

CHEMICAL SAFETY REPORT

Use 1

Use of Octylphenoethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products (NutropinAq® and Lucentis®) of one pharmaceutical company

Substances Names:

4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues) – OPnEO

EC Number: -

CAS Number: -

Applicant's Identity:

Vetter Pharma-Fertigung GmbH & Co. KG

9. EXPOSURE ASSESSMENT

- ⇒ In this CSR, the applicant provides **reliable estimates of environmental exposure to OPnEO** in the EU based on releases from the production sites.
- ⇒ Exposure was calculated with the ‘**Multifate**’ model which reflects the degradation mechanism specific to OPnEO.
- ⇒ **Exposure to the environment** with regard to the use of OPnEO **is reduced** as much as technically and economically feasible by collection and incineration of waste and planned substitution by an alternative emulsifier.
- ⇒ **Risks** related to the continued use of OPnEO **can thus be considered as minimised**.

9.1. Introduction

The CSR was developed to support Vetter’s application for authorisation to continue the use of OPnEO after the sunset date until complete substitution. OPnEO was included in Annex XIV of the REACH regulation because of the endocrine disrupting properties of its degradation products for the environment.

In its note from December 2017 [1], the RAC leaves the decision to the industry to define if a threshold can be derived for the endpoint “endocrine disrupting properties for the environment” of OPnEO and its degradation product (OP). Because of the uncertainties associated with these specific properties, the applicant decided to assume that no threshold applies for this endpoint as the safest option. Therefore, the applicant will demonstrate emission and risk minimisation in this CSR.

In this CSR, the applicant provides reliable estimates of environmental exposure in the EU based on releases from the production sites. The Vetter Group operates several manufacturing sites, whereas for the two different products produced by Vetter for F. Hoffmann-La Roche Ltd one site located in Ravensburg (RVS: Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen 2, 88214 Ravensburg, Germany) and one site located in Langenargen (VLA: Vetter Pharma-Fertigung GmbH & Co. KG, Eisenbahnstrasse 2-4, 88085 Langenargen, Germany) are used. In the RAC note from December 2017, the European Chemicals Agency (ECHA) confirmed that the focus should be on minimisation of the release of OPnEO to the environment with a focus on critical degradation products (i.e. OP) and that risk to human health does not need to be assessed for the purpose of the exposure assessment. Therefore, exposure of workers, consumer and of man via the environment was considered out of scope of the assessment.

The environmental exposure assessment was based on data collected from the specific production sites to estimate release into the STPs. Exposure estimation to all relevant environmental compartments was calculated with the ‘Multifate’ model [3] which reflects the degradation mechanism specific to OPnEO that would not be considered when using the standard European Union System for the Evaluation of Substances (EUSES) model [4]. In agreement with the RAC note of December 2017 [1], the PECs estimated with the ‘Multifate’ model for OPnEO and its expected degradation products including OP were all converted to equivalents of OP as it should be assumed that all OPnEO released to the environment ultimately ends up as OP.

In addition, this CSR shows that the exposure to the environment with regard to the use of OPnEO is being reduced as much as technically and economically feasible and that the risks related to the continued use of OPnEO can be considered as minimised.

Even though, strictly speaking, a risk characterisation is not possible when considering the endocrine disrupting properties of OPnEO as a non-threshold endpoint, a comparison with available reference values such as the EQS data is presented in Section 10 of the present report as supporting information as suggested in the note of the Socio-economic analysis committee (SEAC) on 'SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO' [2].

Overall, the applicant applies for an authorisation for the following use:

- Use of OPnEO as emulsifier in the siliconisation of glass containers used as primary packaging material for two specific medicinal products of one pharmaceutical company – hereafter referred to as 'Use 1'.

Siliconisation of the glass containers for the two medicinal products NutropinAq® and Lucentis® produced for F. Hoffmann-La Roche Ltd. at two Vetter sites (RVS and VLA) in Germany is covered in this application.

9.2. Overview of Uses and Exposure Scenarios

- ⇒ OPnEO is used as **emulsifier** in the siliconisation of glass containers used as primary packaging material for medicinal products.
- ⇒ The maximum annual usage at the sunset date for Use 1 was estimated based on maximum expected orders (0.306 kg/a).
- ⇒ The total annual usage of OPnEO is expected to decrease over time due to completed substitutions of OPnEO in the siliconisation.
- ⇒ If the substitution in the siliconisation is completed as planned, **the total annual tonnage of OPnEO for the use applied for will reach 0 kg/a by the end of 2021**
- ⇒ However, if the substitutions are delayed, a maximum total **release of 0.000107 kg/a OP_{equiv}** to surface water could potentially be maintained until the end of the review period (4th of January 2026).

9.2.1. Overview of Exposure Scenarios and Mass Balances – OPnEO

Vetter purchases silicone oil emulsion containing OPnEO for its use as emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products.

9.2.1.1. Overview of Exposure Scenarios – OPnEO

An overview of the exposure scenarios currently falling in the scope of this application for authorisation of Vetter for OPnEO is provided in Table 2. 0.306 kg/a represents the maximum annual tonnage. Vetter therefore applies for an authorisation for an annual usage of this amount.

Table 2. Overview of exposure scenarios and contributing scenarios for OPnEO.

Identifiers*	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (kg/a)
IW1 – OPnEO Ravensburg site (RVS)	SU 20: Health services PC29: Pharmaceuticals	Use as emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products Industrial PROC5 - Mixing or blending in batch processes for formulation of preparations (multistage and/or significant contact) PROC7 - Industrial spraying PROC8a - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities	0.281

Identifiers*	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (kg/a)
		PROC9 - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)	
IW1 – OPnEO Langenargen site (VLA)	SU 20: Health services PC29: Pharmaceuticals	Use as emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products Industrial PROC5 - Mixing or blending in batch processes for formulation of preparations (multistage and/or significant contact) PROC7 - Industrial spraying PROC8a - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC9 - Transfer of substance or preparation into small containers (dedicated filling line, including weighing) ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)	0.0254

* Manufacture: M-#, Formulation: F-#, Industrial end use at site: IW-#, Professional end use: PW-#, Consumer end use: C-#, Service life (by workers in industrial site): SL-IW-#, Service life (by professional workers): SL-PW-#, Service life (by consumers): SL-C-#.)

9.2.1.2. Mass Balances and Evolution of Used Amounts over Time – OPnEO

From the submission date of the dossier to the sunset date on the 4th of January 2021 and the end of the review period, the total used amount of OPnEO at Vetter is expected to vary mainly due to:

- Change in quantities of OPnEO required for the siliconisation in line with the evolution in the sales of the medicinal products.
- Planned substitutions of OPnEO in the siliconisation covered in the present dossier leading to a stop of OPnEO used (for more information please refer to Section 7 of the analysis of alternatives (AoA)).

For the purpose of this CSR, the total annual usage at the sunset date (0.306 kg/a) serves as a basis for the exposure assessment. As a worst-case, it was assumed that it remains constant over the years from 2021 until the end of the review period on 4th of January 2026 (see AoA for details). This assumption was made in order to ensure that the assessment covers the maximum possible usage of OPnEO. For comparison, the actual annual usage in 2017 was █████ kg (█████ kg in RVS and █████ kg in VLA).

Furthermore, the total annual usage of OPnEO is expected to cease at the latest at the end of the review period due to completed substitutions of OPnEO in the siliconisation covered in the present dossier.

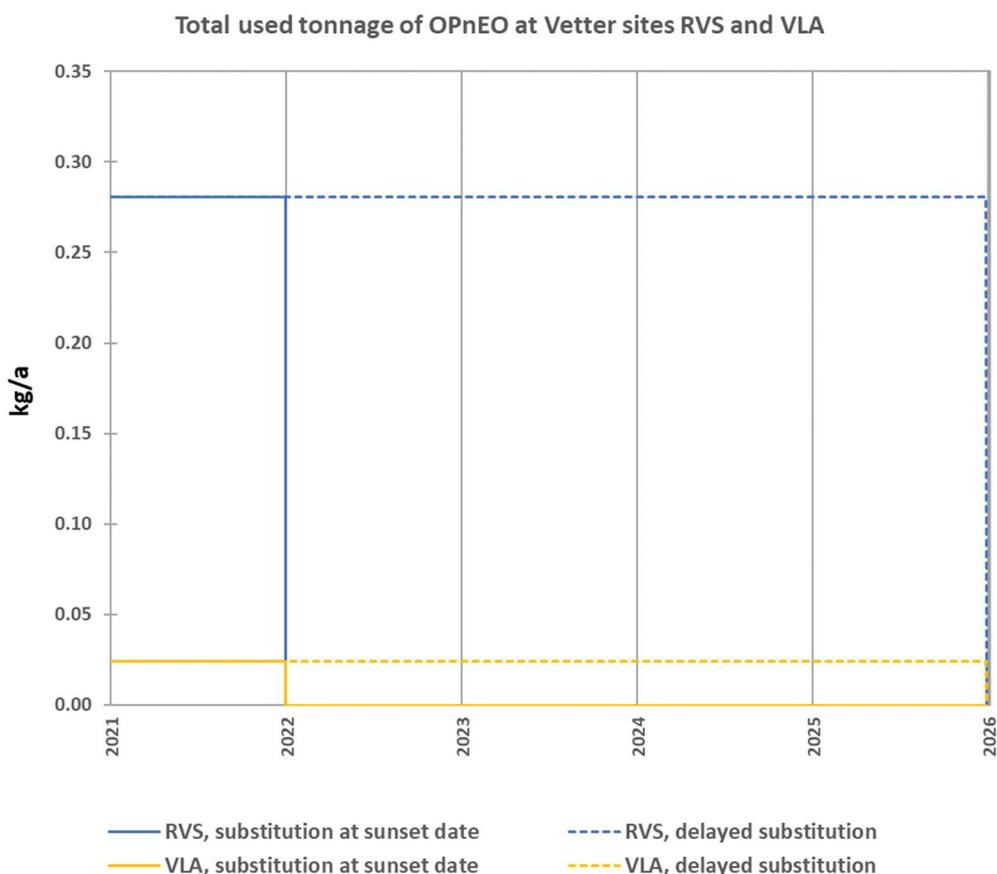


Figure 1. Evolution of the total annual use of OPnEO between 2021 and end of 2025 for Use 1 of this application at Vetter manufacturing sites Ravensburg (RVS) and Langenargen (VLA) considering the planned substitution and maximum expected orders placed by Roche.

