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New drug pollution: risks and solution

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TECHNICAL SYNTHESIS

New drug pollution: risks and solution

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Résumé

En dépit de leurs effets bénéfiques, les médicaments représentent une source de pollution importante pour l'environnement aquatique et terrestre. En France, plus de 3000 substances se retrouvent dans les stations d'épurations, où elles sont éliminées tant bien que mal. Le développement des techniques d'analyses et des procédés de traitement des eaux usées a permis de mieux cerner l'impact de ces molécules et d'apporter des solutions concrètes. Ainsi, les recherches entreprises concernant le risque écotoxicologique ont mises en évidences des effets non souhaités sur un certain nombre d'organisme aquatique. Cependant, les études menées restent sporadiques et les données récoltées parcellaires. Ce travail de synthèse s'intéresse plus particulièrement au cas de la vallée de la Drôme, où les sources de pollution chimique et les issues possibles seront abordées au cours de ce dernier.

Mots clés : micropolluants, risque ecotoxicologique et sanitaire, procédés de traitement, chimie analytique, vallée de la Drôme,

Abstract

Despite of their beneficial effects, drugs are a major source of pollution for both aquatic and terrestrial environments. In France, more than 3000 substances are found in wastewater treatment plants, where they are removed to various degrees. The development of analytical techniques and wastewater treatment processes have enabled a better understanding of molecular impacts and provided practical solutions. In fact, studies on the ecotoxicolocal risks have shown unwanted effects on a certain number of aquatics organisms. Nevertheless, studies are sporadic and the acquired data is fragmented. This work is focused on the Drôme valley, where the source of chemical pollution and the possible outcomes will be adressed.

Key words : micropollutants, ecotoxicological and health risk, treatment process, analytical chemistry, Drôme valley

Summary

List of abbreviations

AFSSA	Agence française de sécurité sanitaire des aliments
AMPERES	Analyse des micropolluants prioritaires et émergents dans les eaux
ANSES	superficiellesAgence nationale de sécurité sanitaire de l'alimentation, de l'environnement et
ANSM	du travailAgence nationale de sécurité du médicament et des produits de santé
ARS	Agence régionale de santé
BOD_5	Biochemical oxygen demand during 5 days
BRGM	Bureau de recherches géologiques et minières
BTEX	Benzène, toluène, éthylbenzène and xylène
CE	Capillary electrophoresis
CEAEQ	Centre d'expertise en analyse environnementale du Quebec
COD	Chemical oxygen demand
COHV	Composé organique hautement volatile
DDASS	Direction départementale des affaires sanitaires et sociales
DGS	Direction générale de la santé
DRAAF	Direction régionale de l'alimentation, de l'agriculture et de la forêt
DSV	Direction des services vétérinaires
EDCH	Eaux destinées à la consommation humaine
EE2	17α-Ethinylestradiol
ELISA	Enzyme-linked immunosorbent assay (dosage d'immunoadsorption par enzyme
ENGREF	liée)Ecole nationale du génie rural, des eaux et des forêts
ENIMED	Drugs unintentioned effects
GC	Chromatographie en phase gazeuse
KNAPPE	Pharmaceutical products in environmental waters
K_{ow}	Octanol-water coefficient
LC	Liquid chromatography
LD_{50}	Median letal dose
LOAEL	Lowest observed adverse effect level
MAP	Marketing authorisation pursuant
MBR	Membrane bioreactors
MIS	Matter in suspension
MRM	Multiple réaction monitoring
MS	Mass spectrometry
MS-MS	Tandem mass spectrometry
NOAEL	No observable adverse effect level
ONEMA	Office nationale de l'eau et des milieux aquatiques
PCB	Polychlorobiphényle
SAGE	Schéma d'aménagement et de gestion des eaux
SATESE	Service d'assistance technique aux exploitants de station d'épuration
SIGMA	Syndicat Intercommunal de Gestion Mutualisée de l'Assainissement
SMRD	Syndicat mixte de la rivière Drôme
TDR	Toxicological data of reference
UV	Ultraviolet
WWTP	Wastewater treatment plant

Introduction

The definition of a drug, according to the Article L5111-1 of the French Public Health Code is: "By a medicine we mean any substance or compound presented as possessing curative or preventive properties in regard to human or animal diseases or any substance or compound that may be administered to humans or animals in order establish a medical diagnosis or restore, correct or modify their organic functions."
The presence of a drug intended for humans or animals has appeared for a few years now, in both terrestrial and aquatic environments. From this assumption, several questions arise, both to the introduction method and the impact of those molecules on the environment and human health. This assumption has been made possible thanks to the development of chemical analysis methods. Finally, if contaminations of potential impacts are demonstrated, decision-makers and administrators must offer concrete solutions to deal with this problem. This bibliographic synthesis intends to address the topics mentioned above, accompanied by the case study of the Drôme catchment area.

Introduction method in the environment of the drug and cosmetic pollution

Nowadays, there are two main causes for the presence of medicinal molecules. Indeed, these residues of pharmacological substances can come from humans and animals. Regarding substances from the cosmetic industry, hundreds of molecules found in the formulation of those products can have a harmful effect, comparable to those of the pharmaceutical substances. For cosmetic substances, the study will be mainly focused on the effects on the endocrinal system (parabens, UV filter)

Drugs designed for human use

Studied molecules

The number of drugs designed for human use represents about 3000 biologically active molecules. Those molecules can be classified according to the pharmacologic effects on different parts of human body. The main ones are pain-killing or analgesic substances, antibiotics, anticonvulsants, anxiolytics and lipid-lowering drugs.

Other substances must be taken into account, even if the observed effects in the environment are significantly lower. Those are β-blokers, anti-cancer drugs and iodinated contrast.

Those molecules can cause metabolites, that is to say the substances mentioned above. They can be created:

- After a transformation in the organism by enzymatic reaction (Mompelat and al., 2009)
- After going through a water treatment plant (STEP), especially because of ozone treatment (Ternes and al., 2003).
- After degradation by the natural environment when exiting STEP (Passananti and al., 2013).

All the listed molecules are set out in Annex 1

Introduction of drugs for human use

Drug residues are mainly from domestic consumption in urban areas, hospital discharges and chemical and pharmaceutical industries (Canchado, 2012). Before being discharged into the environment, these compounds undergo a purification step, which may take place:

- After crossing the WWTP. This strongly influences the chemical composition of water discharged into the environment (Soulier and al., 2011).
- After purification by on-site sanitation systems, septic tanks for example, whose role in the contamination of soils has already been highlighted (Conn and al., 2006).

