring the positioning of specific proteins necessary for the interpretation of gel electrophoresis in vitro diagnostic tests results based on the determination of isoenzymes
Use number:	Use-4

9. EXPOSURE ASSESSMENT

9.1. Introduction

The uses of 4-NPnEO (ES1) concerned by the present AfA have specificities that have to be taken into consideration in order to have a global understanding of the situation:

- ***An application that includes both industrial and professional uses***

SEBIA's AfA covers industrial uses within its production site of LISSES for the production of gels and reagents intended for IVD kits.

SEBIA products are *in fine* used by professionals in hospitals or laboratories to carry out *in-vitro* diagnostics.

- ***An application that includes uses potentially excluded from the scope of the Authorisation process***

In-vitro diagnostics analysis activities are potentially exempted of Authorisation duties as per Art. 56(3) of the REACH regulation. ECHA's Guidance on Scientific Research and Development (SR&D) and Product and Process Orientated Research and Development (PPORD) [Version 2.0, November 2014] specifically mentions *in-vitro* diagnostics at a laboratory scale under controlled conditions as activities falling under this exemption. However, in order to cover their customers, the applicant has decided to integrate this use in a particular exposure scenario (ES-2) in which information about the conditions of use and the category of customers are summarized.

- ***Release management and monitoring***

All process effluents are collected and concentrated on-site (Evapo-concentrator and Osmofilms, see below) and all solid wastes containing potentially the substance collected and treated by certified providers. Regular monitoring (ISO: 18857-2) of potential substance releases in wastewater is being established on the site and realized by independent and certified laboratories.

Concentration of wastewater by Evapo-concentrator and Osmofilms

1) The washing water of equipment containing potentially 4-NPnEO (except washing water of glassware) is collected *via* manholes or reels connected to underground retention reservoirs (n = 2, 5000 L each).

2) The underground reservoirs are connected to the evapo-concentrator and the contaminated water is then boiled at 40°C under low pressure (Max processing capacity = 1000 L/day). The water evaporates is then condensed (distillate) and release in the collective sewerage network. The concentrate resulting from this process is collected in dedicated tanks and then treated by Osmofilms.

3) Osmofilms are permeable plastic bags stored outside in a specific area. Concentrates obtained after dehydration are then collected and treated by a certified company.

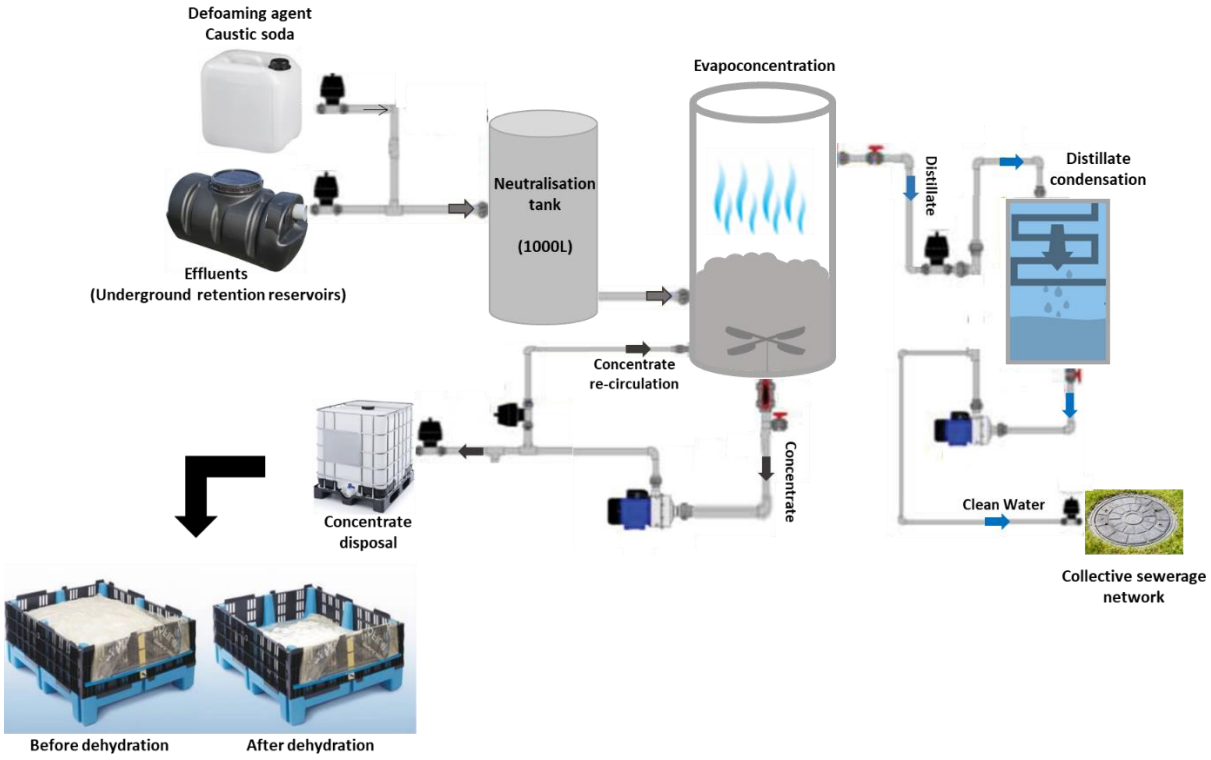

Figure 2. Evapo-concentrator and osmofilms treatments process

9.1.1. Introduction to the assessment

9.1.1.1. *Environment*

The environmental assessment is the main consideration for this CSR dedicated to the Application for Authorisation regarding the SVHC properties stated in column 2 of entry 42 in annexe XIV of REACH (Commission Regulation (EU) No 125/2012).

Firstly it is important to note that the applicant has already implemented a high level of risk management measures for this substance by collecting all the potential releases from the process except the possible washing steps of materials.

