

MEPA Ref.: EPD/A/RD/10/210

Mr. Thomas Paris
Environment Protection Officer
Unit A – Env. Permitting & Industry
EPD – MEPA

18th January, 2011

Dear Mr Paris,

Please find below the revised comments of our BREF replies after we revised them together in the meeting held at your offices in November 2011. The replies that were changed are highlighted in red. A hard copy, signed and stamped has been sent by post to your offices.

Yours' Sincerely,

Ivan Bustos
Solea Pharma

Annex I: Comparison of processes at Solea Pharma with BREF for Organic Fine Chemicals (published August 2006).

Aspect of BAT	BAT	Status at Solea Pharma
Environmental management	Environmental management system (in-house or customised)	This will be obtained once the GMP system in Solea will have been implemented. The GMP system is expected to take till the end of this year to be implemented. Therefore the EMS will only be considered from the next year.
Integration of environmental considerations into process development	To provide an auditable trail for the integration of environmental, health and safety considerations into process development.	All EH&S Considerations are taken into account in the manufacturing batch records. The batch records are all archived for 5 years once the process has been terminated.
	To carry out a structured safety assessment for normal operation and to take into account effects due to deviations of the chemical process and deviations in the operation of the plant.	An H&S Risk Assessment has already been forwarded to the OHSA. This same assessment is revised on a yearly basis. The EH&S Officer in Gadea (Mr. Ildefonso Vaquero) will be in Malta in September to carry out the annual review.
	To establish and implement procedures and technical measures to limit risks from the handling and storage of hazardous substances and to provide sufficient and adequate training for operators who handle hazardous substances	This matter is still being developed. Currently one of the employees is being trained both in-house and externally in the area of H&S, in order to be able to handle hazardous substances handling and storage issues, amongst other things. An introduction to H&S we be started, followed by a NEBOSH certificate.
	To design new plants in such a way that emissions are minimised.	Whereas the process is considered to be a dynamic one with continuous improvements going on, a number of measures have been implemented to reduce emissions to the surroundings. These include the substitution of a liquid ring pump (emitting volatile organic compounds to the air and generating a water-waste mixture containing with VOCs) with an oil vacuum pump (a closed system where all the organic compounds condense and mix with oil, which is then treated as a hazardous waste).
	To design, build, operate and maintain facilities, where substances (usually liquids) which represent a potential risk of contamination of ground and groundwater are handled, in such a way that spill potential is minimised. Facilities have to be sealed, stable and sufficiently resistant against possible mechanical, thermal or chemical stress.	This has already been obtained, since in the case of spillage all chemicals in Solea will be contained within the perimeter in the wastewater reservoir, which has already been certified to be adequate.

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	To enable leakages to be quickly and reliably recognised.	Susceptible points of leakage are found in the drains beneath the ground of Solea. A drain leakage testing of the pipes was carried out by a third party shortly after the accident in Solea in 2009, and these were certified to be intact.
	To provide sufficient retention volumes to safely retain spills and leaking substances, fire fighting water and contaminated surface water in order to enable treatment or disposal.	This has already been obtained, since in the case of firewater, all liquid residues in Solea will be contained within the perimeter in the wastewater reservoir, which has already been certified to be adequate.
Enclosure of sources and airtightness of equipment	To contain and enclose sources and to close any openings in order to minimise uncontrolled emissions. Drying should be carried out by using closed circuits, including condensers for solvent recovery.	In this point a reference to a number of measures needs to be mentioned, amongst which are: -Brine condensers and oil pump in the ovens in order to carry out the drying step in a closed system. -Lids in the Nutsche filters -Air tight reactors -Revision of the Glass condensing system of the Reactors.
	To use recirculation of process vapours where purity requirements allow this.	A number of solvents, mainly methanol and acetone that are obtained from the distillation processes, are reutilised inside the plant for cleaning procedures.
	To minimise the volume flow, to close any unnecessary openings in order to prevent air being sucked to the gas collection system via the process equipment.	Along the process line a number of points where vapours are released have been revised and changed. These measures included: -All the reactors closed in an airtight manner -Contracting a third party for the revision of the glass unions in the condensers -Getting the Maintenance Technicians trained in Spain to revise and close leaks of the glass condensers -Lids for the Nutsche filters -Nitrogen Flowmeters to control the amount of nitrogen dispensed.
	To ensure the airtightness of process equipment, especially of vessels.	The air tightness of the equipment is part of the qualification that needs to be carried out, to comply with the GMP requirements. The protocol for this procedure will be finished by March of this year and will be applied in the plant by the end of this year.