Drugs designed for veterinary use

Studied Molecules

Pharmacologically active substances on animals are represented by hormones, pesticides, antifungals and antibiotics, which are the most studied pharmacological class (Algros, 2005).

Introduction of drugs for veterinary use

In veterinary medicine, drugs may directly or indirectly contaminate surface water and groundwater:

- Indirectly, by infiltration after the spreading agriculture animal', manure on land (Chevance and Moulin, 2013).
- Directly, by fish farming whose livestock water is not purified. In this case, medicinal products for veterinary use are either added to the food eaten by the fish themselves (Perrot, 2000), or used in the preventive chemical treatment of their living environment (Veldhoen and al., 2012). The assumption here is a lack of wastewater treatment.

Compounds from cosmetic products

These compounds represent a significant route of entry with 7000 ingredients used, for which little data is available on their presence in the environment (Dulio and al., 2009). This is partly due to a lack of information on the formulation of these products on the market. The compounds selected for this study are parabens, UV screens, and musks (Geara-Matta and al., 2011). There are two pathways for these compounds:

- Through WWTP effluent.
- Directly to the environment, through bathing water. This is the case of nanomaterials in sunscreens that are found in the Mediterranean (Bertholomey, 2011).

Discussion about entry methods

The common pathway for contamination of natural waters is the lack of information on the exact amounts released in the environment. There are several possible explanations for this:

- The opacity of pharmaceutical companies on sales statistics of products available in pharmacies. Numerous studies are based on the amounts found in the environment with which a pharmacological classification can be established (Figure 2).
- The behavior of drug users. Indeed, substances sold are not necessarily completely used. In principle, non-recyclable and non-recoverable waste is disposed of by burial in accordance with strict environmental standards. However, one study showed that some of households surveyed in the UK eliminated unused drugs directly through the garbage, sinks and toilets (Bound and Voulvoulis, 2005).
- The lack of knowledge about the metabolites of active substances and their degradation by STEP, on-site sanitation and soil (Dulio and al., 2009).

From a qualitative point of view, differences between drugs according to their uses are noted:

- Data about the amounts of antibiotics consumed in France are more common for human than veterinary use (Algros, 2005).
- The following human dynamics temporally continuous and spatially localized pollution. This is not the case for animal pollution, fully diffuse in time and space.
- Veterinary drugs may be denied their marketing authorisation pursuant (MAP) if the ecotoxicological risk is established folder. This is not always the case for a medicinal product for human use, where the molecule can be administered to patients experiencing treatment failure without MAP (Virlouvet, 2006).
- Guideline (EMEA/CHMP/4447/00) oversees the environmental risk assessment of medicinal products for human use (EMEA, 2006). The latter does not take into account the various metabolites and excipients, which is not the case for veterinary medicinal products (Idder, 2012).

A schematic description of different origins and modes of contamination of the aquatic environment is presented below (Figure 1).

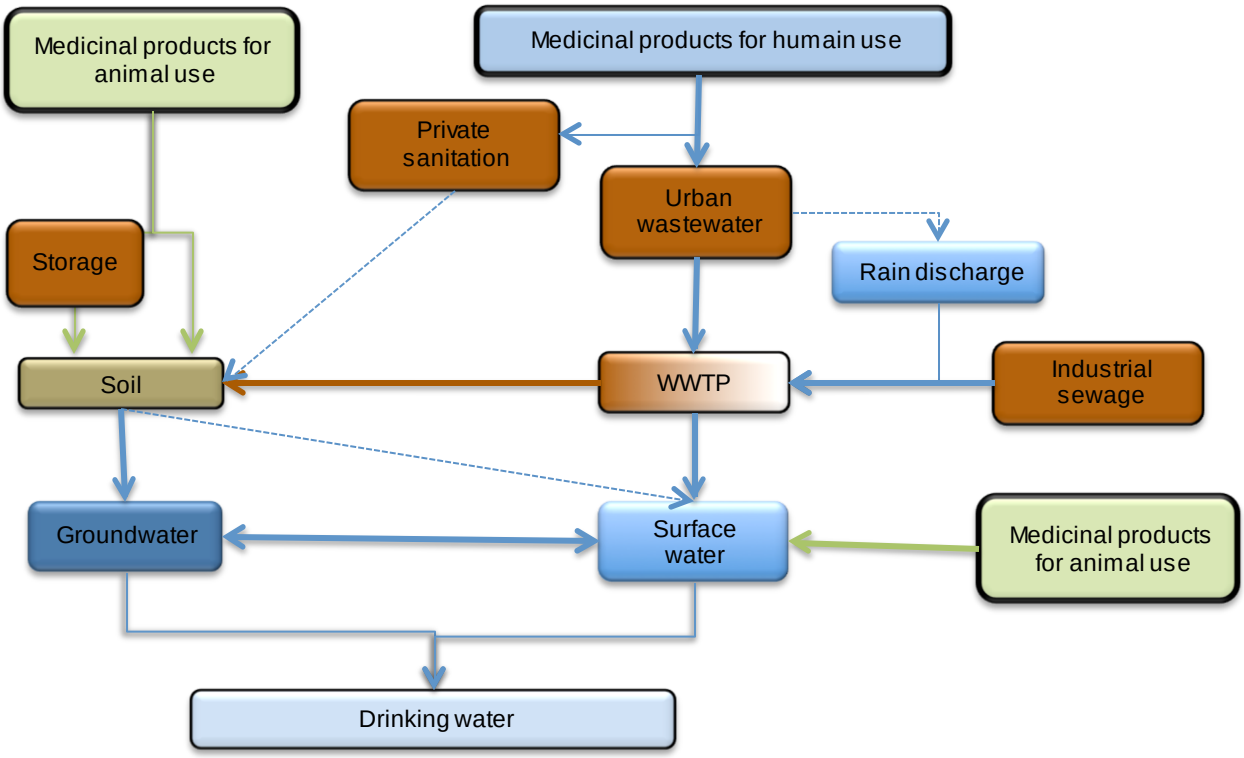

Figure 1: Pathways of medicinal products for human and veterinary use in water intended for human consumption (Casellas et al., 2010)

This diagram shows a further difference between drug known origins. Indeed, human drugs almost always undergo a purification step via a WWTP or on-site sanitation before the final release in the environment. This is not the case for veterinary medicines in contact with the environment without any treatment or after a very brief purification step (Roque d'Orbcastel, 2008). Major drug classes involved are shown below (Figure 2).