Figure 1 provides an overview of the total used amount of OPnEO over time for Use 1 for the following two cases:

- ‘Substitution completed as planned’: Expected decrease in the total used amount of OPnEO considering the planned substitution of OPnEO based on the most likely timeline (see AoA for details).
- ‘Substitution delayed’: Expected development of total used amount of OPnEO over time considering that the planned substitution of OPnEO is delayed to the end of the review period as a worst-case.

If the substitution in the siliconisation is completed in time, the total annual tonnage of OPnEO at both Vetter sites should decrease from a maximum of 0.306 kg/a at the sunset date to reach 0 kg/a by the end of 2021 (see timelines in the AoA, likely completion of substitution for both medicinal products). However, if the substitutions are delayed, a maximum total annual tonnage of 0.281 kg/a (for RVS) and 0.025 kg/a (for VLA) (i.e. a total of 0.306 kg/a) could potentially be maintained until the end of the review period (end of 2025). These numbers are based on the expected maximum orders by Roche after the sunset date (see Table 3).

Table 3. Actual orders and expected maximum orders

Production site	RVS	VLA
batches in 2015	■	■
batches in 2016	■	■
batches in 2017	■	■
batches in 2018	■	■
expected batches in 2019	■	■
expected batches in 2020	■	■
expected batches in 2021	■	■
expected batches from 2022 to end of 2025	■	■

In addition, a mass balance for OPnEO based on amounts used and releases to wastewater is provided for Use 1 in Table 4 for each site (RVS and VLA). The actual values are provided for 2017 as well as values based on maximum expected order for the sunset date in 2021. Any losses to the environment of the OPnEO used per year are directly linked with the release to surface water from the STP as there is no direct release of OPnEO to air/soil.

Table 4. Mass balance for OPnEO based on amounts used at Vetter sites RVS and VLA in the siliconisation process and calculated releases to wastewater and waste for 2017 and at the sunset date 4th January 2021 assuming production for maximum expected orders by Roche.

Production site	RVS		VLA	
	Annual amount based on actual figures in 2017	Annual amount at sunset date 4 th of January 2021	Annual amount based on actual figures in 2017	Annual amount at sunset date 4 th of January 2021
	kg/a	kg/a	kg/a	kg/a
Total annual usage	██████████	0.281 (100%)	██████████	0.0254 (100 %)
Total release to wastewater	██████████	0.00075 (0.27%)	██████████	0.000177 (0.70 %)
Total amount removed during depyrogeneration step	██████████	0.0374 (13.33 %)	██████████	0.00702 (27.7 %)
Total amount incinerated (via RMM)	██████████	0.243 (86.40 %)	██████████	0.0182 (71.60 %)

The main fraction of the total amount of OPnEO used in the siliconisation (i.e. 86.4 % in RVS and 71.6 % in VLA) is removed by incineration of surplus siliconisation solution. During the depyrogeneration step 13.3 % (for RVS) and 27.7 % (for VLA) of the total amount of OPnEO are removed. No OPnEO remains on the final product (see process description for details in Section 9.3.1). The release to wastewater is 0.27 % and 0.70 % at RVS and VLA, respectively. This distribution of OPnEO will remain constant over time independent of actual amounts used.

9.3. Introduction to the Assessment

- ⇒ The releases of OPnEO occur via the release to wastewater to the municipal STP
- ⇒ Based on collected data at the production site and specific adaptation to the municipal STP parameters, **PECs were calculated using the ‘Multifate’ model.**
- ⇒ Expected **biodegradation products** including OP were converted to **equivalents of OP.**
- ⇒ Calculated **PECs** were compared with available reference values (**EQS values** from the EU Water Frame Directive) and monitoring data from the literature as supporting information.

9.3.1. Description of the Activities and Technical Processes covered in the Exposure Scenario

Figure 2 presents a general scheme of the OPnEO flow introduced by siliconisation for glass containers at Vetter’s manufacturing sites including release pathways to wastewater and disposal pathways as waste. Vetter operates several manufacturing sites, whereas for the two products produced by Vetter for F. Hoffmann-La Roche Ltd one site located in Ravensburg (RVS: Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen 2, 88214 Ravensburg, Germany) and one site located in Langenargen (VLA: Vetter Pharma-Fertigung GmbH & Co. KG, Eisenbahnstrasse 2-4, 88085 Langenargen, Germany) is used.

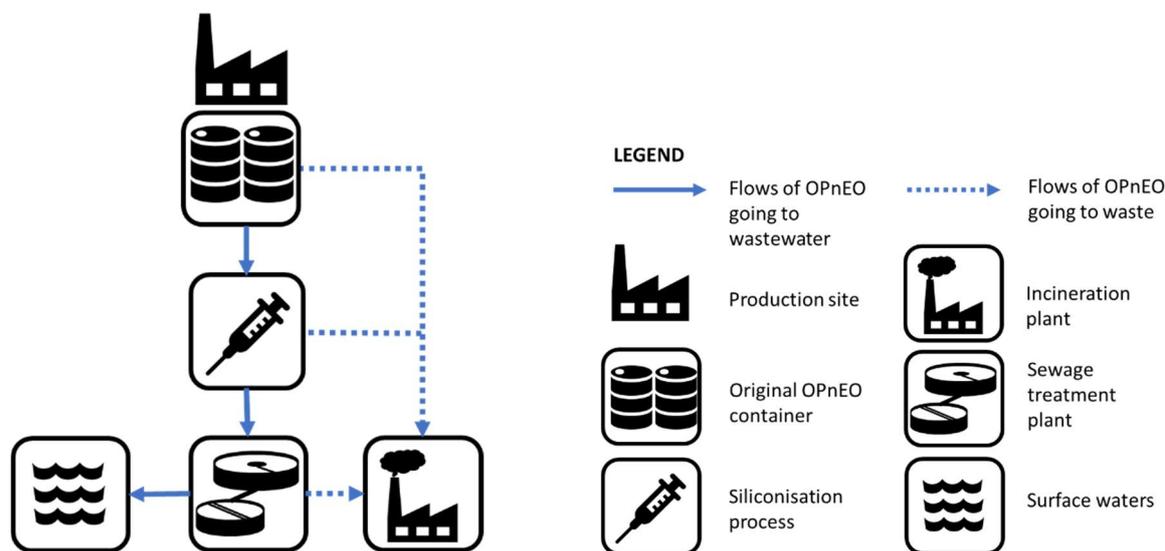


Figure 2. Flows of OPnEO during the siliconisation process taking place at Vetter.

The silicone oil emulsion DC365 containing OPnEO for the siliconisation of glass containers at the two sites RVS (cartridges) and VLA (syringes) is purchased by Vetter. Following a dilution step, the diluted emulsion is sprayed into the glass containers. Afterwards, the glass containers are sterilised and depyrogenated in a dry-heat tunnel. Target condition is a temperature of min. 300 °C for more than 5 minutes prior to being stoppered, aseptically filled with a medicinal product and subsequently closed with the sterile crimp cap or tip cap, respectively.

The entire siliconisation, sterilisation, depyrogenation, and aseptically filling processes of the glass containers take place in a highly-controlled environment, corresponding to EudraLex - Volume 4 - Good Manufacturing Practice Guidelines [15], in isolated and closed compartments without manual handling of the glass containers during the process.

In the following, a general description of the steps performed during the entire process with a focus on possible release to the environment via wastewater or solid waste is presented. Figure 3 gives an overview on the processing steps and potential loss of OPnEO to wastewater.

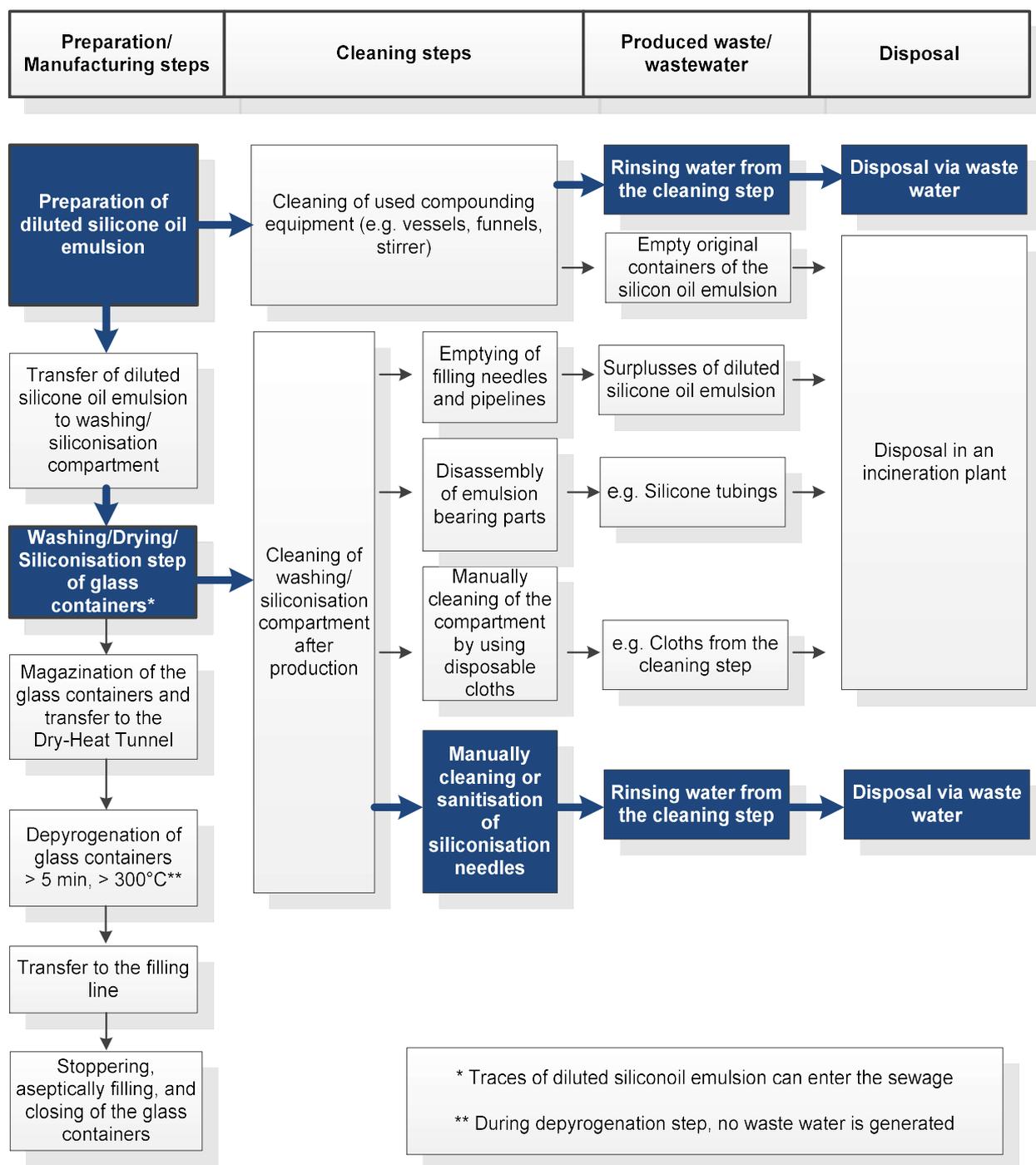


Figure 3. Schematic representation of the manufacturing process. Potential pathways of OPnEO into wastewater are highlighted in blue.