The applicant strategy was to assess the exposure levels of Marine (total dissolved and sediments), freshwater (total dissolved and sediments), soil, STP and secondary poisoning compartments at local **(PEC_{local})** and regional **($PEC_{regional}$)** scales based on the tonnages used by the applicant for the use or a hypothetical end-user. PEC concentrations were calculated in EUSES according to (1) the environmental release category 2 (ES-1), 8b (ES-2) or (2) the released fraction extrapolated thanks to monitoring data and the flow rates going to STP obtained on-site (ES-1). The exposure assessment of the ES is based on the maximum quantity expected in 2022, which is considered to be the maximum quantity of the substance used during the review period. The value of 2017/2018 have been kept in the tables because they were used to calculate the realistic release fraction thanks to monitoring data. To calculate the realistic release fraction of the substance in water. Maximum daily flux of Total alkylphenols (NP, NP1EO & NP2EO) monitored on-sites (Kg/day) were converted, thanks to the number of emission days (number of day worked with the substance), in maximal Yearly flux of Total alkylphenols (Kg/year). This quantity compared to the annual tonnage used is considered to be the realistic release fraction. Monitoring have been performed in 2018 mainly and thus quantity used in 2017/2018 was considered for the calculation of the realistic release fraction. To consider the lowest yearly tonnage used is more conservative for the calculation of the realistic release fraction.

According to the activities performed by the applicant and the RMM implemented, only a potential fraction release in water was considered in EUSES for the PEC estimation. Fractions release to soil and air were considered negligible.

Then, in addition to the SEA analysis route (main route), the PEC values for marine and freshwater compartments (Total) were compared to the predicted no-effect concentrations (PNEC) for freshwater and marine aquatic organisms **(0.33 µg/L and 0.033 µg/L respectively)** derived from the **Environmental quality standards (EQS) of the water framework directive (WFD) for the parent substance (NP/4-NP)**[3]. Concerning sediment (both freshwater and marine) and soil compartments, PNEC used were derived by EUSES based on freshwater and marine PNEC as no relevant studies are available for sediment and soil organisms. For both STP and secondary poisoning PNEC, relevant toxicological data from the European Environmental risk evaluation report[2] were chosen. **Finally, all the PNEC used in the CSR are congruent with them used in the Environmental risk evaluation report of 4-NP[2] and the EQS of the WFD[3] for the different environmental compartments.**

These comparisons have allowed the calculation of Hypothetical Exposures Ratio (HER) for the different compartments at both scales (local and regional)**. However, considering that 4-NPnEO is a non-threshold substance and that the EQS does not cover the potential endocrine disrupting effects of the substance, The HER calculated in the document are not presented to conclude that the risk is controlled by the applicant. However, HER values are used to give an**

overview of the potential environmental exposures linked to the applicant uses. Nevertheless, the applicant considers the socio-economic assessment route as the main route of analysis of present authorization dossier.

9.1.1.2. *Man via environment*

The human health assessment is not the consideration for this CSR dedicated to the Application for Authorisation regarding the SVHC properties stated in column 2 of entry 42 in annexe XIV of REACH (Commission Regulation (EU) No 125/2012).

9.1.1.3. *Workers*

The human health assessment is not the consideration for this CSR dedicated to the Application for Authorisation regarding the SVHC properties stated in column 2 of entry 42 in annexe XIV of REACH (Commission Regulation (EU) No 125/2012).

9.1.1.4. *Consumers*

The human health assessment is not the consideration for this CSR dedicated to the Application for Authorisation regarding the SVHC properties stated in column 2 of entry 42 in annexe XIV of REACH (Commission Regulation (EU) No 125/2012).

9.2. Summary of RMM on-site

NPnEO-containing wastes in both liquid and solid forms are collected in appropriate containers, hermetically closed and stored in specific area dedicated to wastes. Identified workers and services are in charge of the appropriate conditioning of wastes and their traceability among time until their ultimate elimination by incineration. Waste areas are closed in order to avoid external intrusion.

The production site of Lisses (ES-1, Use-4) operates quality management system which complies with the requirements of the ISO 14001:2004 and ISO 13485:2012 international standards for the research, development, production and sales of reagents and equipment for in vitro biological analysis. The site is constituted of three facilities linked by tunnels (Fig.2). Osmofilms resulting solid wastes (high volumes) are stocked in the Waste Storage area situated outside the other facilities (Fig.3).

Figure 3. Plan of the site of Lisses (outside)

In the "Chemistry" Facilities, productions of buffers, strips and gels containing NPnEO are performed on the ground floor (Fig.4). Remaining low volumes of NPnEO containing solutions in equipment are collected in dedicated containers, hermetically closed, properly identified as dangerous wastes and stored in a dedicated room before the final elimination by a certified company *via* incineration. Washing waters of equipment (Tanks, filling lines, gel casting machine, …) are collected via manholes or reels (Fig. 5) present in the different production rooms that are connected to underground retention reservoirs present on site (n = 2, 5000 L each). The soiled water collected in retention reservoirs is treated thanks to an evapo-concentrator (boiling at 40 ° C in low pressure) with a maximum treatment capacity of 1000-L of effluent processed per day. Currently, the average value is 5500-L of effluents processed per month. Distillate is released to the collective sewage network to be treated by the local STP. Concentrates are collected in 1000-L tanks, then transferred and treated with Osmofilms (250-L each) in the outside waste storage area (Fig.6E) and then disposed of by a certified provider company (VEOLIA) *via* incineration. Some particular liquid or semi-solid liquid wastes are not suitable for the evapo-concentrator. Those wastes are stored in a specific room (Fig. 6D) and are directly treated in Osmofilms. Monitoring measurements are performed on wastewater going to collective sewage network in which the distillate produce by the evapo-concentrator is thrown. In this way, measurements are performed on the wastewater released from the site that will be afterwards treated by the local STP. Low volumes solid wastes (single-used equipment, empty containers, soiled wipes, soiled vials….) are collected in dedicated containers and stocked in the waste area present on the ground floor of the "Electronic" facilities (Fig. 6A, 6B, 6C) . Liquid and solid wastes containing NPnEO are considered as dangerous wastes, collected in appropriate containers, hermetically closed, properly identified as Special industrial wastes (DIS) with the appropriate pictograms (Fig.7). Each document, procedure and certificate (Waste transports and treatments) is available for local authorities. Every workers are informed on the precautions to take for the packaging, the identification and the storage of the wastes (liquids and solids) present on site.