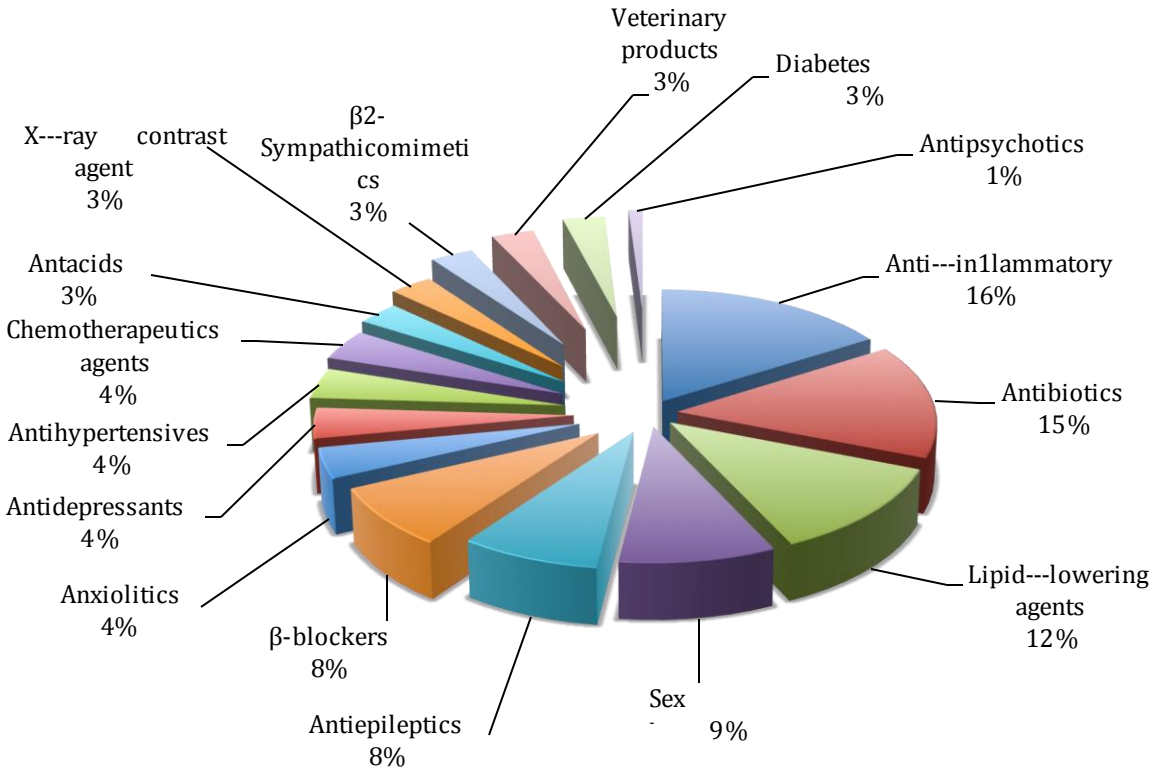

Figure 2: Therapeuticclasses detected in the environment, expressed in relative percentage. Data collected from 134 articles published between 1997 and 2009(Santos et al., .

This chart shows that more than half of the substances found (52%) belong to only four categories: anti-inflammatory drugs, antibiotics, lipid-lowering agents and sex hormones.

Impact of pharmaceutical substances

Risk definition

In this review, it is a question of risk to human activities, as opposed to natural risks. It can be expressed as follows:

$$(\ Risk = (Probability) \times (Gravity)$$

The probability is the potential for an accident to happen. The severity measure the importance of adverse effects, in our case, on the environment and on human (UVED, 2006). The result of this study will look at the risk assessment of pollution of pharmaceuticals in the environment (ecotoxicology) and for human health.

Ecotoxicological risk assessment

Ecotoxicological risk assessment can be defined as a process of identification, comparison and analysis of descriptive measures to make an overall judgment on the environmental behavior with an exogenous source pollution (CEAEQ, 1997). By definition, a drug has an effect on humans or animals at low doses. This means that the impact of the active ingredient on the terrestrial and aquatic environment is possible, insofar as the present organisms are potentially sensitive. To assess this risk, a knowledge of exposure doses and toxicological data is needed. The difficulty lies in the evaluation of these parameters for a molecule or group of molecules on a target organism. Currently, several approaches allow access to the toxicity of molecules impacting the environment:

- The estimation of acute and chronic toxicity of a single molecule.

- The evaluation of the "cocktail effect" of a complex matrix.

In this context, various research programs have been launched to assess the environmental impact (ENIMED, KNAPPE program) of a number of biologically active substances.

Acute toxicity

The identification of this parameter is based on the lethal dose at which 50% of the population exposed to a particular substance dies (LD50). However, to obtain this information, the target organisms (algae, fish, plankton ...) are exposed to very high concentrations (mg.L-1) for a very short time. The acute toxicity data was compiled by several authors (Halling-Sørensen and al., 1998). These show a list of 100 pharmaceuticals substances with acute toxicity proved. A more thorough study has shown that the most harmful drug classes in this category are antidepressants, antipsychotics and anti-bacterials (Webb, 2001). This model, although not representative of the conditions of environmental exposures, remains relevant in the case of accidental pollution (chemical spill in large quantities).

Chronic toxicity

This valuation model takes into account long-term impacts, which is consistent with more current situations. Indeed, the molecules are tested for a longer period at lower concentrations. The evaluation of this data characterizes the maximum concentration causing no significant effect on a population observed (NOAEL). However, the collected data is often incomplete. This is particularly related to the complexity of the life cycle of pharmaceutical molecules once ingested by a living organism in the receiving environment. A molecule has nevertheless been very well studied, it is the synthetic hormone EE2 contained in birth control pills (Länge and al., 2001 ; Parrott and Blunt, 2005). An estrogenic activity of this hormone may cause feminization of fish populations studied. Since then, other synthetic hormones, and many substances belonging to varied drug classes have been identified for chronic toxicity on different target aquatic organisms (Crane and al., 2006).