Figure 4 exemplarily shows a schematic drawing of the washing and siliconisation compartment used at the two sites RVS and VLA.

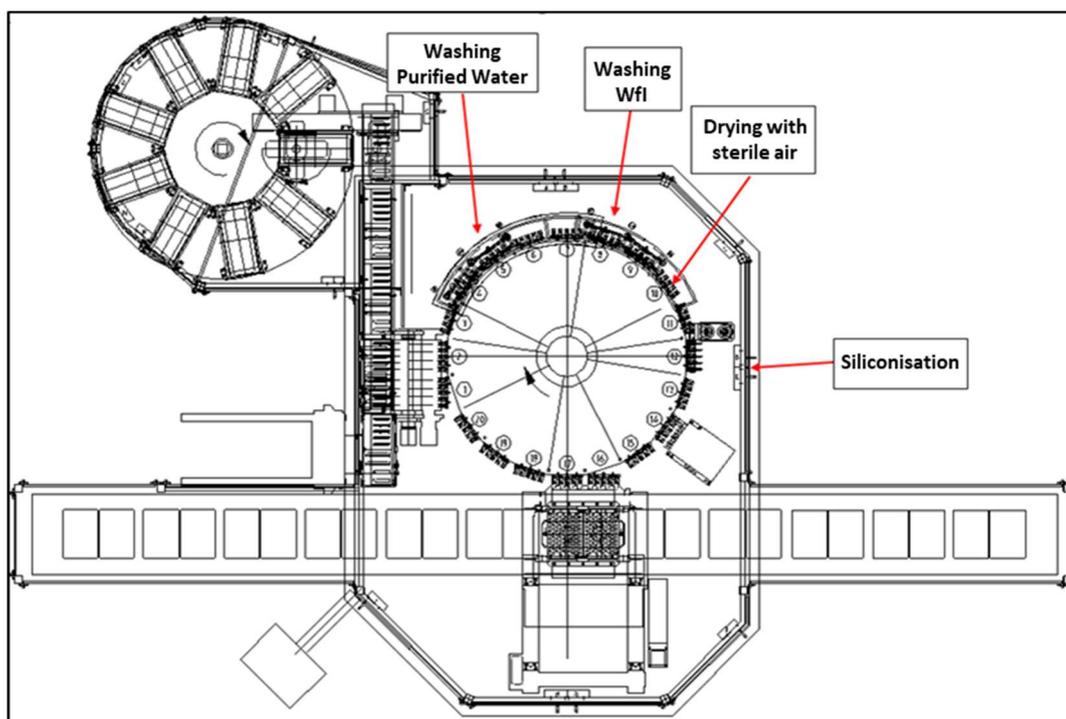


Figure 4. Schematic of the manufacturing equipment at VLA. Magazines with glass containers (left) are unloaded onto the rotary conveyor (centre) for being washed and dried before the siliconisation process (right).

STEP 1: The original containers of the silicone oil emulsion containing OPnEO at a concentration of $\leq 2.6\%$ w/w as indicated by the supplier are received from the distributor by the warehouse and undergo a quality control release test. The original containers are agitated before use. The containers are transferred manually to a ventilated hood to be semi-automatically diluted into flasks. The volume of the flasks and the concentration of these diluted silicone oil emulsions are depending on the product. These flasks are then transferred manually to the conveyer belt of the washing and siliconisation compartment of the production line, from where the solution is automatically transferred to the spraying nozzles via tubes.

During this dilution step, large spilling is not expected to occur. In case of small spills, spilled drops of OPnEO solution would be absorbed with binding material. Empty original containers of the raw material OPnEO emulsion as well as any binding material used for the cleaning of potential spills are sent to the waste disposal station for incineration. No wastewater is generated during this dilution step.

Cleaning of compounding equipment which is used for manufacturing of the diluted silicone oil emulsion (stirrer, vessels, funnels), including vessels used for diluted silicone oil emulsion:

Compounding equipment used in RVS: The compounding equipment is cleaned in an equipment washing machine. Per washing cycle the used cleaning program consumes 271 L purified water and 77 L Water for Injection. One washing cycle is needed for cleaning the whole equipment. The washing and rinsing waters enter the sewer.

Compounding equipment in VLA: Compounding equipment is cleaned manually by using purified water and water for injection.

Rinsing water from cleaning of compounding equipment at RVS and VLA is released to wastewater.

STEP 2: Preparation of the primary packaging material which is used for the manufacturing of the respective pre-filled cartridges or syringes is conducted in the material preparation area of the respective cleanrooms in RVS and VLA. The packaged sets of the primary glass containers are manually loaded into a machine which takes them out of the package and transfers them one by one to the conveyor belt.

The conveyor belt redistributes the primary glass containers in a line and transports them to the washing and siliconizing steps, both occurring in the same, closed, washing compartment. The washing step is performed as follows: each primary glass container is flushed ■ times from below via a nozzle with pressurized purified water. For the first washing steps the purified water may be recycled, the last rinsing step is performed with water for injection. Following the washing step, the primary glass containers are dried by using sterile filtered air. After drying, the primary glass containers are moved to the siliconisation compartment of the machine. In the siliconisation area, the primary glass containers are sprayed via nozzles from below with the diluted silicone oil emulsion. For spraying the needles are moved into the glass barrels which minimizes the probability that sprayed emulsion can escape into the machine compartment. The siliconisation step is an optimized process. Robustness of the spraying process is controlled by determining the spraying rate (volume of liquid sprayed per time) before and after the process. The sprayed volume is derived from the maximum allowed silicone amount in the glass container. As the silicone content in the glass container is essential for correct and reliable performance of the primary packaging material this parameter is checked yearly during requalification of the washing and siliconisation machine. Nevertheless, in case sprayed emulsion escapes into the machine interior, most of the spray is pressed by the laminar air flow on the machine bed or is extracted by the exhaust system.

The amount of non-used diluted silicone oil emulsion is dependent on several factors, e.g. manufactured batch size or robustness of the manufacturing process. In RVS the maximum amount of non-used diluted silicone oil emulsion is approx. ■ L/batch and in VLA approx. ■ L/batch. This surplus is collected in a separate container (Intermediate Bulk Container, IBC) and stored until finally shipped to an incineration plant.

STEP 3: The siliconised primary glass containers are redistributed in racks to the sterilizing and depyrogenation unit (dry heat tunnel).

STEP 4: In the dry-heat tunnel, the primary glass containers are sterilised and depyrogenated for ≥ 5 min at ≥ 300 °C. It has been shown, that under this conditions OPnEO completely decomposes and no traces can be detected on the siliconised glass surface during this treatment [14]. There is no wastewater generated during this step. The only liquid present may be condensation water in the air filter. The filter is checked during maintenance phase. In case a filter change has to be conducted, the used filter is disposed of in ASP-containers (from German: *Abfall-Sammler-Pastös*, container for collecting hazardous, paste-like material) and finally destructed in an incineration plant.

STEP 5: The primary glass containers are automatically covered with sterilised stoppers or closure parts. Afterwards, the primary glass containers are aseptically filled with the required amount of medicinal product and sealed with sterilised crimp cramps (cartridges) or plugged with sterilised stoppers (syringes), both under sterile conditions. Finally, the filled primary glass containers are

taken to a non-sterile compartment for a 100% visual inspection. Each primary glass container is verified for accuracy. Unsatisfactory filled primary glass containers are rejected. The filled primary glass containers are packaged for shipment.

STEP 6: At the end of the batch, the remaining silicone oil emulsion in the delivery container is collected separately and incinerated.

Line Cleaning

Line cleaning is performed after each manufacturing batch. Spraying needles and connected pipelines are drained, whereby the diluted silicone oil emulsion is collected in a vessel (approx. 200 mL). This separately collected diluted silicone oil emulsion is disposed of into a separated container (IBC) which will be shipped to a hazardous waste incineration plant. Afterwards the emulsion bearing parts (silicone tubings) are removed. The silicone tubings are single use equipment. After use they are collected in ASP-containers and disposed of in an incineration plant.

Following this step, the siliconisation needles and teflon-tubings at RVS are sanitized by using clean steam (purified water and water for injection: [REDACTED]). By performing this step OPnEO enters the wastewater (from remaining silicone oil emulsion sticking to the walls of the system after drainage). The system is dried by using sterile pressurized air. Before or after sanitization, the inside of the washing and siliconisation compartment is manually cleaned by using disposable cloths. The used cloths are also disposed of in an ASP-container which is finally destructed in an incineration plant.

At VLA the spraying needles and the riser tubes are manually cleaned (pre-washed with purified water and cleaned with a detergent solution). By performing this step OPnEO can enter the wastewater (from remaining silicone oil emulsion sticking to the components after drainage). The washing and siliconisation compartment in VLA is manually cleaned by using disposable cloths (same as in RVS).

9.3.2. Environment

The current environmental exposure assessment was performed to support Vetter's application for authorisation to continue the use of OPnEO in the siliconisation until substitution is completed.

9.3.2.1. Scope and Type of Assessment

In a first step, the initial release of OPnEO was estimated for the exposure scenario based on data collected on the siliconisation at Vetter in RVS and VLA considering RMMs which were implemented at the time of the assessment in 2018.

For the siliconisation, the main releases of OPnEO occur via the release to wastewater to the municipal STP. There are no direct releases to soil from the Vetter production sites RVS and VLA. Direct releases to the air from the manufacturing process are not expected due to the very low vapour pressure of OPnEO ($1.8 \cdot 10^{-14}$ mmHg). However, releases to soil and air are considered when addressing the removal processes taking place in the STP.

In a second step, the removal processes and setup specific to the STP were described and assessed to be reflected in the model used for the prediction of the exposure concentrations in the relevant environmental compartments after the STP. Details on the approach followed for the estimation

of the initial releases and the site-specific description of the removal processes taking place in the municipal STP are provided in Section 9.3.2.2.