Figure 4. Plan of the site of Lisses (Inside)

Figure 5. Reels and manholes

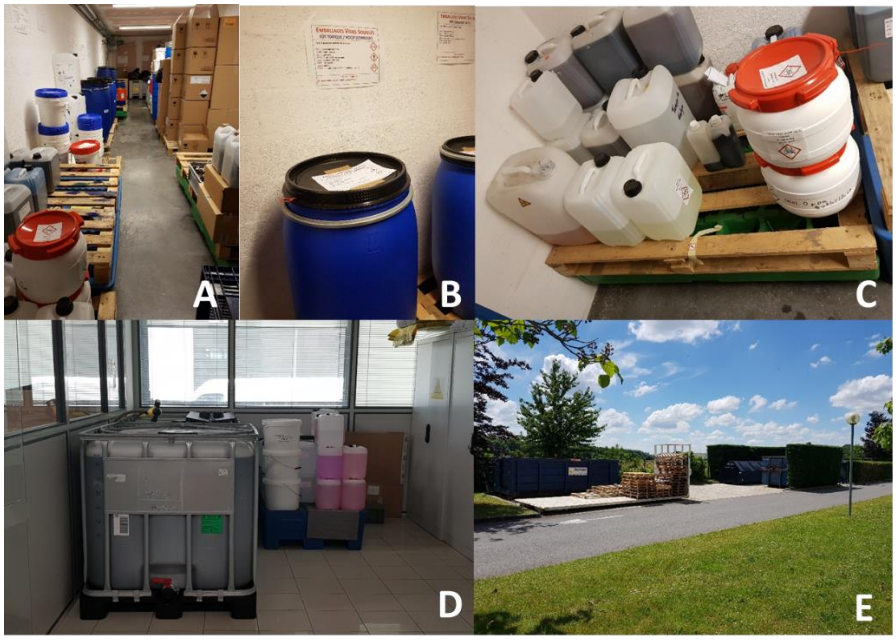

Figure 6. Waste storage area and containers dedicated to waste collection

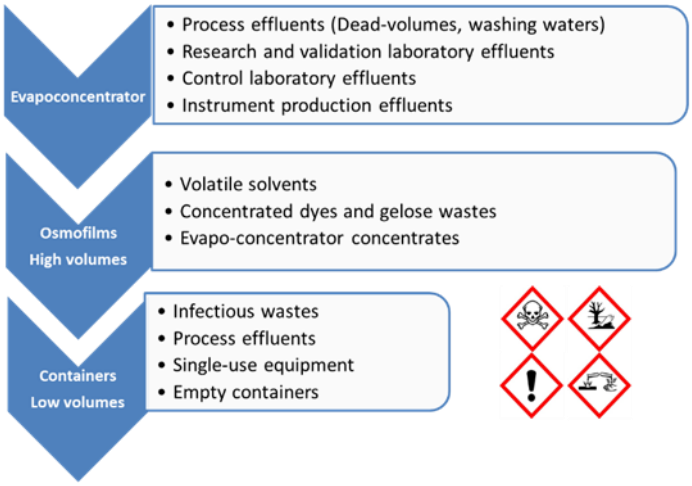

Figure 7. Overview of NPnEO containing wastes and collection routes

In the site of Lisses, training of workers, operational procedures for both manufacturing and collect/disposal of wastes, safety rules and displays in the work rooms are implemented. Every

worker is aware that the use and the production of NPnEO-containing solutions is hazardous for environment. Thus, procedures are implemented in the site to avoid the intentional release of the substance in the collective sewage network (the potential main source of NPnEO contamination of the environment). In case of accidental spills of NPnEO-containing solutions (pure or in mixtures) in the storage area, waste storage area or in the production area, absorbent products (Fig.8 & 9) are used and then placed in a disposable container for incineration. More generally, HSE manuals describe general emergency plans in case of fire, electric & equipment incidents, chemicals or biological solutions incidents. Personal protective equipment and operational procedures are described for each incident sources identified.

sebia

CONSIGNE DE SÉCURITÉ

TAPIS OBTURATEURS ETANCHES

EVITONS LES POLLUTIONS ACCIDENTELLES

Caractéristiques :

- Permettent l'étanchéisation des regards d'évacuation des eaux, présents au sol.
- Résistent à l'eau, à l'huile et aux produits chimiques.
- La matière extrêmement épaisse et flexible s'adapte de manière idéale à tous les sols.

Précautions à prendre :

- Stocker les tapis dans un conditionnement étanche, à l'abri de la lumière, dans un endroit sec et frais : ils sont sensibles aux UV, à l'humidité, à une température trop élevée (≥ 50°C).
- Après utilisation, nettoyage à grande eau au dessus d'un siphon relié à la cuve de rétention.

IL EST IMPERATIF DE RESPECTER CETTE CONSIGNE DE SECURITE.

Figure 8. Absorbent products present in intervention kits

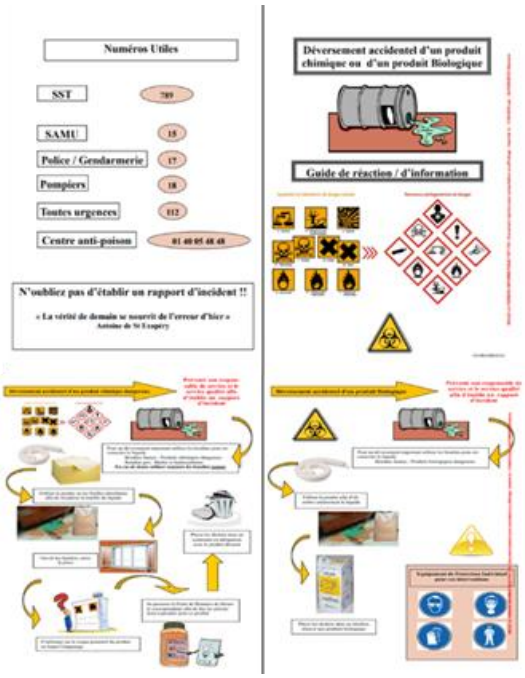

Figure 9. Example of recommendations present in the intervention kits

9.3. Exposure Scenario 1: Use of 4-NPnEO for the production of gels, buffers and reagents involved in *in vitro* gel electrophoresis assays

Life cycle stages:

Formulation or re-packing (F)

Sector of use:

Scientific research and development (SU 24), Health services (SU 20)

Chemical product category:

Laboratory chemicals (PC 21), *In vitro* diagnosis

Environmental contributing scenario:

ECS-1: Formulation into mixture (ERC 2)

Worker contributing scenarios:

WCS-1: Supply and storage (PROC 0)

WCS-2: Quality Controls (PROC15)

WCS-2: Weighing (PROC 9)