Mix effect or "cocktail effect"

For several years, work to determine the joint action of two or more molecules in an organism have been developed. A number of synergistic or antagonistic effects have been characterized. This is the case of the combined action of a mixtures of clofibrinic acid/carbamazepine and diclofenac/ibuprofen as growth inhibitors on small shellfish and algae (Cleuvers, 2003 ; Cleuvers, 2004). Sulfamethoxazole/trimethoprim mixture demonstrated the same effect in green algae (Eguchi and al., 2004). Existing works also highlight a synergistic cytotoxic activity on liver cells of rainbow trout of the fluoxetine / paroxetine and tonalide / celestonide mixtures (Porte and al., 2009).

Health risk assessment

Work commissioned by the French DGS at the ANSES and ANSM was performed on the health risk assessment using water intended for human consumption. This is to define a general evaluation of the risk method. The main steps of this method can be summarized as follows:

- Molecule characterization.
- Identification of metabolites formed in humans or animals.
- Identification of transformation products formed in the environment and in water purification industries.
- Assessment of human exposure via water intended for human consumption.
- Biological effects
- Determination of toxicological data of reference (TDR).
- Determination of a guideline value.

- Risk assessment.

However, several questions can be raised.

- Must we not take into account the spatial and temporal variations in exposure doses?
- Can we extrapolate the data on chronic toxicity from the marketing authorization dossier for much lower exhibition doses?
- Was selecting carbamazepine and Danofloxacin the most appropriate choice for this study?

This report concludes with a negligible risk for ingestion of carbamazepine and Danofloxacin via water intended for human consumption for human health (ANSES and ANSM, 2013).

Discussion on the potential effects of targeted molecules

It seems quite possible that a number of molecules studied have the ability to act on the endocrine system of aquatic organisms. The most commonly cited molecule is the synthetic hormone EE2. Work on the fathead minnow helped highlight adverse effects on growth, development and reproduction of this species after exposure to low concentrations of the hormone EE2 (Länge and al., 2001; Parrott and Blunt, 2005). However, it is necessary to clarify that many molecules are potentially interfering substances in the hormonal system of living beings. This is the case for example of bisphenol A, phthalates, PCB or the brominated flame retardant agents.

Technological developments

Progress made in the field of analytical chemistry revealed the presence of micropollutants in aquatic environments, also identified as emerging pollutants. These technological advances are characterized in particular by the use of more efficient appliances, more varied usage patterns and more specific methods. Indeed, once the quantification threshold limit reached, a considerable amount of molecules could be assayed, which include pharmaceutical and cosmetic products.

Chemical analysis techniques

Currently, the most effective devices detect and identify certain molecules at a concentration of 1ng.L-1. Today, several techniques are used to precisely examine the state of contamination of soils and waterways due to advances attributed to improved analytical methods (Buchberger, 2011). More particularly, immunoassay techniques and those coupling chromatography or electrophoresis with mass spectrometry.

Principle of coupling techniques

Principle of gas chromatography coupled with mass spectrometry (GC-MS)

The equipment used in chemical analysis are techniques for coupling:

- The separation of molecules of an aqueous matrix by gas chromatography (GC) or liquid (LC). The choice of technique depends on the molecules analyzed (physicochemical properties).
- Quantification of the latter by mass spectrometry (MS).

In this case, the molecules to be analyzed are first volatilized to be mixed with a gas (usually helium). This carrier gas (mobile phase) vehicle analytes through an analytical column (stationary phase). The migration velocity of the molecules in the column depends on the volatility and interactions with the stationary phase. The analytes are then detected at the outlet of column by their retention times. After ionization in the mass spectrometer, molecular ions are identified by their spectrum (Bouchonnet, 2009). Note that prior extraction is often necessary to limit the number of molecules on the mass spectrum (Robles-Molina and al., 2013).

Principle of liquid chromatography coupled with mass spectrometry (LC-MS)

This technique differs from the previous one by the use of a solvent or solvent mixture for elution in the column. The use of tandem mass spectrometry (MS/MS) has contributed significantly to the development of methods on these devices. This technique is especially suitable for the analysis of components in trace amounts in a complex matrix. In addition, various modes of use are possible by tandem mass spectrometry (Hoffmann and Stroobant, 2005).

What coupling for which compounds?

For the study of highly volatile compounds (dioxins, furans, residual solvents ...), the choice of GC-MS is unequivocal. As against, for analysis of large molecules (peptides, proteins) and very polar molecules (drugs) LC-MS is most suitable. A comparison between the two techniques revealed a significant difference in the financial cost and the complexity of the methodologies developed on LC-MS. However, a step of chemical derivatization is often necessary during the preparation of the sample on GC-MS, which makes this step. Finally, LC-MS is frequently affected by matrix effects, which complicates the interpretation of the spectra (Van Eeckhaut and al., 2009).

Principle of EC-MS

Capillary electrophoresis (CE) is a complementary technique chromatographic methods presented above. The separation of compounds resulting from transport mechanisms distinct:

- The electromigration phenomenon describing the movement of a charged particle in an electric field.
- The electroosmosis, corresponding to the flow of a liquid filled in a capillary submitted to a tangential electric field.

Capillary electrophoresis comprises several separation modes, depending on the electrical charge and molecular weight (free electrophoresis), hydrophobicity (micellar electrophoresis), mass (gel electrophoresis) or isoelectric point (isoelectric focusing) (Taverna and al., 2003). As with previous techniques, mass spectrometry is used for the determination of the compounds after identifying them.

Immunochemical methods

These methods are based on the recognition between an antigen and an antibody, thereby specifically identifying a desired molecule. Two main methods of immunochemical analysis can be used:

- A qualitative method: immunodiffusion. Antibodies are available on an agar with wells in which antigens are placed. When the antigen / antibody complex is formed, it precipitates. The result is thus observed visually.
- A quantitative method: ELISA (Enzyme-linked immunosorbent assay). The protocol is identical to that described above. The only difference is that a second labeled antibody (with a fluorochrome or an enzyme) is added after the complex formed. Once the substrate binds to the enzyme or the fluorescent signal that is emitted, the formed colored product can be quantified by spectrophotometry (Lafont, 2001).

Applications

Methods continue to be developed on the GC-MS assay for micropollutants (Azzouz and al., 2010). This is due to the ease of implementation and reproducibility of the past (Martínez and al., 2013).