In a third step, exposure estimation to all relevant environmental compartments as listed in Table 5 were calculated with the ‘Multifate’ model [3] which reflects the degradation mechanism specific to OPnEO that cannot be described with the standard EUSES model [4].

Table 5. Type of risk characterisation required for the environment.

Protection target	Exposure estimation	Type of risk characterisation
Freshwater	Quantitative	Qualitative – risk minimisation
Sediment (freshwater)	Quantitative	Qualitative – risk minimisation
Marine water	Quantitative	Qualitative – risk minimisation
Sediment (marine water)	Quantitative	Qualitative – risk minimisation
STP	Quantitative	Qualitative – risk minimisation
Air	Quantitative	Qualitative – risk minimisation
Agricultural soil	Quantitative	Qualitative – risk minimisation

In agreement with the RAC note from December 2017 [1], the PECs estimated with the ‘Multifate’ model for OPnEO and its expected biodegradation products including OP were all converted to equivalents of OP (based on molecular weight) as it should be assumed that all OPnEO released to the environment ultimately ends up as OP. More details on the model are provided in Section 9.3.2.4.1.

Releases to fresh and marine water from the STP and partitioning to sediments are considered for the assessment. In addition, releases to soil and air from the STP are considered when addressing the removal processes taking place in the STP. The exposure to animals was not addressed in this CSR because OP is not expected to bioaccumulate [1].

To confirm that the ‘Multifate’ model used for this assessment is adequate, the calculated PECs in surface water (local) were compared with data obtained from monitoring campaigns [12][13][16].

Exposure assessment for the activities covered in this application are addressed in this section. In addition, for the purpose of the environmental exposure assessment an estimation of regional releases must be performed.

Finally, although a direct comparison of the combined local PECs with a reference value is not applicable to non-threshold endpoints, the calculated PECs were nonetheless compared with available reference values such as EQS values from the EU Water Framework Directive [6] as supporting information in line with the suggestions in the SEAC note [2] (see Section 9.3.2.5 for more details).

9.3.2.2. Specific Approach for the Siliconisation at RVS and VLA

At RVS and at VLA, there is only one operational unit each which uses OPnEO as an emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products of F. Hoffmann-La Roche Ltd. The OPnEO releases from this process occur via the introduction

of liquid waste (i.e. rinsing waters of the sanitizing process step) to wastewater. There is no direct release to the soil or the air. The wastewater streams are sent directly to the respective municipal STPs (RVS: Abwasserzweckverband Mariatal, Klärwerk Langwiese, Ravensburg, VLA: Zweckverband Abwasserreinigung, Klärwerk Kressbronn-Langenargen).

To estimate the total usage and releases of OPnEO to the municipal STPs, information was collected on the amount of OPnEO remaining in the spray nozzles and Teflon tubings after a batch was processed and the equipment was drained. This was done by weighing the respective equipment parts before and after the sanitizing/cleaning process step.

Based on this collected data, the total usage and releases of OPnEO at the sunset date were estimated considering the maximum expected orders as detailed in Section 9.4.3.1. to reflect maximum expected usage and release of OPnEO. The corresponding usage and release to the municipal STP were then calculated for the exposure scenario developed for the purpose of the current assessment. Details for the siliconisation can be found in 'SD3_CSR_Data_collected-_Vetter_Use1_CONFIDENTIAL'.

In addition to the calculated usage and release to the municipal STPs, information on the specific parameters of the municipal STPs as well as the removal steps occurring in these STPs, to which the production sites are connected, are required as input for the model 'Multifate' used to estimate the releases after the STP and PECs in the relevant environmental compartments. A description of the setup and removal processes specific to the municipal STPs are described in the following paragraphs. Both municipal STPs are equipped with special infrastructure targeted to remove a range of micropollutants such as contrast agents used in medicinal imaging and phthalates used e.g. as plasticisers and also OPnEO and its degradation products that are otherwise not well degraded in STPs.

RVS

The municipal STP Langwiese in Ravensburg is equipped with special infrastructure targeted to remove a range of micropollutants. Specific characteristics of the municipal STP which are relevant for the fate of OPnEO are provided in the following list (also refer to Figure 5):

- The municipal STP is designed for treatment of wastewater from 184'000 population equivalents,
- Nitrification / denitrification step,
- Sand filter step,
- Activated carbon filter step (additional step to remove micropollutants, 100% of wastewater is treated),
- Discharge into the river Schussen,
- Treatment of sewage sludge: Digester (biogas), dehydration, use as substitute fuel for cement plant. Sludge is not applied to (agricultural) soil.

Further STP parameters that were used as input parameters in the model 'Multifate' are provided in the supporting document 'SD2b_CSR_Model_description_partII_Vetter_Use1'.

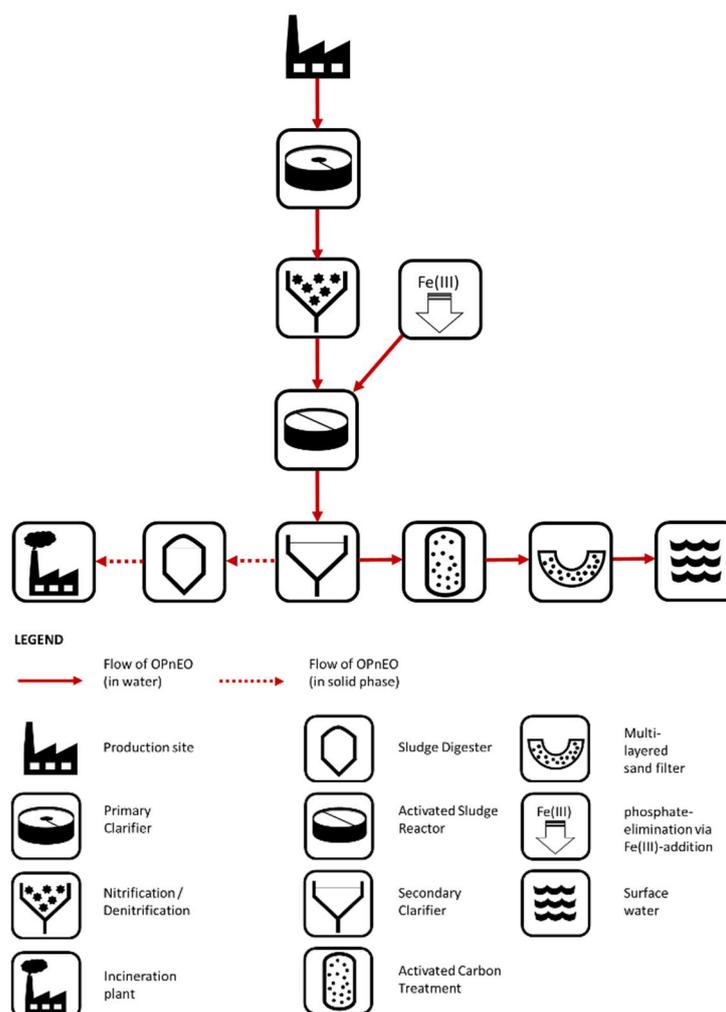


Figure 5. Scheme of the municipal wastewater treatment in STP Langwiese

VLA

The municipal STP Kressbronn-Langenargen is equipped with special infrastructure targeted to remove a range of micropollutants. Specific characteristics of the municipal STP which are relevant for the fate of OPnEO are provided in the following list (also refer to Figure 6):

- The municipal STP is designed for treatment of wastewater from 24'000 population equivalents,
- Nitrification / denitrification step,
- Phosphate-elimination via Fe(III)-addition,
- Three-layered sand filter step,
- Activated carbon filter step (additional step to remove micropollutants, 100% of wastewater is treated),
- Discharge into Lake of Constance,
- Treatment of sewage sludge: Digester (biogas), dehydration, use as substitute fuel for cement plant or thermal utilization in incineration plant. Sludge is not applied to (agricultural) soil.

Further STP parameters that were used as input parameters in the model 'Multifate' are provided in the supporting document 'SD2b_CSR_Model_description_partII_Vetter_Use1'.

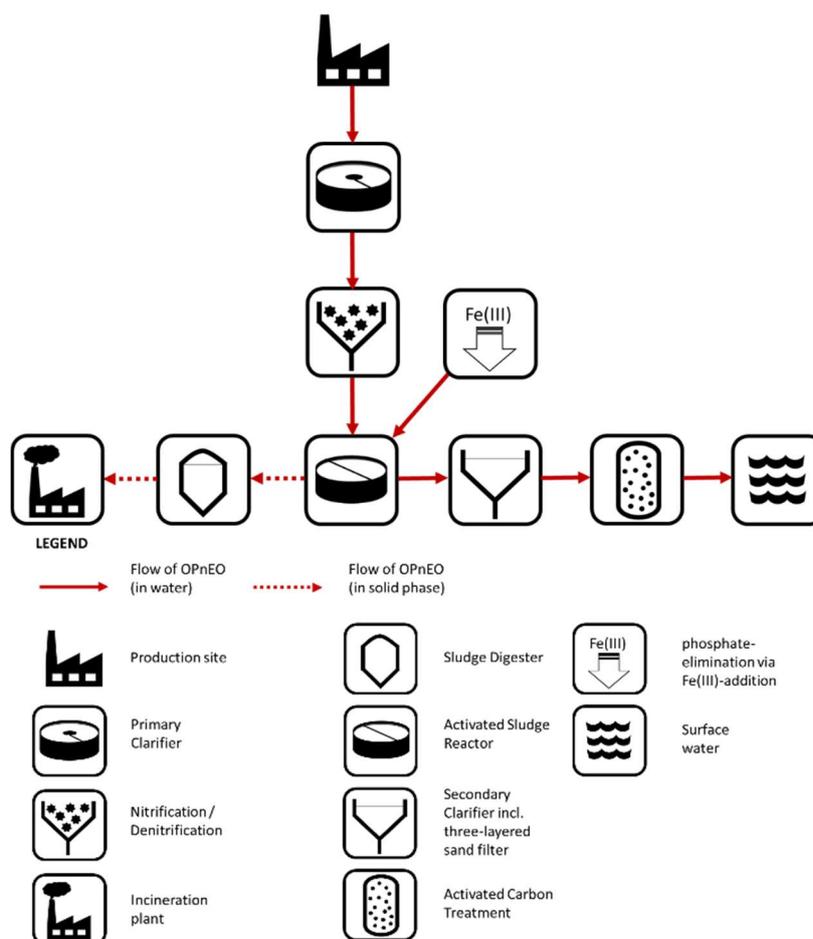


Figure 6. Scheme of the municipal wastewater treatment at STP Kressbronn-Langenargen.