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	To apply shock inertisation instead of continuous inertisation. Still, continuous inertisation has to be accepted due to safety requirements, e.g. where processes generate O ₂ or where processes require further loading of material after inertisation.	This kind of method is NOT POSSIBLE in our installations for health and safety reasons. Continuous inertisation is necessary to avoid any risks of explosions. This is obtained by ensuring a nitrogen-rich atmosphere at all times in a Class 0 ATEX-classified zone. These zones tend to be rich in vapours from distillation processes and the presence of oxygen creates an explosive hazard.
Layout of distillation condensers	BAT is to minimise the exhaust gas volume flows from distillations by optimising the layout of the condenser.	Three condensers in series have already been installed. However, the reduction of exhaust gases is being avoided by exchanging the liquid ring pumps with an oil pump.
Liquid addition to vessels, minimisation of peaks	BAT is to carry out liquid addition to vessels as bottom feed or with dip-leg, unless reaction chemistry and/or safety considerations make it impractical. In such cases, the addition of liquid as top feed with a pipe directed to the wall reduces splashing and hence, the organic load in the displaced gas. If both solids and an organic liquid are added to a vessel, BAT is to use solids as a blanket in circumstances where the density difference promotes the reduction of the organic load in the displaced gas, unless reaction chemistry and/or safety considerations make it impractical.	Dip-legs have been installed in reactors where chemical reactions take place, meaning RE01S, RE02S and RE04S.
	BAT is to minimise the accumulation of peak loads and flows and related emission concentration peaks by, e.g. optimisation of the production matrix and application of smoothing filters.	The extraction system in Solea Pharma, which collects both vacuum and extraction exhausts, lead to a scrubber. This allows for the destruction of the fumes released by the processes before these are released into the atmosphere. One example consists in the addition of Sodium Hydroxide solution, which counteracts any Hydrogen Chloride fumes that might be released from the processes. The quantity of solution to be added is according to the manufacturing process and the quantity charged is within a safety margin.

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Alternative techniques for product work-up	BAT is to avoid mother liquors with high salt content or to enable the work-up of mother liquors by the application of alternative separation techniques, e.g. membrane processes, solvent-based processes, reactive extraction, or to omit intermediate isolation.	Whilst Halogenated Aqueous Wastes (arising from the use of sodium chloride salt) compose less than 25% of the hazardous wastes produced, these are clearly identified and separated from the rest of the hazardous wastes. The HAWs are then shipped to a certified waste management dealer, that treats these wastes accordingly.
	BAT is to apply countercurrent product washing where the production scale justifies the introduction of the technique.	N/A
Vacuum, cooling and cleaning	BAT is to apply water-free vacuum generation by using, e.g. dry running pumps, liquid ring pumps using solvents as the ring medium or closed cycle liquid ring pumps. However, where the applicability of these techniques is restricted, the use of steam injectors or water ring pumps is justified.	An oil pump has been recently purchased and will soon be installed.
	For batch processes, BAT is to establish clear procedures for the determination of the desired end point of the reaction.	A Control in-process by TLC or HPLC has been established for every reaction.
	BAT is to apply indirect cooling. However, indirect cooling is not applicable for processes which require the addition of water or ice to enable safe temperature control, temperature jumps or temperature shock. Direct cooling can also be required to control “run away” situations or where there are concerns about blocking heat exchangers.	With regards to temperature control, as a general rule indirect cooling is used, whereby a mixture of Monoethylene Glycol and Water (60:40) is added in the jacket of the reactor. Therefore the cooling solution never comes into contact with the contents of the reactor. The solution is in a closed circuit, thus enabling it to be re-cooled and reused several times. This proves to be a very efficient manner of cooling and at the same time a safe one. However, in highly exothermic reactions it is noteworthy mentioning that one system of direct cooling is used in Solea Pharma, consisting in the injection of liquid/gaseous nitrogen into the reactor. This method is used because of the sudden release of exothermic heat, which would otherwise be incapable of controlling through the indirect cooling system.
	BAT is to apply a pre-rinsing step prior to rinsing/cleaning of equipment to minimise organic loads in wash-waters. Where different materials are frequently transported in pipes, the use of pigging technology represents another option to reduce product losses within cleaning procedures.	This procedure is already implemented in Solea.