The LC-MS/MS method is currently used in particular for the determination of antiinflammatories, analgesics, lipid regulators, of β-blockers and antibiotics in the aquatic environment (Petrović and al., 2005). Recently, this technique was used for the separation of compounds with molecular structures that are very close, like the molecules belonging to the

family of steroids (Keevil, 2013), of benzotriazoles and of benzothiazoles (Loi and al., 2013). As pointed out earlier, different types of uses are possible. One of them is particularly suitable for the analysis of metabolites, that is to say molecules derived from pharmaceuticals, the MRM (multiple reaction monitoring) mode. This helped to develop, among other things, a method of analysis of veterinary drug residues in infant formulas (Zhan and al., 2013).
As indicated above, the CE-MS is an excellent alternative to chromatographic techniques. Especially when confirmation of results is required. A method for analysis of antidepressants in surface water and effluent treatment plants has been developed (Himmelsbach and al., 2006).
As the CE-MS, immunochemistry is used in addition to the GC-MS or LC-MS. Various immunoassays developed to quantify antibiotics in food have been adapted for the analysis of water (Kumar and al., 2005).

Treatment processes of organic micropollutants

If the molecules analyzed are present in low or very low levels, this is due to different processes of elimination of these substances. Although natural environments have a significant assimilative capacity (Oraison and al., 2011), this work is carried out largely by the WWTP. The various stages of treatment have very variable rate reductions, depending on the process followed and molecules. In this study, the pretreatment phase (screening, grit removal, degreasing) will not be discussed.
The results presented here are derived largely from the AMPERES program. This project aims to measure the composition of micro and treated wastewater, and quantify the effectiveness of different courses of treatment vis-à-vis these contaminants: activated sludge, reed bed filters, submerged membrane bioreactors and tertiary treatment (Coquery and al., 2009).

Primary treatment

This phase contains physical and physico-chemical processes. It enables the interception of some colloidal and particulate pollution (MIS). In general, the primary treatment methods are not designed for the removal of pharmaceuticals. Indeed, it is necessary to distinguish between the hydrophilic and hydrophobic molecules, defined by the octanol-water partition coefficient or Kow. Thus, the settling phase promotes the removal of hydrophobic substances, characterized by a "log Kow" greater than 5. However, drugs are mainly hydrophilic, they will not be retained by the primary clarifier. This is also the case for the coagulation-flocculation, which only intervenes to remove organic macromolecules (carbohydrates, proteins) (Cardot, 2010).

Secondary treatment

Also called biological treatment, these treatment processes are designed to recreate artificially the treatment capacity of the soil. There are two principles of purification:

- Fixed culture: microorganisms (bacterial flora) colonize the surface of a solid in the form of a trickling filter. In practice, it is the biofilters (biofilters) and planted macrophyte beds (reeds).
- Free culture: the purifying biomass is kept in suspension in the form of flocs in the water to be purified. The most common modes are activated sludge and lagoons (Actu-Environnement, 1999).

Unlike primary treatment, biological cultures showed a significant reduction in rates for micropollutants (Table 1).

Fixed cultures

Biofiltration

The results of a study on the Seine-Center WWTP (800 000 pe) show a significant change in the rate of elimination of micropollutants. Indeed, if VOHC (volatile organic halogenated

compounds) and BTEX (Benzene, Toluene, Ethylbenzene and Xylene) are eliminated more than 50%, hydrophilic and low volatile molecules are almost none. This is due to the process involved in purifying biofilters (V Rocher, 2011). Thus, if one is interested in drug molecules, mostly hydrophilic and non-volatile, it is likely that the reduction rate of the latter is low, or even zero.

Planted macrophyte beds (reeds)

Studies in the AMPERES project helped to highlight the performance of eliminations between 60 and 100% for β-blockers. The molecules studied were acebutolol, metoprolol, bisoprolol, propranolol and atenolol on a pond with a WWTP followed by a planted bed of vertical reeds (Gabet-Giraud and al., 2010).

Free cultures

Activated sludge

The removal efficiencies of several therapeutic classes were studied for sewage activated sludge. This work was carried out under the AMPERES project (Coquery and al., 2009). The results are shown in Table 1.

Table 1: Removal efficiency for WWTP extended aeration activated sludge (for molecules quantified more than 100 ng/L in raw sewage) (Choubert and al., 2012)

Pharmaceutical classes	Removal efficiency > 70%	Removal efficiency between 30 et 70%	Removal efficiency < 30%
Analgesics and antiinflammatory	Ibuprofen, Paracetamol, Ketoprofen, Naproxen, Aspirin	Indometacin	Diclofenac
Antibiotics		Sulfamethoxazole, Roxithromycin	
Antidepressants	Imipramine, Bromazepam	Amitriptyline, Fluoxetine	Carbamazepine, Diazepam, Nordiazepam, Doxepin
Lipid-lowering agents	Gemfibrozil		
Bronchodilators	Clenbuterol		Salbutamol, Terbutaline
B-blockers	Nadolol, Acebutolol, Bisoprolol, Betaxolol	Metoprolol, Timolol, Aténolol	Oxprenolol, Propranolol, Sotalol
Hormones	Estrone, Estriol, Estradiol (Ea2, Eb2)		

The results of this study show a significant reduction rate for pharmaceutical substances. Indeed, nearly half of these are eliminated by more than 70% in WWTP activated sludge at low load. Among the substances not successfully eliminated is carbamazepine. As indicated earlier in this study, this substance has been thoroughly investigated by HANDLES and MSNA, which concluded with a negligible health risk from even the highest dose exposures measured in a study national campaign. Studies in animals indicate toxic effects for a minimum dose resulting in an lowest observed adverse effect level (LOAEL) of 25 mg/kg/day in rats (Cunningham and al., 2010).

Membrane bioreactors (MBR)

In the case of pharmaceuticals, the purifying efficiency of membrane bioreactors is comparable to conventional activated sludge treatment operating at a similar age of sludge (Delgado Zambrano and Albasi, 2009). An improvement of the latter for the purification of substances resistant should be noted. This is due to the average age of the sludge, higher in the case of MBR (20-50 days) compared to activated (10-15 days) sludge.

Tertiary treatment

The addition of this step is made necessary by new purifying requirements, in particularly against urban areas to treat a big load of organic pollution of 120 kg/day of BOD_5 (Gouvernement français, 2007). Only advanced tertiary processes will be examined in this study. Indeed, refining processes (fast settling, sand filtration, finishing lagoon) proved ineffective in eliminating micropollutants (Choubert and al., 2012). The reduction rate of pharmaceutical substances described in the Table 1 was calculated for the processes of ozonation, activated carbon filtration and reverse osmosis in the AMPERES project. The results showed a yield of greater than 70% for the majority of molecules followed by elimination. Note a yield between 30 and 70% for two β-blocker (timolol and nadolol) by activated carbon filtration and less than 30% for aspirin by ozonation.