Efficiency of activated carbon towards OPnEO and degradation products removal:

The elimination of OP by activated carbon was not studied in the STPs to which the Vetter sites are connected. However, it was studied at the municipal STP of Mannheim. The analytical data showed that OP was efficiently eliminated by activated carbon (85%) [11]. Similar high removal rates of OP through activated carbon were found in a range of other studies, e.g. 50-90% [7].

These results were supported by laboratory studies (e.g., 95±5% removal of 5-10 mg/L OP with 0.1 g/L of activated carbon [8]). Some laboratory studies indicate that also OPnEO is removed using activated carbon (e.g. 95±5% removal of 2-10 mg/L of OPnEO as Triton-X-100 with 0.5 g/L of activated carbon [8]). However, in comparison to OP, much larger amounts of activated carbon to adsorb OPnEO had to be employed. Furthermore, data on the efficiency of activated carbon on OPnEO removal in STPs are lacking. In addition, the logK_{oc} (see supporting document ‘SD2a_CSR_Model_description_partI_Vetter_Use1’), which is an important factor for sorption also to activated carbon, for all compounds (OPnEO and degradation products) other than OP is smaller than that for OP, indicating that sorption of these compounds to activated carbon will be smaller as well.

Hence, a removal rate of 85% for OP through activated carbon (as observed in the municipal STP of Mannheim) and, as worst-case, a removal rate of zero % for OPnEO and all other degradation

products of OPnEO (except for OP) were utilized in the model. Measurements in the river Schussen and in the outlet of the municipal STP Langwiese (RVS) were performed to evaluate the efficiency of the installed activated carbon treatment step between June 2010 and July 2014 for other substances [12]. These measurements (though not measured / published for OPnEO or OP) show an additional elimination by the activated carbon step of several micropollutants from 60% (diclofenac) to 91% (5-methyl benzotriazole).

To allow a realistic estimation of the total releases of OPnEO and its degradation products after the STP and the corresponding exposure estimation for all relevant environmental compartments, the specific parameters and removal processes of OPnEO taking place in the municipal STPs were implemented in the 'Multifate' model using the parameters provided in the supporting documents 'SD2a_CSR_Model_description_partI_Vetter_Use1' and 'SD2b_CSR_Model_description_partII_Vetter_Use1'.

9.3.2.3. Approach for the Regional Exposure

The predicted regional environmental concentrations were calculated with 'Multifate' based on the use at industrial sites. The tonnage for the regional release estimation is equal to 100% of the tonnages used at both Vetter sites.

9.3.2.4. Environmental Exposure Modelling and Monitoring

9.3.2.4.1. Environmental Exposure Modelling

Instead of the classical approach where the initial release to a STP is typically calculated from the total used amount considering the standard release factors to wastewater for a given scenario, the maximum daily release to wastewater based on the collected data was used as input for the model used to estimate the PECs in the relevant environmental compartments.

The model 'Multifate' [3] was developed in the framework of a scientific research project. This project had the overall goal to assess the relevance of endocrine disruptors to humans, animals and ecosystems¹. An application of the model to various substances exhibiting endocrine disruptive potential has been published [3]. 'Multifate' is a model based on fugacity and hence calculates mass flows to and from all environmental compartments (air, groundwater, soil, surface water and sediment) based on phase equilibria. In contrast to EUSES [4], 'Multifate' incorporates specific degradation products. The fate of these degradation products is also calculated, making 'Multifate' a combined multi-compartment and multi-substance model. 'Multifate' was developed for NPnEO and its degradation products nonylphenoldiethoxylate (NP2EO), 4-nonylphenoxyethoxyacetic acid (NP2EC), nonylphenolmonoethoxylate (NP1EO), 4-nonylphenoxyacetic acid (NP1EC) and 4-nonylphenol (NP). The degradation mechanism used in 'Multifate' is shown in the supporting document 'SD2a_CSR_Model_description_partI_Vetter_Use1'. The same degradation mechanism was assumed for OPnEO based on the general degradation mechanism that holds for all alkylphenol polyethoxylates according to [10] and [1].

9.3.2.4.2. Monitoring

A monitoring campaign was not envisaged because both Vetter sites (RVS and VLA) are connected to municipal STP where not only water from the respective production sites is treated.

¹ Scientific research project in the framework of which the model was developed: <http://www.snf.ch/en/researchinFocus/nrp/nrp50-endocrine-disruptors-relevance-to-humans-animals-and-ecosystems/Pages/default.aspx>

Hence, measured data of OPnEO and its degradation products at the outlet of the STP would not only reflect emissions from the Vetter sites, but would likely represent a mixture of several sources: from a larger area with several industries and population equivalents of 184'000 (RVS) and 24'000 (VLA).

9.3.2.5. Comparison with Reference and Background Values

EQS values from the water framework directive [6] selected for the comparison in the assessment are given in Table 6.

Table 6. Selected EQS values from the water framework directive. AA-EQS: Annual average environmental quality standard; MAC-EQS: Maximum allowable concentration environmental quality standard.

Value type	Value specific for	Value (µg/L)	Substance	Source
AA-EQS	Inland surface waters*	0.1	Octylphenol, CAS 140-66-9	[6]
AA-EQS	Other surface waters	0.01	Octylphenol, CAS 140-66-9	[6]
MAC-EQS	Water	not applicable**	Octylphenol, CAS 140-66-9	[6]

* Inland surface waters encompass rivers and lakes and related artificial or heavily modified water bodies

** According to the water frame directive [6]: "Where the MAC-EQS are marked as 'not applicable', the AA-EQS values are considered protective against short-term pollution peaks in continuous discharges since they are significantly lower than the values derived on the basis of acute toxicity".

Background values

Available and current levels of OP in a range of surface waters and in marine water are shown in Table 7. These values are used for comparison of the modelled and measured data.

Table 7. Concentrations of OP measured in surface and marine water (ICPR: International Commission for the Protection of the Rhine, EIONET: European Environment Information and Observation Network).

Substance	Value (µg/L) or result	Source	Link	Remark
OP	OP exceeded the EQS in five or less (of ten) river basin districts in Germany	[9]	www.mdpi.com/2073-4441/8/6/217/pdf	Germany
OP	0.022±0.08	ICPR database	http://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2015

Substance	Value (µg/L) or result	Source	Link	Remark
OP	0.021±0.08	ICPR database	http://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2016
OP	France: 0.71 GB: 0.037 Slovakia: <1.00	EIONET database	https://forum.eionet.europa.eu/nrc-eionet-freshwater/library/hazardous-substances-report/country-review-hazardous-substances-water-etc-icm-report-2014/hs_data_etc-icm_technical-report_2014_for_country_review	Maximum concentrations (groundwater; µg/L), 2002-2011
OP	0.098	[16]		River Schussen, before activated carbon was implemented in STP Langwiese

9.3.2.5.1. Man via Environment

Risks to human health via the environment do not need to be assessed in the CSR included in an application for authorisation for OPnEO as it was listed on Annex XIV only on the basis of their endocrine disrupting properties for the environment (Article 62(4)).

9.3.2.5.2. Workers

Risks to human health do not need to be assessed in the CSR included in an application for authorisation for OPnEO as it was listed on Annex XIV only on the basis of their endocrine disrupting properties for the environment (Article 62(4)).

9.3.2.5.3. Consumers

Risks to human health do not need to be assessed in the CSR included in an application for authorisation for OPnEO as it was listed on Annex XIV only on the basis of their endocrine disrupting properties for the environment (Article 62(4)).

9.4. Exposure Assessment for OPnEO

- ⇒ Exposure assessment was performed separately for the two Vetter sites
- ⇒ Due to RMMs, the total release of OPnEO to wastewater is 0.755 g/a (maximum 28.0 mg/d) at RVS and 0.177 g/a (maximum 13.6 mg/d) at VLA for the use applied for assuming production at maximum expected orders.

9.4.1. Exposure Scenario 1: IW1 – OPnEO - Use as Emulsifier in the Siliconisation of Glass Containers used as Primary Packaging for Medicinal Products - RVS

Sector of use: SU20 – Health services

Article categories: PC29: Pharmaceuticals

Environment contributing scenario(s):

ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)

Worker/Consumer contributing scenario(s):

PROC5 - Mixing or blending in batch processes for formulation of preparations (multistage and/or significant contact)

PROC7 - Industrial spraying

PROC8a - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities

PROC9 - Transfer of substance or preparation into small containers (dedicated filling line, including weighing)

Subsequent service life: Professional use / waste of the filled glass containers

Exposure scenario(s) of the uses leading to the inclusion of the substance into the article(s):
not applicable

A detailed description of the activities and technical processes covered in the exposure scenario can be found in Section 9.3.1.

9.4.1.1. Environmental Contributing Scenario

9.4.1.1.1. Conditions of Use

The following table summarises the conditions of use. Details on the technical and organisational measures to minimise releases to the environment are provided in Section 9.4.3.1.

Amount used, frequency and duration of use (or from service life)	
▪ Total EEA tonnage (kg/a):	0.281
▪ Percentage of total EEA tonnage used at regional scale:	100 %
▪ Fraction of regional tonnage used at local scale:	1
▪ Annual site tonnage (kg/a):	0.281
▪ Maximal number of emission days per year:	50
▪ Maximum daily site tonnage (kg/d):	0.0104
▪ Type of release:	Continuous release
Technical and organisational conditions and measures	
▪ Surplus / solid waste is collected and incinerated	
▪ Handling only by trained personnel	
▪ All steps take place in a highly controlled environment, corresponding to EudraLex - Volume 4 - Good Manufacturing Practice Guidelines and are described in SOPs	
Conditions and measures related to STP	
▪ Municipal STP: Yes (effectiveness: 68.9 % OP equivalents)	
▪ Discharge rate of STP:	35'000 m ³ /d
▪ Application of the STP sludge on agricultural soil:	No, STP sludge is incinerated.
Conditions and measures related to external treatment of waste (including article waste)	
▪ The liquid / solid waste is collected and incinerated in an industrial waste incinerator (ARStec GmbH, Konrad-Zuse-Straße 6, D-89231 Neu-Ulm; Bausch GmbH, Bleicherstr. 35, D-88212 Ravensburg)	
Conditions and measures related to external recovery of waste (including article waste)	
▪ No waste recovery (incineration in an industrial waste incinerator)	
Other conditions affecting environmental exposure	
▪ Receiving surface water flow rate:	River Schussen, 3.51 m ³ /s
▪ Resulting dilution factor:	1:9.7
Additional good practice advice.	
▪ Specific SOP documents have been created to ensure compliance at all levels with Eudralex	

9.4.1.1.2. RMMs implemented

In this CSR, the aim of the applicant is to demonstrate that emissions were minimised as far as practically and technically feasible. RMMs were already in place at the time of assessment for the purpose of this dossier. The main RMM is to drain the system after each batch and to collect any surplus or rests of (diluted / non-diluted) silicone oil emulsion and incinerate them. Additional RMMs include the collection and subsequent disposal into solid waste of any cleaning cloths/materials used for regular wiping of all equipment surfaces. Risk is furthermore minimised by substitution. However, because the substitution will not be possible before the sunset date for the siliconisation, RMMs already implemented at the time of assessment for this dossier ensure minimisation of releases immediately. All RMM are already considered in the process description above.