Aspect of BAT	BAT	Status at Solea Pharma
Mass balances and analysis of waste streams	BAT is to establish mass balances for VOCs (including CHCs), TOC or COD, AOX or EOX (Extractable Organic Halogen) and heavy metals on a yearly basis.	The first emission tests have been carried out in September and December 2010. Two more tests are expected for March and June 2011. Once the results will be completed, one whole report will be handed.
	BAT is to carry out a detailed waste stream analysis in order to identify the origin of the waste stream and a basic data set to enable management and suitable treatment of exhaust gases, waste water streams and solid residues.	Stream Analysis is determined in the manufacturing batch records. Once these are produced all wastes are labelled accordingly, therefore giving all the necessary information for identification and traceability.
	<p>BAT is to assess at least the parameters given in Table I for waste water streams, unless the parameter can be seen as irrelevant from a scientific point of view.</p> <p><i>Standard parameters</i></p> <p>Volume per batch Batches per year Volume per day Volume per year COD or TOC BOD5 pH Bioeliminability Biological inhibition, including nitrification</p> <p><i>Other parameters (where they are expected)</i></p> <p>AOX CHCs Solvents Heavy metals Total N Total P Chloride Bromide SO₄²⁻ Residual toxicity</p>	The parameters analysed are those required by the WSC, which are analysed on an annual basis or daily basis, depending on the requirements.

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Monitoring of emissions to air	Emission profiles should be recorded instead of levels derived from short sampling periods. Emission data should be related to the operations responsible. For emissions to air, BAT is to monitor the emission profile which reflects the operational mode of the production process.	Such a procedure is not feasible currently in our plant. This option can be considered in the future, but for the moment only the annual measurements will be carried out.
	In the case of a non-oxidative abatement/recovery system, BAT is to apply a continuous monitoring system (e.g. Flame Ionisation Detector, FID), where exhaust gases from various processes are treated in a central recovery/abatement system.	Such a procedure is not feasible currently in our plant. This option can be considered in the future, but for the moment only the annual measurements will be carried out.
	BAT is to individually monitor substances with ecotoxicological potential if such substances are released.	N/A
Individual volume flows	BAT is to assess the individual exhaust gas volume flows from process equipment to recovery/abatement systems.	An extraction system is already in place. Any raw materials having risk phrases R50 to R57 will be measured individually.
Re-use of solvents	BAT is to re-use solvents as far as purity requirements allow. This is carried out by using the solvent from previous batches of a production campaign for future batches, collecting spent solvents for on-site or off-site purification and re-use, or collecting spent solvents for on-site or off-site utilisation of the calorific value.	Acetone is already being recovered and reutilised for cleaning purposes.
Selection of VOC treatment techniques	One or a combination of techniques can be applied as a recovery/abatement system for a whole site, an individual production building, or an individual process. This depends on the particular situation and affects the number of point sources. BAT is to select VOC recovery and abatement techniques according to the flow scheme in Figure I.	An extraction system leading to the scrubber is already in place.
Non-oxidative VOC recovery or abatement: achievable emission levels	Where non-oxidative VOC recovery or abatement techniques are applied, BAT is to reduce emissions to the levels given in Table II.	Pending of air emissions results.
Thermal oxidation/incineration or catalytic oxidation:	Where thermal oxidation/incineration or catalytic oxidation are applied, BAT is to reduce VOC emissions to the levels given in Table III.	N/A