Activated carbon filtration

This method has the advantage of being well integrated into the existing WWTP and purify a large part of micropollutants (Matsui and al., 2002 ; Choi and al., 2005). This is due to the operating characteristics of the coal, in particular porosity. To maximize its effectiveness, the association with a biological treatment is necessary. There are two ways of using activated carbon:

- Powdered activated carbon, mixed with the effluent to be treated and filtered. Another use is possible in conventional post-filter, such as adsorbent beds (Moore and al., 2001).
- Granular activated carbon, used as a filter substrate. Once saturated, it is reprocessed and reused. Little data is available for this product range.

As previously described, the use of activated carbon for the removal of micropollutants has been widely described. Particularly for endocrine disrupters (Snyder and al., 2007 ; Fuerhacker and al., 2001). Once again the adsorption of the molecules depends on intrinsic parameters to them. The most important being the Kow. According to Mr. Montiel, adsorption on activated carbon is maximum for a logKow between 2 and 3.5. Below that threshold, the molecules are not retained (Montiel, 2006). Finally, there is the problem of waste management, requiring an additional step at a non-negligible cost.

Ozonation

This method has proven effective repeatedly for the removal of antibiotics in wastewater. Including amoxicillin, wherein the oxidation process leads to the formation of a chemically stable compound (Andreozzi and al., 2005). The combination of ozonation with UV radiation has also provided interesting results for fluoxetine (Prozac ®) with removal efficiencies close to 100% after 10 minutes of reaction in the laboratory (Méndez-Arriaga and al., 2011). A different study proved effective for eliminating oxidation of clofibric acid, ibuprofen and diclofenac (Zwiener and Frimmel, 2000).
However, the major drawback of this method is the formation of reaction by-products, due to the high reactivity of ozone. Additionally, byproducts formed may be more toxic than the parent molecule.

Reverse osmosis

Semi-permeable membranes can retain much of the drug substances as a result of a pressure gradient. An effective biological treatment is required upstream in order to avoid premature clogging of the system. As an advanced technique, the use of these membranes has been very effective for the removal of residual pharmaceuticals in the final drinking water treatment (Boleda and al., 2011). However, the extra cost caused by this type of process is not acceptable for a WWTP (plus 0.5 € / m2). A second problem is posed by waste management, like activated carbon filtration.

Conclusion on the treatment processes

According to the information collected from the various processing steps in WWTP, two remarks can be made:

- The methods of secondary treatment (bed planted with macrophytes, activated sludge, MBR) are not transparent vis a vis pharmaceutical residues (Table 1).
- Tertiary treatment processes provide very high costs against the followed molecules.

Currently, requiring high removal efficiencies for the molecules studied in this report would cause updates to expensive WWTP standards, some of which currently have difficulties in meeting existing requirements (Annex 3). However, the addition of drug residues on the watch list of emerging pollutants could cause their inclusion in the list of priority substances under the Water Framework Directive (Roussel, 2013). The secondary treatment processes have shown their limits for the elimination of diclofenac added to the list of monitored substances (Roussel, 2013). In this respect, the choice of the most appropriate treatment seems to be the use of a tertiary stage and more particularly, activated carbon filtration. Indeed, this treatment technique offers very satisfactory removal efficiencies for most studied drug classes, apart from the β-blockers (nadolol and timolol). It should be noted that the reverse osmosis cleans hormones poorly (Estrone, EE2) and aspirin is removed less than 30% by ozonation (Annex 2). But the hormone EE2 has already been added to the list of substances to be monitored (Roussel, 2013) and the removal efficiency of aspirin is not acceptable, in view of the very widespread use of this molecule.

Case study: Drôme catchment area

Context

The Drôme catechment covers an area of 1640km2 and includes 82 municipalities. The Drôme River runs 106km from the source to La Bâties des Fonds to the outlet in the Rhône between Livron-sur-Drôme and Loriol-sur-Drôme (SMRD, 2012).

The particularity of this river is that it was chosen in 1997 as an experimental site for the establishment of the first SAGE in France. This development plan follows the first river contract signed in 1990. The objectives of the SAGE deepened this initial contract, especially as regards the quantitative, qualitative and physical management of the Drôme River. These commitments are reflected in the development of a second river contract in 1999. It keeps the orientations of the first contract, but diversifies through aspects of development environments and development of recreation and tourism.

The issue of new sources of pollution on the territory of SAGE has arisen in the inventory for its revision in 2011 (SMRD, 2011a).

Sources of identified pollution

In response to concerns raised by drug pollution of in this river, it is necessary to take stock of the different identified sources.

Drugs designed for human use

Domestic discharges

Domestic discharges into the Drôme catchment area are treated either by municipal WWTP, or by on-site sanitation.
When all WWTP of the catchment area are listed, the total nominal treatment capacity is estimated at 106,000 PE (Annex 3). With on-site sanitation, these facilities purify water from 50,000 inhabitants in the territory of SAGE.
If the law requires municipalities to implement the Public Service for Non Collective Waste Water Treatment, only 19 of them are provided in 2009. Among the unions which holders this service, the Syndicat Intercommunal de Gestion Mutualisée de l'Assainissement (SIGMA) is the one which gathers the most common (13). For other municipalities in the SAGE perimeter (63), there is no discharge data available. Tourism and recreational activities are developing in the Drôme catchment area. Sixty campsites are listed in the SAGE perimeter with a good sanitation service for the majority of them.

Hospital discharges

Hospital effluent mostly comes from two care facilities: the Die and Crest hospitals. The two main types of drugs found and followed in hospital effluents are antibiotics and anticancer drugs. One study revealed that antibiotic consumption in hospitals represents only 5-10% of total consumption (Rogues and al., 2004). Anticancer compounds are discharged into the wastewater system via oncology and ambulatory care (Canchado, 2012). This type of pollution seems minimal for these two structures because they do not have cancer services. In addition, one study showed that there is a concentration gradient decreasing in anticancer molecules between the source and the WWTP (Catastini and al., 2010).