WCS-3: Mixture-Formulation (PROC 5)

WCS-4: Production of final products (PROC 8b)

WCS-5: Final packaging (PROC 9)

WCS-6: Distribution (PROC 0)

WCS-6: IVD tests (PROC 15)

9.3.1. Process description – Exposure Scenario 1

9.3.1.1. *Process overview*

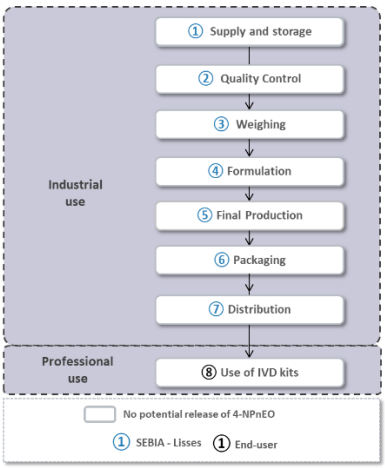

Figure 10. Process overview, ES1

For some process steps, it is indicated “no **potential** releases” considering that only an extremely low amount of substances could be released during cleaning steps.

9.3.1.2. *Lifecycle of 4-tert-OPnEO*

→ ① *Supply and storage*

In the site of Lisses (ES-1), 1-L plastic bottles of Nonidet-P40 solution are provided by Sigma-Aldrich. Pure solutions are stored in a dedicated and a locked storage room on retention (Fig.11). A maximum of 1-L of Nonidet-P40 are stored in the room at a given time. Nonidet-P40 is provided approximately once a year.

Figure 11. Storage area for Nonidet-P40

Movements between storage locker and the room dedicated to weighing are performed thanks to a trolley. The solution Nonidet® P 40, replacement product is never open in the locker.

No release of 4-NPnEO occurs during this step

→ ② *Quality control*

The quality control step is performed in a laboratory dedicated to the validation of all SEBIA products. Samples of Nonidet® P 40, replacement product (≈ 10.6 g) are sampled in the room dedicated to the weighing (Step 3) in Falcon® tubes, hermetically closed and brought to the laboratory. Then, samples are analysed in order to verify the conformity of the products (certificate of analysis) sell by the main supplier and the functionalities of the products by formulating buffers and testing them in operating conditions (gel electrophoresis). A part of the sample is kept in the sample bank.

Every SEBIA products are also controlled in the dedicated laboratory at the end of their production and before their conditioning.

All potential wastes (liquids and/or solids) with 4-NPnEO are collected in dedicated containers, concentrated on-site (liquids by evapo-concentrator and osmofilms) and then solid wastes disposed of by a certified provider as a substance with hazardous properties for the environment.

No release of 4-NPnEO occurs during this step.

→ ③ *Weighing*

Nonidet® P 40, replacement product solution is weighed under a laminar flow cabinet in a semi-enclosed and ventilated area. Each weighing batch is then hermetically closed prior to any movement in the production area.

Filters of the laminar flow cabinet are controlled and changed when required. The used filters are collected in dedicated containers for solid materials and then disposed of by a certified provider.

After the weighing, glassware is rinsed one time and the first washing water is added in the in-process solution (final mixture) to recover the entire weighed quantity of NPnEO needed. Thereafter, glassware is sent in the laundry room for the final washing step. Washing water coming from the laundry room are discarded in the collective sewage network and thus even if the quantity and the concentration of the final mixture in the glassware before the laundry washing are really low (potentially negligible), this could be considered as a potential release source. In order to eliminate the potential release of OPnEO from the glassware washing process, the applicant has begun a process of analysis and reflection in order to collect the second rinse of glassware used under the Weighing Step. The rinsed glassware will be then sent to the laundry washing.

Potential release of 4-NPnEO occurs during this step

→ ④ *Mixture/Formulation*

This step consists of general mixture and dilution of the Nonidet® P 40, replacement product solution in order to prepare reagents for gel production (cf. step 5: production of final products) and reagents destined to IVD kits.

For gel reagents, this operation is performed in the semi-enclosed and ventilated weighing room using semi-automatic mixers and barrels or tanks (≤ 200 L).

For reagents, this operation is performed in the semi-enclosed and ventilated room dedicated to reagent productions using semi-automatic reagent mixing tanks (for low volume = 200 L to 500 L).

The washing of semi-automated mixers and semi-automatic reagent mixing tanks (the lid, the tank, and the rotating blade) is performed with tap water and then rinsed with demineralized water. The washing water is collected in a dedicated container. Every part of the equipment are then dried with cloths (Essuisoft®) except the tanks which are dried in the open air.

Movements between mixture rooms and production (gel) or packaging (reagent) rooms are performed thanks to a trolley. The mixtures are hermetically closed during this step. No contact with workers is expected.

All potential wastes (liquids and/or solids) with 4-NPnEO are collected in dedicated containers, concentrated on-site (liquids by evapo-concentrator and osmofilms) and disposed of by a certified provider as a substance with hazardous properties for the environment. The only potential released of 4-NPnEO could rely to the glassware washing. However, considering that only an extremely low amount of 4-NPnEO remains in the glassware, this release can be considered negligible.

No potential release of 4-NPnEO occurs during this step

→ ⑤ *Production of final products*

This operation consists of the gel production thanks to mixtures prepared in the past step (4) and intermediate plastic material coated (GBR support) produced by the subcontractor REXOR. This operation is carried out in an automated casting machine in a dedicated clean room under controlled atmosphere.

Movements between mixture rooms and the production room are performed thanks to a trolley. The buffered mixture is hermetically closed during this step. No contact with workers is expected.

The pipes of the automated machine are washed with tap water and then demineralized water. The washing water is collected in a dedicated container. The other parts of the automated machine are disinfected (ANIOSPRAY) using disposable cleaning cloths.

All potential wastes (liquids and/or solids) with 4-NPnEO are collected in dedicated containers, concentrated on-site (liquids by evapo-concentrator and osmofilms) and then solid wastes disposed of by a certified provider as a substance with hazardous properties for the environment.

No potential release of 4-NPnEO occurs during this step

→ ⑥ *Packaging*

Once produced, coated gels are immediately packaged with their respective buffers with dedicated and automated equipment. Reagents are directly packaged after their formulation using semi-automated and automated equipment.

All the packaging equipment is washed with tap water and demineralized water. The washing water is then collected in dedicated containers. The equipment is then disinfected (ANIOSPRAY) using disposable cleaning cloths collected in dedicated containers.