Aspect of BAT	BAT	Status at Solea Pharma
achievable emission levels		
Recovery/abatement of NO_x	For thermal oxidation/incineration or catalytic oxidation, BAT is to achieve the NO _x emission levels given in Table IV and, where necessary, to apply a DeNO _x system (e.g. SCR or SNCR) or two stage combustion to achieve such levels.	The production of NO _x gases results only from the combustion of the fuel oil for the boiler. The amount of such gases produced is expected to be minimal, and thus not worth of consideration. Kindly refer to the emission testing results.
	For exhaust gases from chemical production processes, BAT is to achieve the NO _x emission levels given in Table IV and, where necessary to apply treatment techniques such as scrubbing or scrubber cascades with scrubber media such as H ₂ O and/or H ₂ O ₂ to achieve such levels. Where NO _x from chemical processes is absorbed from strong NO _x streams (about 1000 ppm and higher) a 55 % HNO ₃ can be obtained for onsite or off-site re-use. Often, exhaust gases containing NO _x from chemical processes also contain VOCs and can be treated in a thermal oxidiser/incinerator, e.g. equipped with a DeNO _x unit or built as a two stage combustion (where already available on-site).	
Recovery/abatement of HCl, Cl₂, HBr, NH₃, SO_x and cyanides	HCl can be efficiently recovered from exhaust gases with high HCl concentrations, if the production volume justifies the investment costs for the required equipment. Where HCl recovery is not preceded by VOC removal, potential organic contaminants (AOX) have to be considered in the recovered HCl. BAT is to achieve the emission levels given in Table VI and, where necessary, to apply one or more scrubbers using suitable scrubbing media.	The extraction system in Solea Pharma, which leads the fumes from the reactors to a scrubber. This allows for the destruction of the fumes released by the processes before these are released into the atmosphere. One example consists in the addition of Sodium Hydroxide solution, which counteracts any Hydrogen Chloride fumes that might be released from the processes. The production of such gases is expected to be minimal, and thus not worth of consideration. Kindly refer to the emission testing results.
Removal of particulates	Particulates are removed from various exhaust gases. The choice of recovery/abatement systems depends strongly on the particulate properties. BAT is to achieve particulate emission levels of 0.05 – 5 mg/m ³ or 0.001 – 0.1 kg/hour and, where necessary, to apply techniques such as bag filters, fabric filters, cyclones, scrubbing, or wet electrostatic precipitation (WESP) in order to achieve such levels.	Since the exhaust air goes through the outlet filtering system of the HVAC, the production of such particulate matter is expected to be minimal, and thus not worth of consideration. Kindly refer to the emission testing results.

Aspect of BAT	BAT	Status at Solea Pharma
Typical waste water streams for segregation and selective pretreatment	BAT is to segregate and pretreat or dispose of mother liquors from halogenations and sulphochlorinations.	This procedure is already in place.
	BAT is to pretreat waste water streams containing biologically active substances at levels which could pose a risk either to a subsequent waste water treatment or to the receiving environment after discharge.	N/A
	BAT is to segregate and collect separately spent acids, e.g. from sulphonations or nitrations for on-site or off-site recovery or to apply BAT about pretreatment of refractory organic loadings.	N/A
Pretreatment of waste water streams with refractory organic loadings	BAT is to segregate and pretreat waste water streams containing relevant refractory organic loadings according to this classification: Refractory organic loading is not relevant if the waste water stream shows a bioeliminability of greater than about 80 - 90 %. In cases with lower bioeliminability, the refractory organic loading is not relevant if it is lower than the range of about 7.5 - 40 kg TOC per batch or per day. For the segregated waste water streams, BAT is to achieve overall COD elimination rates for the combination of pretreatment and biological treatment of >95 %.	This procedure is already in place.
Recovery of solvents from waste water streams	BAT is to recover solvents from waste water streams for on-site or off-site re-use, where the costs for biological treatment and purchase of fresh solvents are higher than the costs for recovery and purification. This is carried out by using techniques such as stripping, distillation/rectification, extraction or combinations of such techniques.	N/A
	BAT is to recover solvents from waste water streams in order to use the calorific value if the energy balance shows that overall natural fuel can be substituted.	N/A
Removal of halogenated compounds from waste water streams	BAT is to remove purgeable CHCs from waste water streams, e.g. by stripping, rectification or extraction and to achieve levels given in Table VII.	Non-Halogenated and Halogenated Wastes are separated at source.