9.4.1.1.3. Releases

OPnEO is used in the siliconisation of the glass containers at Vetter's site RVS. During the siliconisation step, a minimal amount of OPnEO is sprayed into the individual glass containers. Considering the removal during the sterilisation and depyrogenation step, the remaining amount on the glass containers is further reduced to a level where an analysis on an individual glass container is hardly possible. The remaining amount are unintended residues that do not fulfil a function anymore. Therefore, the relevant environmental release category is ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article). The default environmental release factors for ERC 4 are 100 % release to air, 100 % release to water (before STP) and 5 % release to soil (soil only to be taken into account at the regional scale based on deposition from the air).

However, site and process specific information are available to substantiate the fact that the default factors of ERC 4 are not applicable to the siliconisation taking place at Vetter's manufacturing sites. Therefore, specific release factors instead of default values were used in this CSR, which are described in the following.

Emission to air

Considering the conditions of the heat treatment during the depyrogenation step, significant emission to air can be expected. However, due to the very low volatility of OPnEO at room temperature ($V_p=1.8 \cdot 10^{-14}$ mmHg, [1]) and the condensation taking place on the high efficiency particulate air (HEPA) filter, no direct emissions to air arise at the manufacturing sites. Releases to air are thus not expected. The release factor to air before the municipal STP can be considered as 0%. However, release to the air from the municipal STP through the aeration of the aerobic tank may still take place even if the release is expected to be extremely low.

Emission to wastewater

Release of OPnEO to wastewater occurs from the cleaning/sanitizing of the spray nozzles and distribution lines inside the equipment performed after drainage of the equipment as well as from cleaning of the compounding equipment which is used for manufacturing of the diluted silicone oil emulsion. By weighing the respective equipment parts before and after cleaning/sanitizing this amount was found to be [REDACTED] g of the diluted siliconisation solution per batch ([REDACTED] g OPnEO per batch). Since this is the only amount of OPnEO entering the wastewater the percentage of OPnEO entering the wastewater is 0.27 % of the total amount of OPnEO used for the processing.

Emission to soil

Due to the fact that no direct emissions to soil arise at the production sites during the siliconisation and that the sludge generated by the STPs is collected and incinerated, releases to soil are not expected at both sites. Therefore, the release fraction to soil from the siliconisation is 0. However, release to the soil after the STP via the air by way of (wet or dry) deposition can still occur even if the emission to air is expected to be very small (see above).

A summary of the initial and final release factors before the STP selected for the exposure assessment is provided in Table 8.

Table 8. Local releases to the environment.

Compartment	Release factor estimation method	Explanation / Justification
Water	Based on specific data from the production sites	Local release factor: 0.27 % Local release rate: 0.000028 kg/d of OPnEO Explanation / Justification: Release factor determined based on the data collected considering RMMs (i.e. collection and incineration of surplus, drainage of the system before cleaning)
Air	Based on substance-specific data and specific data from the production sites	Local release factor: 0 % Local release rate: 0 kg/d Explanation / Justification: OPnEO is not volatile ($V_p = 1.8 \cdot 10^{-14}$ mmHg, [1])
Soil	Based on specific data from the production sites	Local release factor: 0 % Explanation / Justification: There is no direct release to soil (sludge from STP is incinerated)

Releases to waste

Release factor to waste from the process:

As described above, 0.27 % of the total daily amount of OPnEO used is sent to wastewater while 86.4 % is collected as surplus, rests or waste or collected with the HEPA filter (13.3 %, taking into account the decomposed OPnEO during the dry-heat tunnel treatment) and incinerated. Since all waste from the process is incinerated a separate waste scenario was not developed.

Release factor to waste from on-site treatment:

There is no on-site treatment of waste at the Vetter site RVS. All waste (hazardous and non-hazardous) is sent to the respective incineration stations.

9.4.1.1.4. Exposure and Risks for the Environment and Man via the Environment

Table 9. Exposure concentrations and risks for the environment – on local scale.

Protection target	Unit	Exposure concentration local in OP _{equiv.} based on the applied for use
		RVS
STP effluent	µg/L	0.0000850
Freshwater	µg/L	8.80·10 ⁻⁶
Sediment (freshwater)	µg/kg	0.000258
Marine water	µg/L	8.50·10 ⁻⁷
Sediment (marine water)	µg/kg	0.0000249
Agricultural soil	pg/kg	1.72·10 ⁻¹³
Air (from the municipal STP)	pg/m ³	0.00000127

The exposure concentration given in Table 9 refer to the local scale only. The regional exposure is discussed in Section 10 of this CSR.

Remarks on measured exposure:

Specific monitoring data for STP effluents is not available for the Vetter site RVS as wastewater is released into a municipal STP. However, measurements of OP in the effluent of the STP Langwiese (RVS) are available (see Section 9.3.2.4.2 for more details).

Conclusion on risk characterisation:

Risk characterisation was not assessed because no threshold can be derived for the endpoint ‘endocrine disrupting properties’ for the degradation products of the substance. Instead risk/exposure minimisation are demonstrated in this CSR. PECs per site are compared with Environmental Quality Standards as an indication of remaining risk in Section 10.

9.4.1.2. Workers

Not required.

9.4.2. Exposure Scenario 1: IW1 – OPnEO - Use as Emulsifier in the Siliconisation of Glass Containers used as Primary Packaging for Medicinal Products - VLA

Sector of use: SU20 – Health services

Article categories: PC29: Pharmaceuticals

Environment contributing scenario(s):

ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)

Worker/Consumer contributing scenario(s):

PROC5 - Mixing or blending in batch processes for formulation of preparations (multistage and/or significant contact)

PROC7 - Industrial spraying

PROC8a - Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities

PROC9 - Transfer of substance or preparation into small containers (dedicated filling line, including weighing)

Subsequent service life: Professional use / waste of the filled glass containers

Exposure scenario(s) of the uses leading to the inclusion of the substance into the article(s):
not applicable

A detailed description of the activities and technical processes covered in the exposure scenario can be found in Section 9.3.1.

9.4.2.1. Environmental Contributing Scenario

9.4.2.1.1. Conditions of Use

The following table summarises the conditions of use. Details on the technical and organisational measures to minimise releases to the environment are provided in Section 9.4.3.1

Amount used, frequency and duration of use (or from service life)	
▪ Total EEA tonnage (kg/a):	0.0254
▪ Percentage of total EEA tonnage used at regional scale:	100%
▪ Fraction of regional tonnage used at local scale:	1
▪ Annual site tonnage (kg/a):	0.025
▪ Maximal number of emission days per year:	50
▪ Maximum daily site tonnage (kg/d):	0.00195
▪ Type of release:	Continuous release
Technical and organisational conditions and measures	
▪ Surplus / solid waste is collected and incinerated	
▪ Handling only by trained personnel	
▪ All steps take place in a highly controlled environment, corresponding to EudraLex - Volume 4 - Good Manufacturing Practice Guidelines and are described in SOPs	
Conditions and measures related to STP	
▪ Municipal STP: Yes (effectiveness: 57 % of OP equivalents)	
▪ Discharge rate of STP:	21'700 m ³ /day
▪ Application of the STP sludge on agricultural soil:	No, STP sludge is incinerated.
Conditions and measures related to external treatment of waste (including article waste)	
▪ The liquid / solid waste is collected and incinerated in an industrial waste incinerator (ARStec GmbH, Konrad-Zuse-Straße 6, D-89231 Neu-Ulm; Bausch GmbH, Bleicherstr. 35, D-88212 Ravensburg)	
Conditions and measures related to external recovery of waste (including article waste)	
▪ No waste recovery (incineration in an industrial waste incinerator)	
Other conditions affecting environmental exposure	
▪ Receiving surface water flow rate:	Lake Constance
▪ Resulting dilution factor:	1:10 (assumption due to discharge to lake)
Additional good practice advice.	
▪ Specific SOP documents have been created to ensure compliance at all levels with Eudralex	

9.4.2.1.2. RMMs implemented

In this CSR, the aim of the applicant is to demonstrate that emissions were minimised as far as practically and technically feasible. RMMs were already in place at the time of assessment for the purpose of this dossier. The main RMM is to drain the system after each batch and to collect any surplus or rests of (diluted / non-diluted) silicone oil emulsion and incinerate them. Additional RMMs include the collection and subsequent disposal into solid waste of any cleaning cloths/materials used for regular wiping of all equipment surfaces. Risk is furthermore minimised by substitution. However, because the substitution will not be possible before the sunset date for the siliconisation, RMMs already implemented at the time of assessment for this dossier ensure minimisation of releases immediately. All RMM are already considered in the process description above.

9.4.2.1.3. Releases

OPnEO is used in the siliconisation of the glass containers at Vetter's site VLA. During the siliconisation step, a minimal amount of OPnEO is sprayed into the individual glass containers. Considering the removal during the sterilisation and depyrogenation step, the remaining amount on the glass containers is further reduced to a level where an analysis on an individual glass container is hardly possible. The remaining amount are unintended residues that do not fulfil a function anymore. Therefore, the relevant environmental release category is ERC 4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article). The default environmental release factors for ERC 4 are 100 % release to air, 100 % release to water (before STP) and 5 % release to soil (soil only to be taken into account at the regional scale based on deposition from the air).

However, site and process specific information are available to substantiate the fact that the default factors of ERC 4 are not applicable to the siliconisation taking place at Vetter's manufacturing sites. Therefore, specific release factors instead of default values were used in this CSR, which are described in the following.