Once packaged, gels and reagents are identified and stocked until their conditioning in IVD kits.

Finally, gels and reagents are conditioned in cardboard IVD packs before their distribution.

No potential release of 4-NPnEO occurs during this step

→ ⑦ *Distribution*

Cardboard IVD packs containing IVD kits are distributed to end-users, all SEBIA product remain hermetically closed at all time until their use.

No release of 4-NPnEO occurs during this step

→ ⑧ *IVD Tests*

IVD kits are used by hospitals and analysis laboratories, by trained staff, in semi-enclosed conditions (automated analysis equipment) or open conditions (manual operations). These operations are exempted from Authorisation duties.

No potential release of 4-NPnEO occurs during this step.

9.3.2. Environmental contributing scenario 1: Formulation into mixture

9.3.2.1. *Conditions of use*

Parameter	Information
Product characteristics	
• Product	*Nonidet® P 40, replacement product*
• Physical form	*Liquid*
• Amount	*2 kg*
• Weight fraction of the substance in the liquid mixture	*Depending of the process step, nevertheless, at the beginning of the process it is around 100% of Nonidet® P 40, replacement product*
Operational conditions	
• Emission Sources	*Considering the vapour pressure and the use of the substance, the only source of environmental exposure is via waste water.*
• Atmospheric emissions	*No atmospheric emission is expected regarding the physicochemical properties of the substance, the use and the RMM.*
• Liquid effluents	*The applicant has decided to collect all the possible effluents except the potential releases coming from the washing steps of glassware. The effluents are then concentrated on-site by an evapo-concentrator, osmofilms, or both. Then, the solid wastes coming from the osmofilms treatment are collected in dedicated containers and collected by a certified company to be incinerated.*
• Waste production	*All the solid waste potentially contaminated are collected in dedicated containers and collected by a certified company to be incinerated.*

Table 11. Condition of use for the contributing scenario 1

9.3.2.1. *Parameters used in EUSES for the environmental exposure assessment*

Considering that the substance is not biodegradable, the applicant uses the physicochemical values of the 4-NP support document[1] to provide a worst case model. The parameters listed below were chosen in order to represent the most relevant scenario of emission for ES-1.

Input data on EUSES:

Criteria	Value
Molecular weight (g/mol)	220.35
Melting point (°C)	80.5
Boiling point (°C)	281.5
Vapour pressure (Pa)	0.3 at 25°C
Water solubility (mg/L)	7 at 25°C
Log Kow (20.5°C)	5.76
Chemical class	Predominantly hydrophobic
Biodegradability	Not readily biodegradable
Use patterns	Formulation
STP	Yes (Standard)

9.3.2.2. *Releases*

In Table 12, release estimations are presented. Two different estimations were performed by the applicant:

- (1) An estimation using the local estimated quantity of total alkylphenols (Total of NP1EO, NP2EO and NP) released in water on-site per year (10 days of emission, using maximum concentration of total alkylphenols observed in monitored values (ISO188957:2) and water flows going to STP)

- (2) An estimation using the local estimated quantity released in water on-site calculated by EUSES based on tonnage and according to ERC2 (10 days, 2% released in water).

Default estimated releases are calculated based on ERC2 **(2% of the amount released to water, default worst case)**, however, the real fraction released in water on-site, estimated using monitoring data and the tonnage of 2017 (1.3 kg), is **0.008 % (realistic worst case)** (Table 13).

Both release estimations are used in order to characterize the PEC. (Table 14-ERC2 & 15-Monitoring). Public data available on the connected STP (SIACRE-EXONA)[4] and water flow rates of the Seine (Alfortville)[5] were inputted in EUSES.

The monitoring data are provided in annexe.

Company	Use	Site	Total tonnage in 2017 (kg/year)	Tonnage in 2022 (kg/year)	Number of emission days per year (d/year)	Daily mean water flow rate on-site (L/day)	Measured releases (on-site waste water output) (µg/L)	Estimation of the daily maximum quantity of total alkylphenols released on-site considering the monitoring values (g/day)	Estimation of the maximum quantity of total alkylphenols released on-site during the emission period considering the monitoring values (g/year)	EUSES estimation of daily local quantity released on-site based on tonnage and ERC2 (g/day)	EUSES estimation of local quantity released for the emission period based on tonnage and ERC2 (g/year)
SEBIA	Use-4	Lisses	1.3	2	10	23760	0.26 for NP < 0.05 for NP1EO 0.13 X for NP2EO **= 0.44 Total alkylphenols**	0.01	0.10	4	40

Table 12. Summary of release data on the site of Lisses

Production volume of Chemical in UE for the Use-4 (kg/y) (input)	2
Fraction released to water (input)	0.02 (2%)
Estimated fraction released to water based on monitoring data (input)	0.00008 (0.008 %)
Number of emission days per year (input)	10
Local emission to wastewater during episode calculated by EUSES (Kg/d) (output)	4E-03 (ERC2) 1.6E-05 (Monitoring)
Number of inhabitants feeding this STP (eq.)(input)	9.6E+04
Flow rate of the river (Alfortville, Seine, m^3/d)	1.89216E+07

Table 13. Data input and output in EUSES for PEC determination

The worst case estimation of exposure is as follows:

Use	Site	Total tonnage (kg)	Fraction released to water ERC2	PEC_{local} Freshwater (µg/L)	$PEC_{regional}$ Freshwater (µg/L)	PEC_{local} Freshwater Sediment (µg/Kg WW)	$PEC_{regional}$ Freshwater Sediment (µg/Kg WW)	PEC_{local} Seawater (µg/L)	$PEC_{regional}$ Seawater (µg/L)	PEC_{local} Marine Sediment (µg/Kg WW)	$PEC_{regional}$ Marine Sediment (µg/Kg WW)	PEC_{local} agricultural soil_180 d (µg/Kg WW)	$PEC_{regional}$ agricultural soil (µg/Kg WW)
Use-4	LISSES	2	0.02	3.54E-05	1.29E-07	0.0449	1.91E-04	3.48E-04	1.17E-08	0.442	2.76E-05	6.25	7.48E-04

WW = Wet weight.