Aspect of BAT	BAT	Status at Solea Pharma
	BAT is to pretreat waste water streams with significant AOX loads and to achieve the AOX levels given in Table VII in the inlet to the on-site biological Waste Water Treatment Plant (WWTP) or in the inlet to the municipal sewerage system.	A COD limit still is to be established. Recently a reference limit of 900mg/L has been given as a reference point to which compliance needs to be achieved.
Removal of heavy metals from waste water streams	BAT is to pretreat waste water streams containing significant levels of heavy metals or heavy metal compounds from processes where they are used deliberately and to achieve the heavy metal concentrations given in Table VII in the inlet to the on-site biological WWTP or in the inlet to the municipal sewerage system. If equivalent removal levels can be demonstrated in comparison with the combination of pretreatment and biological waste water treatment, heavy metals can be eliminated from the total effluent using only the biological waste water treatment process, provided that the biological treatment is carried out on-site and the treatment sludge is incinerated.	N/A
Free cyanides	BAT is to recondition waste water streams containing free cyanides in order to substitute raw materials where technically possible. BAT is to pretreat waste water streams containing significant loads of cyanides and to achieve a cyanide level of 1 mg/l or lower in the treated waste water stream or to enable safe degradation in a biological WWTP.	N/A
Biological waste water treatment	BAT is to treat effluents containing a relevant organic load, such as waste water streams from production processes, rinsing and cleaning water, in a biological WWTP.	N/A

Aspect of BAT	BAT	Status at Solea Pharma
	<p>BAT is to ensure that the elimination in a joint waste water treatment is overall not poorer than in the case of on-site treatment. For biological waste water treatment, COD elimination rates of 93 – 97 % are typically achievable as a yearly average. It is important that a COD elimination rate cannot be understood as a standalone parameter, but is influenced by the production spectrum (e.g production of dyes/pigments, optical brighteners, aromatic intermediates which create refractory loadings in most of the waste water streams on a site), the degree of solvent removal and the degree of pretreatment of refractory organic loadings. Depending on the individual situation, retrofitting of the biological WWTP is required in order to adjust, e.g. treatment capacity or buffer volume or the application of a nitrification/denitrification or a chemical/mechanical stage.</p>	N/A
	<p>BAT is to take full advantage of the biological degradation potential of the total effluent and to achieve BOD elimination rates above 99 % and yearly average BOD emission levels of 1 - 18 mg/l. The levels relate to the effluent after biological treatment without dilution, e.g. by mixing with cooling water. BAT is to achieve the emission levels given in Table VIII.</p>	
Monitoring of the total effluent	<p>BAT is to regularly monitor the total effluent to and from the biological WWTP.</p>	N/A
	<p>BAT is to carry out regular biomonitoring of the total effluent after the biological WWTP where substances with ecotoxicological potential are handled or produced with or without intention.</p>	N/A
	<p>Where residual toxicity is identified as a concern (e.g. where fluctuations of the performance of the biological WWTP can be related to critical production campaigns), BAT is to apply online toxicity monitoring in combination with online TOC measurement.</p>	N/A