Emission to air

Considering the conditions of the heat treatment during the depyrogenation step, significant emission to air can be expected. However, due to the very low volatility of OPnEO at room temperature ($V_p=1.8 \times 10^{-14}$ mmHg, [1]) and the condensation taking place on the HEPA filter, no direct emissions to air arise at the manufacturing sites. Releases to air are thus not expected. The release factor to air before the municipal STP can be considered as 0%. However, release to the air from the municipal STP through the aeration of the aerobic tank may still take place even if the release is expected to be extremely low.

Emission to wastewater

Release of OPnEO to wastewater occurs from the cleaning / sanitizing of the spray nozzles and distribution lines inside the equipment performed after drainage of the equipment as well as from cleaning of the compounding equipment which is used for manufacturing of the diluted silicone oil emulsion. By weighing the respective equipment parts before and after cleaning / sanitizing this amount was found to be █████ g of the diluted siliconisation solution per batch (█████ g OPnEO per batch). Since this is the only amount of OPnEO entering the wastewater the percentage of OPnEO entering the wastewater is 0.7 % of the total amount of OPnEO used for the processing.

Emission to soil

Due to the fact that no direct emissions to soil arise at the production sites during the siliconisation and that the sludge generated by the STPs is collected and incinerated, releases to soil are not expected at both sites. Therefore, the release fraction to soil from the siliconisation at both sites is 0. However, release to the soil after the STP via the air by way of (wet or dry) deposition can still occur even if the emission to air is expected to be very small (see above).

A summary of the release factors before the STP selected for the exposure assessment is provided in Table 10.

Table 10. Local releases to the environment.

Compartment	Release factor estimation method	Explanation / Justification
Water	Based on specific data from the production sites	<p>Local release factor: 0.7 %</p> <p>Local release rate: 0.000014 kg/d OPnEO</p> <p>Explanation / Justification: Release factor determined based on the data collected considering RMMs (i.e. collection and incineration of surplus)</p>
Air	Based on specific data from the production sites	<p>Local release factor: 0%</p> <p>Local release rate: 0 kg/d</p> <p>Explanation / Justification: OPnEO is not volatile ($V_p = 1.8 \times 10^{-14}$ mmHg, [1])</p>
Soil	Based on specific data from the production sites	<p>Local release factor: 0%</p> <p>Explanation / Justification: There is no direct release to soil (sludge from STP is incinerated)</p>

Releases to waste

Release factor to waste from the process:

As described above, 0.7 % of the total daily amount of OPnEO used is sent to wastewater while 71.6 % is collected as surplus, rests or waste or collected with the HEPA filters (27.7% taking into account the decomposed OPnEO during the dry-heat tunnel treatment) and incinerated. Since all waste from the process is incinerated a separate waste scenario was not developed.

Release factor to waste from on-site treatment:

There is no on-site treatment of waste at the Vetter site VLA. All waste (hazardous and non-hazardous) is sent to the respective incineration stations.

9.4.2.1.4. Exposure and Risks for the Environment and Man via the Environment

Table 11. Exposure concentrations and risks for the environment – on local scale.

Protection target	Unit	Exposure concentration local in OP equiv. based on the applied for use
		VLA
STP effluent	µg/L	0.0000724
Freshwater	µg/L	$7.24 \cdot 10^{-6}$
Sediment (freshwater)	µg/kg	0.000210
Marine water	µg/L	$7.23 \cdot 10^{-7}$
Sediment (marine water)	µg/kg	0.0000210
Agricultural soil	pg/kg	$1.65 \cdot 10^{-14}$
Air (from the municipal STP)	pg/m ³	$2.29 \cdot 10^{-6}$

The exposure concentration given in Table 11 refer to the local scale only. The regional exposure is discussed in Section 10 of this CSR.

Remarks on measured exposure:

Specific monitoring data for STP effluents is not available for the Vetter site VLA as wastewater is released into municipal STP.

Conclusion on risk characterisation:

Risk characterisation was not assessed because no threshold can be derived for the endpoint 'endocrine disrupting properties' for the degradation products of the substance. Instead risk/exposure minimisation are demonstrated in this CSR. PECs per site are compared with Environmental Quality Standards as an indication of remaining risk in Section 10.

9.4.2.2. Workers

Not required.

9.4.3. Minimisation of Releases to the Environment and Expected Evolution over the Review Period

In this section, the aim of the applicant is to demonstrate that emissions and releases to the environment from the activities covered in this application are minimised as far as practically and technically feasible as well as to provide an overview of the expected evolution of the releases of OPnEO to wastewater from the sunset date (4th of January 2021) to the end of the review period (4th of January 2026).

The influence of the implementation of RMMs on the total release to wastewater is addressed in Section 9.4.3.1 while the total release of OP equivalents after the STP to surface water from the siliconisation is discussed in Section 9.4.3.2.

9.4.3.1. Minimisation of Releases to Wastewater at RVS and VLA

For the siliconisation, data on used amounts and generated waste fractions for 2017 were collected at the time of the preparation of the dossier (see supporting document 'SD3_CSR_Data_collected_Vetter_Use1_CONFIDENTIAL').

During the siliconisation of the glass containers, different waste fractions are generated i.e.:

- The surplus/rests of the (diluted) silicone oil emulsion,
- The rinsing waters used for cleaning of the compounding equipment,
- The rinsing waters used for the cleaning and sanitizing of the spray nozzles and the distribution lines after a production cycle after drainage of the system,
- The solid waste that may be generated during the activities, i.e. mainly plastic containers and wipes.

At the time of the preparation of the dossier, any solid waste was already separately collected and incinerated. These waste fractions were therefore not considered further as the measures were already in place to minimise the release. Concerning the other liquid waste fractions i.e. surplus / rests of the (diluted) silicone oil emulsion, these were also all sent to the incinerator.

A small amount of OPnEO is released to wastewater during the washing / sanitisation step after drainage of the equipment and during cleaning of the compounding equipment. Collecting the wastewater from the washing step (VLA) or the sanitization step (RVS) would be a great effort as these steps take place in a good manufacturing practice (GMP) area. Further, the washing area in VLA is used for other machine equipment from non-OPnEO containing processes. Separate collection would require an evaluation project, a requalification and could not be done during productive runs. The additional shut-down would require all customers (even those not using OPnEO processes) to be involved and production delayed. Therefore, the implementation period of such a reconstruction would be in the same range as the period of this application for authorization. Moreover, additional measures are not feasible to minimize the OPnEO fraction entering the wastewater.

Considering the RMMs in place and planned substitutions, the total release of OPnEO to wastewater of 0.177 g/a at VLA to 0.755 g/a at RVS (based on maximum orders expected) in 2021 to reach 0 by the end of 2021 if the substitution is completed in time (see timeline in the AoA). However, if the substitution is delayed to the end of the review period, the total annual release to wastewater could be observed as a worst-case (assuming production at maximum orders expected) until the end of the review period.

9.4.3.2. Minimisation of Releases after the STP to Surface Water

The remaining wastewater containing OPnEO is released to the STP Langwiese (RVS) and the STP Kressbronn-Langenargen (VLA). Both STPs are equipped with an activated carbon filter as an additional RMM to remove micropollutants such as contrast agents used in medicinal imaging and phthalates used e.g. as plasticizers and also OPnEO. OP precursor substances (OPnEO) are degraded (partially) to OP in the course of the wastewater treatment and are (partially) removed with the sewage sludge (which is incinerated) and the activated carbon filter. This is also reflected in the model assumptions. Table 12 gives an overview of the modelled total annual release of OP equiv. to surface water at the sunset date and by the end of the review period, for both scenarios (delay of substitution or not), as well as the total (integrated) release of OP_{equiv} to surface water over the review period (2021 to end of 2025).

Table 12. Expected and worst-case releases of OP_{equiv} to surface water after the STP per year (or per 5 years of the review period) from 2021 until the end of the review period based on model calculations.

		Unit	RVS	VLA	Total
Release to surface water after the STP at the sunset date (04th of January 2021)	Expected release considering substitution	kg/a OP _{equiv}	0.0000804	0.0000261	0.000107
	Max total releases with delayed substitution	kg/a OP _{equiv}	0.0000804	0.0000261	0.000107
Release to surface water after the STP 6 months before the end of the review period (4th of July 2025)	Expected release considering substitution	kg/a OP _{equiv}	0	0	0
	Max total releases with delayed substitution	kg/a OP _{equiv}	0.0000804	0.0000261	0.000107
Total release to surface water after the STP over the review period (2021-end of 2025)	Expected release considering substitution	kg OP _{equiv} in 5 years	0.0000804	0.0000261	0.000107
	Max total releases with delayed substitution	kg OP _{equiv} in 5 years	0.000402	0.000131	0.000533

10. EXPOSURE ASSESSMENT RELATED TO COMBINED EXPOSURE & COMPARISON WITH AVAILABLE REFERENCE VALUES

- ⇒ In this exposure assessment, the **local releases from the Vetter sites and regional release is estimated.**
- ⇒ Compared to available measurements the releases of OP equivalents to surface water due to the use of OPnEO at the Vetter sites are small.

10.1. Exposure Assessment Related to Combined Exposure and Comparison with Available Reference Values – OPnEO

10.1.1. Overview of the Uses Applied For and their Interrelation

Exposure assessment was performed to support Vetter's applications for authorisation for the following use:

- Use of OPnEO as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products of one pharmaceutical company

For the purpose of the exposure assessment, the local release per site and a regional release must be estimated. The estimation of the regional tonnage (fraction of 'the tonnage for the use' in the region) depends on the geographical distribution of the substance's use. By default, the tonnage at the regional level for the uses at industrial sites is set equal to 100% of the tonnage for the use [5].



Figure 7. Map of the two Vetter sites RVS and VLA and the respective STPs

As shown in Figure 7, both Vetter sites are in the same region. The only release of OPnEO to the environment occurs during manufacturing of the products. Therefore, the release to wastewater for the regional exposure was set equal to the sum of the release from the sites RVS and VLA to wastewater (0.932 g/year OPnEO).

10.1.2. Environment (combined for all Emission Sources)

10.1.2.1. Environment

10.1.2.1.1. All Uses (Regional Scale)

10.1.2.1.1.1. Total Releases

Table 13. Total releases of OP_{equiv} to surface water after the STP per year from all life cycle stages at the sunset date.

SURFACE WATER	Unit	RVS	VLA	Total releases after the STP per year
Use 1	kg/a OP _{equiv}	0.0000804	0.0000261	0.000107
TOTAL	kg/a OP_{equiv}	0.0000804	0.0000261	0.000107

Table 14. Total releases of OP_{equiv} to soil from STP by wet and dry deposition per year from all life cycle stages at sunset date.