Industrial discharges

For the study area followed, there is only one company in the pharmaceutical sector, based in Livron-sur-Drôme (Haupt Pharma). In the field of chemistry, a manufacturer of hygiene products is based Crest (laboratory Hagral). It is very difficult to assess the direct impact of these firms on the quality of wastewater. It seems necessary that monitoring of wastewater products being put in place to control the quantity spilled.

Discharges from WWTP

WWTP sludge can be used for crop spraying. This practice is framed in the Drôme department (Préfecture de la Drôme, 2012). Sludge quality must meet specific criteria. The analysis of 2009 data from the water agency Rhone-Mediterranean and Corsica indicates that sludge applied are good (Agence de l'eau rhône-méditerranée et corse, 2010). However, no drug substance is sought in the applied material. According the SATESE of Drôme, sludge management is problematic for small WWTP (<200 PE). Indeed, most of them do not have spreading plane (SATESE, 2011). **Drugs designed for veterinary use**

Agricultural effluents

According to the DRAAF Rhône-Alpes, goat farms dominate the views of many operating in the Drôme valley (DRAAF Rhône-Alpes, 2013). However, there are no details on the quantities of drugs used in the Drôme valley. The proportion of certified organic farming is not known either. According to a report by the BRGM, some veterinary drugs are present in manure and other agricultural waste (Togola and Desforges, 2009). It should be noted that the molecules used will depend largely on the type of farming. This report did not provide the use of pharmaceutical substances in goat breeding. It is difficult to conclude from the information collected here on a massive soil contamination by agricultural farms in the study area.

Fish farming

Currently, two farms are established in the catchment area:

- The pisciculture of Font Rome at Beaufort sur Gervanne.
- The pisciculture on l'Archiane at Treschenu Creyers.

According to the DSV 26 releases of these farms are in accordance with the current legislation (SMRD, 2011a).

Identified risks

Identified risks relate mainly to domestic waste through WWTP, which can affect the health of aquatic, terrestrial and human populations. The test results ordered by the water agency RMC indicate the presence of 26-50 micropollutants in the Drôme river (Agence de l'eau Rhône Méditerranée Corse, 2013).
On the SAGE territory, 44 WWTP were listed for 2011. The evaluation of the effectiveness of the purifying process with respect to standard parameters (BOD5, COD, MIS) is presented in Annex 3. The number of units by sector is presented in Annex 4.

Ecotoxicological risk

Continuing pollution

The presence of polychlorinated biphenyls (PCBs), organochlorine pesticides and some metals may explain the disappearance of otters in the early century in the Drôme department (Richard-Mazet, 2005).
As regards to drug compounds, information on purifying efficiency is needed to assess the effectiveness of different WWTP discharging into the river. Thus, according to the inventory for the revision of SAGE, the largest pollution discharges come from 4 stations: Allex-Grane, Crest, Die and Livron with 60% of total releases or 3480 PE (SMRD, 2011a). Nevertheless, the purifying efficiency of these stations is very good at between 91 and 94%. On the other hand, stations (clarifier/digester) of Montclar-sur-Gervanne (120 PE) and Vercheny (440 PE) were reported as defective. Purification by settling and digestion are obsolete processes, allowing only prepurifying (Noir, 2014). Then, the two stations (natural lagoon) of Luc-enDiois (1600 PE) and Chatillon-en-Diois (2100 PE) are also implicated by the DASS and SATESE for average quality treatment. The information provided by the SATESE about the WWTP of Luc-en-Diois indicate that purifying efficiency are ditches by the presence of clear water in at the station entrance (Noir, 2014). The case of WWTP of Recoubeau-Jansac and Barnave are of greater concern. Indeed, they are geographically close (about 6 km) and represent real black spots on the sewerage network, evidenced by the chemical quality of the Drôme river and classified in poor condition in this sector (SMRD, 2011b). However, the WWTP of Barnave uses reed bed filters, renowned for their efficiency and low maintenance requirements. It seems that the transit time of effluents is too fast, causing their malfunction (Noir, 2014).
The massive use of pharmaceutical and cosmetic products is currently the focus of parliamentary debate, as confirmed by the work carried out on the Mediterranean Sea by a senator (Courteau, 2011). This later aspect relates the adverse effects of rivers heavily loaded with pollutants. Besides the usual chemical contaminants (PCBs, PAHs and POPs), this work points out the emerging pollutants such substances to be taken into account in future pollution governance policies.

Diffuse pollution

As regards the risks of accidental pollution, the data indicates at least seven abandoned on the territory landfills. These landfills are located at the edge of the river, which can cause massive discharges during floods. This was the case in December 2004, when a portion of the discharge Beaufort-sur-Gervanne was swept 10 kilometers (Richard-Mazet, 2005).

Health risk

The Drôme River is a stream of average quality for swimming, ARS Rhône-Alpes confirmed with bacteriological tests (E. coli, total coliforms, streptococci totals). No analysis on the presence of drug residues was carried out by the LRA in the river.

Proposed solutions

The proposed solutions are designed initially to reduce the amount of waste, in the event of malfunction of one or more existing facilities. Indeed, if the monitored parameters (nitrogen, TSS, BOD5, COD) does not meet discharge standards, it is likely that non-monitored substances are also poorly eliminated. Then, a second area of improvement for analytical monitoring of the study area can be cleared. Finally, the questioning of routine practices visà-vis domestic waste will be discussed.

Improvement of WWTP

Some sectors are associated with activated sludge tertiary treatment (Crest, Die, Saillans), the purification performance are maximum for these facilities. This is not the case for AllexGrane, Livron-sur-Drôme and Loriol-sur-Drome. Indeed, with a capacity between 10,000 and 150,000 PE, these treatment courses can be improved by adding a tertiary process. The case of Recoubeau-Jansac is about to be solved. Indeed, a new project has just been approved and a work desk study on the latter (Noir, 2014).

The municipalities of Barnave, Laval Aix Montclar-sur-Gervanne, Ombreze (Imhoff tank) and Le Chaffal were also distinguished for their respective malfunction STEP (Annex 3). Replacement of common facilities Ombrèze would be beneficial for all methods used here (septic tank, spreading decanter + digester) offers very average treatment performance (SATESE, 2011).

Despite the problems observed, the purifying Park study area is in good condition, with 80% of facilities that work well (SATESE, 2011).