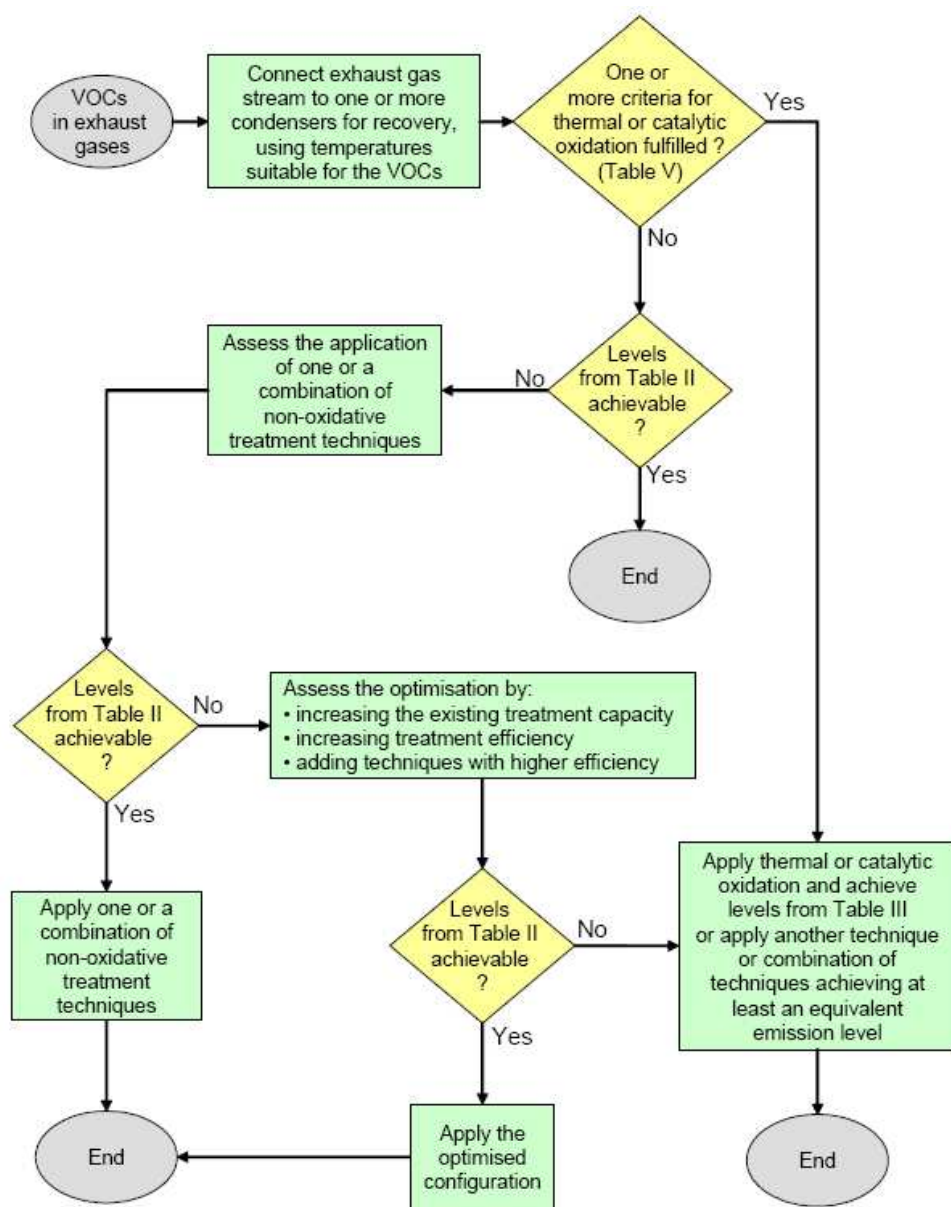


Figure I: BAT for the selection of VOC recovery/abatement techniques

Parameter	Average emission level from point sources*
Total organic C	0.1 kg C/hour or 20 mg C/m ³ **
* The averaging time relates to the emission profile, the levels relate to dry gas and Nm ³	
** The concentration level relates to volume flows without dilution by, e.g. volume flows from room or building ventilation	

Table II: BAT associated VOC emission levels for non-oxidative recovery/abatement techniques

Thermal oxidation/incineration or catalytic oxidation	Average mass flow kg C/hour		Average concentration mg C/m ³
Total organic C	<0.05	or	<5
The averaging time relates to the emission profile, levels relate to dry gas and Nm ³			