SOIL	Unit	RVS	VLA	Total releases from the STP per year
Use 1	kg/a OP _{equiv}	$7.25 \cdot 10^{-23}$	$2.81 \cdot 10^{-24}$	$7.53 \cdot 10^{-23}$
TOTAL	kg/a OP_{equiv}	$7.25 \cdot 10^{-23}$	$2.81 \cdot 10^{-24}$	$7.53 \cdot 10^{-23}$

Table 15. Total releases of OP_{equiv} to air from STP per year from all life cycle stages at sunset date.

AIR	Unit	RVS	VLA	Total releases from the STP per year
Use 1	kg/a OP _{equiv}	$1.31 \cdot 10^{-10}$	$1.08 \cdot 10^{-10}$	$2.39 \cdot 10^{-10}$
TOTAL	kg/a OP_{equiv}	$1.31 \cdot 10^{-10}$	$1.08 \cdot 10^{-10}$	$2.39 \cdot 10^{-10}$

10.1.2.1.2. Regional Exposure

The predicted regional environmental concentrations listed in Table 16 were calculated with 'Multifate' based on the regional release to wastewater of 0.932 g/year. This is the combined amount of the releases to wastewater of the two Vetter sites in the region and only used for calculating a background concentration. Environmental concentrations for the two sites based on local release are additionally given.

Table 16. Local and regional environmental concentrations in OP equivalents.

Protection target	Unit	Local concentration RVS	Local concentration VLA	Regional concentration
Freshwater	µg/L	$8.80 \cdot 10^{-6}$	$7.24 \cdot 10^{-6}$	$1.93 \cdot 10^{-8}$
Sediment (freshwater)	µg/kg	0.000258	0.000210	$9.69 \cdot 10^{-10}$
Marine water	µg/L	$8.50 \cdot 10^{-7}$	$7.23 \cdot 10^{-7}$	$2.05 \cdot 10^{-6}$
Sediment (marine water)	µg/kg	0.0000249	0.0000210	$1.93 \cdot 10^{-10}$
Agricultural soil	pg/kg	$1.72 \cdot 10^{-13}$	$1.65 \cdot 10^{-14}$	$6.74 \cdot 10^{-13}$
Air	pg/m ³	$1.27 \cdot 10^{-6}$	$2.29 \cdot 10^{-6}$	$1.04 \cdot 10^{-10}$

Remarks on measured regional concentrations: Regional concentrations of OPnEO were not measured specifically for the purpose of the present CSR. However, measurements of environmental background concentrations are available for the RVS site (see Table 18). Measured values for OP from literature shown in Table 7 are in the range of 0.021 to 0.7 µg/L. The calculated regional concentration of $1.93 \cdot 10^{-8}$ µg/L is several orders of magnitude lower than these values.

Remarks on risk characterisation for regional concentrations: Risk characterisation was not assessed because no threshold can be derived for the endpoint 'endocrine disrupting properties' of the degradation products for the substance. Instead, risk / exposure minimisation are demonstrated in this CSR. For illustrative purposes a comparison of the combined local PEC (sum of the predicted local environmental concentration and the predicted regional environmental concentration) to the EQS value of 0.1 µg/L is shown in Table 18.

10.1.2.1.3. Comparison of Combined Exposure with Available Background Concentrations and Available Reference Values

The PEC_{local} is calculated as the sum of the predicted local environmental concentration and the predicted regional environmental concentration (see individual values in Table 16). In Table 17 a comparison of the local PECs with background values is shown. The measured freshwater value of 0.098 µg/L [12] in 2012 (i.e. without activated carbon treatment) is 3 orders of magnitude higher than the calculated combined freshwater concentration of $8.82 \cdot 10^{-6}$ µg/L for the site RVS. Taking into account that the local concentration was calculated using 85 % adsorption of OP to activated carbon in the local STP, the concentration before the installation of the activated carbon treatment would have been slightly higher but still at least 3 orders of magnitude lower than the measured value. Therefore, the contribution of the release of OP equivalents from the site in RVS to the

concentration of OP in the River Schussen is low. A similar situation is expected for the VLA site even though no monitoring data are available.

Table 17. Comparison of local freshwater PECs in OP equivalents with available background values for fresh waters for OP.

Location	Unit	Local freshwater PEC* (OP equivalents)	Background values (OP)
RVS	µg/L	$8.82 \cdot 10^{-6}$	0.098**
VLA	µg/L	$7.25 \cdot 10^{-6}$	Not available

*including the regional concentration given in Table 16

** River Schussen downstream of STP Langwiese [12]

As a worst-case, a combined PEC_{local} is additionally calculated as the sum of the two predicted local concentrations (RVS and VLA) and the predicted regional concentration due to the location of the two STPs close to each other (see Figure 7).

Even though it is assumed that no threshold can be derived for OP, the combined local PEC for both sites is compared to the EQS value of 0.1 µg/L for illustrative purposes in Table 18. The combined local PEC for freshwater is several orders of magnitude below the EQS.

Table 18. Combined predicted local environmental concentrations (PEC_{local}) in OP equivalents.

Protection target	Unit	Local PEC* RVS	Local PEC* VLA	Combined local PEC (both sites)	EQS	PEC_{local}/EQS
Freshwater	µg/L	$8.82 \cdot 10^{-6}$	$7.25 \cdot 10^{-6}$	0.000163	0.1	0.000163
Sediment (freshwater)	µg/kg	0.000259	0.000211	0.000470	n.a.	not assessed
Marine water	µg/L	$2.90 \cdot 10^{-6}$	$2.78 \cdot 10^{-6}$	$5.68 \cdot 10^{-6}$	n.a.	not assessed
Sediment (marine water)	µg/kg	0.0000251	0.0000212	0.0000463	n.a.	not assessed
Agricultural soil	pg/kg	$8.45 \cdot 10^{-13}$	$6.90 \cdot 10^{-13}$	$1.54 \cdot 10^{-12}$	n.a.	not assessed
Air	pg/m ³	$1.27 \cdot 10^{-6}$	$2.29 \cdot 10^{-6}$	$3.56 \cdot 10^{-6}$	n.a.	not assessed

* including the regional concentration given in Table 16

10.1.2.2. Man via the Environment

Not required.

10.1.3. Human Health (related to Combined Exposure)

10.1.3.1. Workers

Not required.

10.1.3.2. Consumers

Not required.

10.2. Conclusions

By implemented RMMs (incineration of surplus and rests of the diluted silicone oil emulsion, minimised release to wastewater by drainage of the equipment before cleaning) the emissions to the environment with regard to the use of OPnEO are reduced as much as technically and practically feasible. Therefore, the risks related to the continued use of OPnEO can be considered as minimised. Maximum yearly emissions into wastewater after the sunset date will be 0.932 g/a OPnEO until substitutions are completed. The respective combined local PEC was calculated to 0.00882 ng/L (RVS) and 0.00725 ng/L (VLA). Mass flows of OP_{equiv} to surface water are calculated to 0.0804 g/a (RVS) and 0.0261 g/a (VLA), respectively.

REFERENCES

- [1] ECHA (2018) Committee for Risk Assessment, Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO (Agreed at RAC-43)
- [2] ECHA (2017) SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO, (Agreed at SEAC 37)
- [3] C. Braun, R. Gälli (2008). Integrative Risk Assessment of Endocrine Disruptors in Switzerland. 2008. *Chimia*, 62(5), 417-423
- [4] EUSES 2.0 (2003) EUSES, the European Union System for the Evaluation of Substances, version 2.0. National Institute of Public Health and the Environment (RIVM), the Netherlands. Available via http://www.chemsafetypro.com/Topics/CRA/how_to_use_EUSES_to_estimate_predicted_environmental_concentrations_PEC.html
- [5] Guidance on information requirements and Chemical Safety Assessment, Chapter R.16: Environmental exposure assessment, version 3,0, Feb 2016, European Chemicals Agency
- [6] DIRECTIVE 2013/39/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy (EU Water Framework Directive)
- [7] T. Tanghe, W. Verstraete (2001). Adsorption of Nonylphenol onto Granular Activated Carbon. *Water, Air, and Soil Pollution*, 2001, 131(1-4), 61-72
- [8] C. C. Borghi, M. Fabbri (2014). Magnetic recovery of modified activated carbon powder used for removal of endocrine disruptors present in water. *Environ Technol.* Mar-Apr 2014; 35(5-8):1018-26
- [9] J. Arle, V. Mohaupt and I. Kirst (2016). Monitoring of Surface Waters in Germany under the Water Framework Directive – A Review of Approaches, Methods and Results. *Water* 2016, 8, 217; doi:10.3390/w8060217
- [10] EA, 2005. Environmental Risk Evaluation Report: 4-tert-Octylphenol. Environment Agency, Bristol, UK
- [11] A. Rößler, H. Kapp (2012) Erweiterung des Klärwerks Mannheim um eine Adsorptionsstufe zur Verbesserung der Abwasserreinigung. Verminderung von estrogen wirksamen Substanzen im Abwasser durch den Einsatz von Pulveraktivkohle. Überprüfung der Wirksamkeit anhand eines Fischmonitorings sowie begleitender Analytik. <http://docplayer.org/28755209-Verminderung-von-estrogen-wirksamen-substanzen-im-abwasser-durch-den-einsatz-von-pulveraktivkohle.html>
- [12] R. Triebkorn (2012) Modellstudie zur Effizienz der Reduktion der Gehalte an anthropogenen Spurenstoffen durch Aktivkohle in Kläranlagen: Monitoring vor Inbetriebnahme der Adsorptionsstufe auf der Kläranlage Langwiese «SchussenAktiv», Final report for project 206/2010 for the Ministry of the Environment, Climate Protection and the Energy Sector Baden-Württemberg

- [13] P. Thellmann et al. (2017), Does Waste Water Treatment Plant Upgrading with Powdered Activated Carbon Result in Reduced Water and Sediment Toxicity of the Receiving Stream? *Int Water Wastewater Treat* 3(2), doi <http://dx.doi.org/10.16966/2381-5299.141>
- [14] T. Mundry (1999), Einbrennsilikonisierung bei pharmazeutischen Glaspackmitteln – Analytische Studien eines Produktionsprozesses, Dissertation, Humboldt-Universität zu Berlin
- [15] EudraLex - Good Manufacturing Practice (GMP) guidelines - Volume 4: Human & Veterinary, European Commission, Brussels, December 2010, ISBN 92-828-2029-7
- [16] R. Triebkorn, H. Hetzenauer (2012). Micropollutants in three tributaries of Lake Constance, Argen, Schussen and Seefelder Aach: a literature review. *Environmental Science Europe* 24:8