Use	PEC_{local} in STP (µg/L)	Concentration in fish for secondary poisoning (freshwater) (mg/kg WW)	Concentration in fish for secondary poisoning (Seawater) (mg/kg WW)	Concentration in earthworm from agricultural soil (mg/kg)	Concentration in fish-eating marine top-predators (mg/kg WW)
Use-4	3.79E-05	9.43E-05	7.51E-04	0.0192	1.52E-03

Table 14. PECs calculated by EUSES using ERC2.

The full EUSES report is given in Annexes (Section X)

The realistic worst case (monitored) estimation of exposure is as follows:

Use	Site	Total tonnage in 2022 (kg)	Measured releases (µg/L)	PEC_{local} Freshwater (µg/L)	$PEC_{regional}$ Freshwater (µg/L)	PEC_{local} Freshwater Sediment (µg/Kg WW)	$PEC_{regional}$ Freshwater Sediment (µg/Kg WW)	PEC_{local} Seawater (µg/L)	$PEC_{regional}$ Seawater (µg/L)	PEC_{local} Marine Sediment (µg/Kg WW)	$PEC_{regional}$ Marine Sediment (µg/Kg WW)	PEC_{local} agricultural soil (µg/Kg WW)	$PEC_{regional}$ agricultural soil (µg/Kg WW)
Use-4	LISSES	2	0.26 for NP < 0.05 for NP1EO 0.13 X for NP2EO	1.42E-07	5.18E-10	1.8E-04	1.18E-06	1.39E-06	4.69E-11	1.77E-03	1.1E-07	0.025	2.99E-06

WW = Wet weight.

Use	PEC_{local} in STP (mg/L)	Concentration in fish for secondary poisoning (freshwater) (mg/kg WW)	Concentration in fish for secondary poisoning (Seawater) (mg/kg WW)	Concentration in earthworm from agricultural soil (mg/kg)	Concentration in fish-eating marine top-predators (mg/kg WW)
Use-4	1.51E-07	3.77E-07	3E-06	7.66E-05	6.06E-06

Table 15. PECs calculated by EUSES using estimated fraction released to water based on monitoring data.

Considering on-site monitored exposure and implemented risk management measures, the actual level of environmental exposure is expected to be extremely low. The full EUSES report is given in Annexes (Section X)

9.3.1. Worker Contributing Scenario

Considering that the substance is only a concerned for environmental hazards, the applicant will shortly resume the risk management measures to protect the workers, without going into details to estimate the worker exposures, which is out the scope of the assessment.

9.3.1.1. *Conditions of use*

Parameters	Condition of use
• Product	Nonidet® P 40 replacement product
• Type of product	Liquid form
• Risk management measure to protect the worker	The workers performed the different steps with PPE such as: - Gloves - Protective suit & lab coats - Safety goggles In addition, the activities are performed in a ventilated area

Table 16. Condition of use of the Worker Contributing Scenario

9.3.1.2. *Number of workers exposed*

Under the ES-1, 17 workers are performing the production using 4-NPnEO during 10 days per year, this value is used in the exposure assessment as it represents the number of emission days.

9.4. Exposure Scenario 2: Use of IVD products containing 4-tert-OPnEO/4-NPnEO by SEBIA end-users

Life cycle stages:

Widespread use by professional worker (PW)

Sector of use:

Scientific research and development (SU 24), Health Services (SU 20)

Chemical product category:

Laboratory chemicals (PC 21), *In vitro* diagnosis

Environmental contributing scenario:

ECS-2.1: Widespread use of reactive processing aid (ERC 8b)

Worker contributing scenarios:

WCS-2.1: Supply and storage (PROC 0)

WCS-2.2: Use of IVD products (PROC 15)

9.4.1. Process description – Exposure Scenario 2

Considering the number of customers and their various activities, no generic process may be described in this part. The applicant has decided to describe general information concerning its end-users even if an SR & D exemption could be applicable. The applicant has chosen to include them in the authorization dossier in order to cover their uses concerning IVD kits sold by SEBIA.

Table 17 summarize information obtained by the applicant concerning the quantity of IVD products sold in Europe to SEBIA end-users in 2017 and the quantity of substances received by end-users.

Number of IVD Kits sold per year	Total quantity of 4-tert-OPnEO/4-NPnEO received in end-users laboratories (Kg/year)	Quantity of 4-tert-OPnEO/4-NPnEO received in liquid products by the end-users laboratories (Kg/year)	Quantity of 4-tert-OPnEO/4-NPnEO received in solid products by the end-users laboratories (Kg/year)
175327	**101**	**97**	**4**

Table 17. Estimation of IVD products containing 4-tert-OPnEO/4-NPnEO sold in Europe in 2017

In 2017, the sales in Europe represented 55 % of world sales (316292 kits sold worldwide). Almost 70 % of the products sold are distributed among five main countries in Europe. France is considered as the main consumers followed respectively by Germany, Italia, United Kingdom and Belgium (Table 18).

Country	Kits sold (U)	Fraction per country (%)

France	43181	36
Germany	32408	27
Italia	21482	18
UK	13576	11
Belgium	7690	6
Total	**118337**	**100**

Table 18. Estimation of IVD kits sold to the main European end-users in 2017

In each country except in Germany, the most important part of end-users is small customers using from 1 to 40 kits per year (Table 19). In Italia, they represent 83 % of the total end-users. In other countries, the number of kits used is more equilibrated between the different categories (Table 19).

Country	Number of end-users	Number of kits used by end-users (%)			
		[1-40]	[41-60]	[61-120]	> 120
France	**597**	53	13	16	18
Italia	**907**	83	9	6	3
Germany	**415**	15	30	25	30
UK	**93**	44	14	22	20
Belgium	**174**	47	13	29	11

Table 19. IVD kits used to the main European end-users in 2017

In France, the applicant estimated a total of 20 kg of 4-tert-OPnEO/4-NPnEO distributed among its end-users in 2017. The end-users are divided into two main categories, the public facilities (hospitals mainly) and the private laboratories which represent around 50/50 % of the customers in 2017.

Concerning the quantities of 4-tert-OPnEO/4-NPnEO used by the end-users in 2017, private laboratories used approximately 14 kg/year against 6 kg/year in public facilities (Table 20). The most important quantities used by days are expected to occur in private laboratories (> 1000 kits/year) (Table 20).

Nevertheless, whatever the customer typology or the country considered, releases in the environment linked to the uses of SEBIA products are not expected to occur. Every SEBIA products are handled by professional staff in laboratory conditions.