Table III: BAT associated emission levels for total organic C for thermal oxidation/incineration or catalytic oxidation

Source	Average kg/hour [*]	or	Average mg/m ³ [*]	Comment
Chemical production processes, e.g. nitration, recovery of spent acids	0.03 – 1.7		7 – 220 ^{**}	The lower end of the range relates to low inputs to the scrubbing system and scrubbing with H ₂ O. With high input levels, the lower end of the range is not achievable even with H ₂ O ₂ as the scrubbing medium
Thermal oxidation/incineration, catalytic oxidation	0.1 – 0.3		13 – 50 ^{***}	
Thermal oxidation/incineration, catalytic oxidation, input of nitrogenous organic compounds			25 – 150 ^{***}	Lower range with SCR, upper range with SNCR
[*] NO _x expressed as NO ₂ , the averaging time relates to the emission profile				
^{**} Levels relate to dry gas and Nm ³				
^{***} Levels relate to dry gas and Nm ³				

Table IV: BAT associated NO_x emission levels

	Selection criteria
a	The exhaust gas contains very toxic, carcinogenic or cmr category 1 or 2 substances, or
b	autothermal operation is possible in normal operation, or
c	overall reduction of primary energy consumption is possible in the installation (e.g. secondary heat option)

Table V: Selection criteria for catalytic and thermal oxidation/incineration

Parameter	Concentration		Mass flow
HCl	0.2 – 7.5 mg/m ³	or	0.001 – 0.08 kg/hour
Cl ₂	0.1 – 1 mg/m ³		
HBr	<1 mg/m ³		
NH ₃	0.1 – 10 mg/m ³		0.001 – 0.1 kg/hour
NH ₃ from SCR or SNCR	<2 mg/m ³		<0.02 kg/hour
SO _x	1 – 15 mg/m ³		0.001 – 0.1 kg/hour
Cyanides as HCN	1 mg/m ³		3 g/hour

Table VI: BAT associated emission levels for HCl, Cl₂, HBr, NH₃, SO_x and cyanides

Parameter	Yearly average	Unit	Comment
AOX	0.5 - 8.5	mg/l	The upper range relates to cases where halogenated compounds are processed in numerous processes and the corresponding waste water streams are pretreated and/or where the AOX is very bioeliminable
Purgeable CHCs	<0.1		Alternatively achieve a sum concentration of <1 mg/l in the outlet from pretreatment
Cu	0.03 - 0.4		The upper ranges result from the deliberate use of heavy metals or heavy metal compounds in numerous processes and the pretreatment of waste water streams from such use
Cr	0.04 - 0.3		
Ni	0.03 - 0.3		
Zn	0.1 - 0.5		

Table VII: BAT associated levels in the inlet to the on-site biological WWTP or in the inlet to the municipal sewerage system

Parameter	Yearly averages*		Comment
	Level	Unit	
COD	12 - 250	mg/l	
Total P	0.2 - 1.5		The upper range results from the production of mainly compounds containing phosphorus
Inorganic N	2 - 20		The upper range results from production of mainly organic compounds containing nitrogen or from, e.g. fermentation processes
AOX	0.1 - 1.7		The upper range results from numerous AOX relevant productions and pretreatment of waste water streams with significant AOX loads
Cu	0.007 - 0.1		The upper ranges result from the deliberate use of heavy metals or heavy metal compounds in numerous processes and the pretreatment of waste water streams from such use
Cr	0.004 - 0.05		
Ni	0.01 - 0.05		
Zn	– 0.1		
Suspended solids	10 - 20		
LID _F	1 - 2	Dilution factor	Toxicity is also expressed as aquatic toxicity (EC ₅₀ levels)
LID _D	2 - 4		
LID _A	1 - 8		
LID _L	3 - 16		
LID _{EU}	1.5		

* The levels relate to the effluent after biological treatment without dilution, e.g. by mixing with cooling water

Table VIII: BAT for emissions from the biological WWTP