Furthermore, in SDS of every product is being indicated that both liquid and solid components of kits have to be collected in specific containers and treated by a certified company (for incineration).

In this way, even in case of accidental releases, very low environmental exposure at a site scale (Local) are expected.

For the ES-2, considering the diversity of end-users both in terms of frequency of activities and quantity of products used by year, the exposure assessment was performed on a hypothetical worst-case end-user receiving 1.6 kg/year of 4-tert-OPnEO/4-NPnEO and working 240 days per year (Table 20, private laboratory using more than 1000 kits per year)

	Number of kit used per year	Estimated quantity of 4-tert-OPnEO/4-NPnEO distributed to end-users (g/year)	number of end-users	Estimated quantity of 4-tert-OPnEO/4-NPnEO used by an End-user (g/year)	Estimated quantity of 4-tert-OPnEO/4-NPnEO used by an End-user based on 240 days worked (g/day)
Private laboratories	**[0-100 kits]**	5097	227	22	0.0935638
	[101-430 kits]	5208	50	260	1.08493517
	> 1000 kits	3254	2	1627	6.7782605
Public facilities	**[0-100 kits]**	2585	261	10	0.04127358
	[0-420 kits]	2690	52	52	0.21557247
	> 420 kits	492	5	98	0.41025026

Table 20. Estimated quantities of 4-tert-OPnEO/4-NPnEO used by end-users in 2017

9.4.2. Environmental contributing scenario 1: Widespread use of reactive processing aid

9.4.2.1. *Conditions of use*

Parameter	Information
Product characteristics	
• Product	*SEBIA IVD kits containing Triton™ X-100 & X-405 & Nonidet P40*
• Physical form	*Liquid & solid*
• Amount	*1.6 kg*
• Weight fraction of the substance in the products	*Between 0.1 and 5 %*
Operational conditions	
• Emission Sources	*Considering the vapour pressure and the use of the substance, the only source of environmental exposure is via waste water.*
• Atmospheric emissions	*No atmospheric emission is expected regarding the physicochemical properties of the substance, the use and the RMM.*
• Liquid effluents	*The end-users are informed by SDS, how to collect and treat all the possible effluents.*
• Waste production	*The end-users are informed by SDS, how to collect and treat all the possible wastes.*

Table 21. Condition of use for the contributing scenario 1

9.4.2.2. *Parameters used in EUSES for the environmental exposure assessment*

Considering that the substance is not biodegradable, the applicant uses the physicochemical values of the 4-NP support document[1] to provide a worst case model. The parameters listed below were chosen in order to represent the most relevant scenario of emission for ES-2.

Input data on EUSES:

Criteria	Value
Molecular weight (g/mol)	220.35
Melting point (°C)	80.5
Boiling point (°C)	281.5
Vapour pressure (Pa)	0.3 at 25°C
Water solubility (mg/L)	7 at 25°C
Log Kow (20.5°C)	5.76
Chemical class	Predominantly hydrophobic
Biodegradability	Not readily biodegradable
Use patterns	Formulation
STP	Yes (Standard)

9.4.2.3. *Releases*

In Table 22, release estimations are presented for a typical end-user working 240 days per year and receiving 1.6 kg of 4-tert-OPnEO/4-NPnEO (Worst case scenario, see section 9.3.1). The estimate was calculated by EUSES based on tonnage and according to ERC8b (240 days, 2 % released in water).

The release estimation is used in order to characterize the PECs. (Table 23)

Production volume of Chemical in UE for the ES-2 (kg/y) (input)	1.6
Fraction released to water (input)	0.02 (2%)
Number of emission days per year (input)	240
Local emission to wastewater during episode calculated by EUSES (Kg/d) (output)	1.33E-04 (32 g/year)

Table 22. Condition of use for the contributing scenario 1

The worst case estimation of exposure is as follows:

ES	Total tonnage (kg)	Fraction released to water ERC8b	PEC_{local} Freshwater (µg/L)	$PEC_{regional}$ Freshwater (µg/L)	PEC_{local} Freshwater Sediment (µg/Kg WW)	$PEC_{regional}$ Freshwater Sediment (µg/Kg WW)	PEC_{local} Seawater (µg/L)	$PEC_{regional}$ Seawater (µg/L)	PEC_{local} Marine Sediment (µg/Kg WW)	$PEC_{regional}$ Marine Sediment (µg/Kg WW)	PEC_{local} agricultural soil_180 d (µg/Kg WW)	$PEC_{regional}$ agricultural soil (µg/Kg WW)
2	1.6	0.02	1.11E-03	1.04E-07	1.41	2.36E-04	6.13E-04	9.4E-09	0.778	2.21E-05	2	5.98E-04

WW = Wet weight.

ES	PEC_{local} in STP (mg/L)	Concentration in fish for secondary poisoning (freshwater) (mg/kg WW)	Concentration in fish for secondary poisoning (Seawater) (mg/kg WW)	Concentration in earthworm from agricultural soil (mg/kg)	Concentration in fish-eating marine top-predators (mg/kg WW)
2	1.21E-05	0.0575	0.0317	6.13E-03	0.0633

Table 23. PECs calculated by EUSES using ERC8b.

The full EUSES report is given in Annexes (Section X)

9.4.3. Worker Contributing Scenario

Considering the fact that the substance is only a concerned for environmental hazards, the applicant will shortly resume the risk management measures to protect the workers, without going into details to estimate the worker exposures, which is out the scope of the assessment.

9.4.3.1. *Conditions of use*

Parameters	Condition of use
• Product	SEBIA IVD kits containing NONIDET
• Type of product	Liquid and solid forms
• Risk management measure to protect the worker	The workers performed the different steps with PPE such as: - Gloves - Safety goggles and shoes In addition, the activities are performed in strict laboratory conditions

Table 24. Condition of use of the Worker Contributing Scenario

9.5. Commentaries on PEC estimations

- **Commentaries on PEC estimations for ES-1**

PEC Aquatic (freshwater and marine, total dissolved and sediments):

The production site is situated in freshwater environments thus the PECs marine at the local scale are not relevant.

PEC soil:

The PECs presented in both estimation of the applicant are potentially overestimated. Sludge application on agricultural soil at the local and regional scale is a defaults parameter kept in the estimates presented above. However, in the applicant context, no sludge application are expected at the local scale, sludge application at the regional scale is not expected either. The modification of default parameters would highly decrease the PEC agricultural soil at both local and regional scales.

- **Commentaries on PEC estimations for ES-2:**

The PECs presented in the estimation consider a worst-case user releasing 2% of the substance in wastewater going to STP. Considering the condition of use of the SEBIA products by end-users (laboratory conditions) and the SDS recommendations, no releases are expected in wastewater. Thus the values presented in the document are potentially over-estimated.

10. EXPOSURE RATIO CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1. Human

Regarding the reasons for the inclusion of the substance in Annexe XIV, no SVHC properties have been mentionned for human health. So no risk has been estimated for humans.

10.2. Environment

In introduction of this exposure ratio assessment, it is important to mention that the following assessment presents the ratio (HER) between the potential worst-case PECs based on applicant monitoring estimations and **hypothetical PNECs congruent with them used in the European risk evaluation report**[2] **and the EQS of the WFD**[3] **for the different environmental compartments** (Table 25)**.**

Considering that 4-tert-NPnEO is a non-threshold substance and that the EQS does not cover the potential endocrine disrupting effects of the substance, **The HER calculated in the document are not presented to conclude that the risk is controlled by the applicant. However, HER values are used as a tool giving information about the low environmental exposure linked to the applicant use.**

Consequently, it is important to keep in mind that this assessment presents a significant overestimation of environmental exposure considering that SEBIA collects all effluents potentially containing 4-NPnEO.

No conclusion on risk could be discussed regarding the endocrine disrupting properties of the substance. The only conclusion of this assessment is that for ES-1 (use-4, Table 26) and ES-2 (end-user, Table 27), the environmental exposure levels are expected to be extremely low even considering worst-case releases monitored on the site (ES-1, Table 26).

The full EUSES reports are given in Annexes.

Input data on EUSES:

Criteria	Value
PNEC for aquatic organisms	0.33 µg/L
PNEC for marine organisms	0.33 µg/L
PNEC for Freshwater sediment	31.9 µg/kg wet weight
PNEC for Marine sediment	31.9 µg/kg wet weight
PNEC for Terrestrial organisms	340 µg/kg wet weight
PNEC for Secondary Poisoning	10 mg/kg
PNEC for micro-organisms in a STP	9.5 mg/L

Table 25. Data input in EUSES for the HER estimations for the ES-1

10.2.1. ES-1

	Local Freshwater	Regional Freshwater	Local Marine	Regional Marine	Local Freshwater sediment	Regional Freshwater sediment	Local Marine sediment	Regional Marine sediment	Local Soil	Regional Soil
PEC (µg/L or µg/Kg WW)	1.42E-07	5.18E-10	1.39E-06	4.69E-11	1.8E-04	1.18E-06	1.77E-03	1.1E-07	0.025	2.99E-06
PNEC (µg/L or µg/Kg WW)	0.33	0.33	0.33	0.33	31.9	31.9	31.9	31.9	340	340
HER (worst case)	4.29E-07	1.42E-09	4.22E-06	1.36E-10	4.29E-06	2.81E-08	2.27E-05	2.83E-09	7.37E-04	8.81E-08

	For STP	For fish-eating birds and mammals (freshwater)	For fish-eating birds and mammals (Marine)	For Top predators (Marine)	For worm-eating birds and mammals
PEC (mg/L or mg/Kg WW)	1.51E-07	3.77E-07	3E-06	6.06E-06	7.66E-05
PNEC (mg/L or mg/Kg)	9.5	10	10	10	10
HER (worst case)	1.59E-08	3.77E-08	3E-07	6.06E-07	7.66E-06

Table 26. HER for ES-1

10.2.1. ES-2

	Local Freshwater	Regional Freshwater	Local Marine	Regional Marine	Local Freshwater sediment	Regional Freshwater sediment	Local Marine sediment	Regional Marine sediment	Local Soil	Regional Soil
PEC (µg/L or µg/Kg WW)	1.11E-03	1.04E-07	6.13E-04	9.4E-09	1.41	2.36E-04	0.778	2.21E-05	2	5.98E-04
PNEC (µg/L or µg/Kg WW)	0.33	0.33	0.33	0.33	31.9	31.9	31.9	31.9	340	340
HER (worst case)	3.71E-03	3.13E-07	2.04E-03	3E-08	0.0222	7.39E-06	0.0122	6.94E-07	5.89E-03	1.76E-06

	For STP	For fish-eating birds and mammals (freshwater)	For fish-eating birds and mammals (Marine)	For Top predators (Marine)	For worm-eating birds and mammals
PEC (mg/L or mg/Kg WW)	1.25E-05	0.0575	0.0317	0.0633	6.13E-03
PNEC (mg/L or mg/Kg)	9.5	10	10	10	10
HER (worst case)	1.28E-06	5.75E-03	3.17E-03	6.33E-03	6.13E-04

Table 27. HER for ES-2

11. CONCLUSIONS & UNCERTAINTIES

In conclusion, the applicant has implemented the highest risk management measures possible considering that all the effluents containing 4-NPnEO are collected. The applicant will perform regular monitoring to verify the efficiency of its RMM and the congruence of the future measures with them presented in this CSR.

Worst-case hypothetical exposure ratios (HER) modelled by EUSES for every compartment are always below one, suggesting that RMM implemented by the applicant are relevant and effective.

For an accurate calculation of the fraction released to water, the quantity of 4-NPnEO used the day of the monitoring should be recorded and thus compared with the releases measured. In the present CSR, the released fraction have been calculated considering that the yearly tonnage is equally distributed among the number of emission days.

However, the values presented in the document can still be considered as a worst-case estimation.

Firstly, the applicant decided to consider the substance as non-biodegradable even if some studies suggest a potential (low) biodegradability in the environment.

The Marine scenario is not relevant at a local scale as the applicant facility is situated in a freshwater environment. Nevertheless, Worst-case default values are presented in the present AfA.

For soil, no sludge spreading is expected to occur at the local scale in the real applicant scenario. Thus, the PECs soil presented in the present document are potentially over-estimated as the sludge spreading have been kept in the model in order to represent the worst-case scenario possible. Indeed, the sludge spreading is an important source of soil contamination kept by EUSES default parameters for the calculation of PEC soil.

Considering the non-threshold toxicity of the substance, the applicant considers the socio-economic assessment route as the main route of analysis of the present authorization dossier.

12. REFERENCES

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