Improved analytical monitoring

The lack of analytical data on the chemical quality of the river Drôme is striking. This problem can be extended to the entire national territory. If the comprehensive monitoring for the molecules used for different uses is economically unrealistic alternatives can be identified. Indeed, looking for witness molecules seems to be a good compromise for regular assessment and localized streams. The choice of substances to be followed can be based on several criteria, including biological activity, the amounts used or the use of pharmacological molecules.

Behavior change

The massive use of substances, drug and cosmetics, has highlighted adverse effects in the aquatic environment. It would appear interesting to educate residents and tourists about the exact mix of products sold and best practices for "greener" behavior. This translates in practice into:

- Rational use of medicines. WHO showed that 50% of drugs consumed are not prescribed, dispensed or sold appropriately.
- Avoid using cosmetic products containing substances listed for their impact on the environment.

Conclusion

This report provided an overview on medicines and cosmetics from some knowledge on modes of introduction to the receiving environment, purifying the channels involved and the potential impacts on human health and the environment. This latter aspect has clearly highlighted the lack of information on the molecules studied, both the quantities released into household waste output in WWTP. These gaps are now beginning to disappear, thanks to the development of analytical chemistry in the field of detection and quantification of emerging pollutants. This helps to develop legislative decisions to add new discharge standards for drug molecules identified as having a significant environmental impact.

Thus, the assessment of the good chemical status of rivers is interested more in the presence of drug residues in the environment. However, the evolution of discharge standards certainly poses new constraints related to current WWTP purifying streams, as shown in the watershed of the Drôme. Indeed, if the efforts prescribed by SAGE led to a qualitative improvement of the river, adding new parameters could jeopardize its apparent good condition. From this perspective, the introduction of concrete solutions seems necessary, such as improving the analytical monitoring of rivers, improving WWTP planning and the adoption of simple collective responses.

More generally, the pollution of rivers by drugs and cosmetics is added to an already long list of pollutants of anthropogenic origin. As with the others, the effects of these molecules accumulate to potentially affect every aspect of the food chain. Unlike other chemicals, drugs are designed to be active at very low doses, making their inclusion necessary for the preservation of terrestrial and aquatic ecosystems in the long term. Thus, the implementation of solutions should be simultaneous with changing drug processes by the pharmaceutical industry, making them align more closely with the evolving use of green chemistry.

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Annexes

Substances studied	Pharmaceutical properties	Context of the study	Sources
17α-Ethinylestradiol (EE2)	Hormone	• Induces potentially feminization of fish populations studied • Removal efficiency tertiary treatment > 70% for ozonation and activated carbon filtration, between 30 and 70% by reverse osmosis	(Länge et al., 2001; Parrott et Blunt, 2005; Choubert et al., 2012)
Acebutolol **Clofibrinic acid**	β-blocker	• Removal efficiency > 70% by activated sludge • Removal efficiency between 50 and 100% per bed planted with macrophytes • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012; Gabet-Giraud et al., 2010)
Alprazolam	Lipid-lowering agent	• Growth inhibitory effect of the clofibrinic acid / carbamazepine combination • Good removal efficiency by ozonation	(Cleuvers, 2003; Zwiener et Frimmel, 2000)
Amitriptyline	Antidepressant	• Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Amoxicillin	Antidepressant	• Removal efficiency between 30 and 70% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Aspirin	Antibiotic	• Formation of secondary products by ozonation	(Andreozzi et al., 2005)
Atenolol	Analgesic, antipyretic and anti-inflammatory	• Removal efficiency > 70% by activated sludge • Removal efficiency by tertiary treatment > 70% for reverse osmosis and activated carbon filtration, <30% for ozonation	(Choubert et al., 2012)

	β-blocker	• Removal efficiency between 30 and 70% by activated sludge Removal • efficiency between 50 and 100% per bed planted with macrophytes • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012; Gabet-Giraud et al., 2010)

Betaxolol	β-blocker	• Removal efficiency > 70% by activated sludge	(Choubert et al., 2012)
Bisoprolol	β-blocker	• Removal efficiency > 70% by activated sludge • Removal efficiency between 50 and 100% per bed planted with macrophytes • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012; Gabet-Giraud et al., 2010)
Bromazepam	Antidepressant	• Removal efficiency > 70% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Carbamazepine	Antidepressant	• Growth inhibitory effect of the clofibrinic acid / carbamazepine combination • Trivial health risk by ingestion via EDCH • Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Cleuvers, 2003; ANSES et ANSM, 2013; Choubert et al., 2012)
Celestonide	Synthetic musk	• Cytotoxic effect of the tonalide / celestonide combination	(Porte et al., 2009)
Clenbuterol	Bronchodilator	• Removal efficiency > 70% by activated sludge	(Choubert et al., 2012)
Danofloxacin	Antibiotic	• Trivial health risk by ingestion via EDCH	(ANSES et ANSM, 2013)
	Antidepressant	• Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)

Diazepam **Diclofenac**	Analgesic, antipyretic and anti-inflammatory	• Growth inhibitory effect of the clofibrinic acid / carbamazepine combination • Removal efficiency < 30% by activated sludge • Good removal efficiency by ozonation • Removal efficiency by tertiary treatment > 70%	(Cleuvers, 2004; Choubert et al., 2012; Zwiener et Frimmel, 2000)
Doxepin	Antidepressant	• Removal efficiency < 30% by activated sludge	(Choubert et al., 2012)
Estradiol **Estriol**	Hormone	• Removal efficiency > 70% by activated sludge	(Choubert et al., 2012)
Estrone	Hormone	• Removal efficiency > 70% by activated sludge • Removal efficiency tertiary treatment > 70% for ozonation and activated carbon filtration, between 30 and 70% by reverse osmosis	(Choubert et al., 2012)
Fluoxetine **Gemfibrozil**	Antidepressant	• Cytotoxic effect of the fluoxetine / paroxetin combination Removal efficiency between 30 and 70% by activated sludge • Good removal efficiency by ozonation/UV • Removal efficiency by tertiary treatment > 70%	(Porte et al., 2009; Choubert et al., 2012; Méndez-Arriaga et al., 2011)
Ibuprofen	Lipid-lowering agent	• Removal efficiency > 70% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Imipramine **Indometacin**	Anti-inflammatory	• Growth inhibitory effect of the clofibrinic acid / carbamazepine combination • Removal efficiency > 70% by activated sludge • Good removal efficiency by ozonation	(Cleuvers, 2004; Choubert et al., 2012; Zwiener et Frimmel, 2000)
	Antidepressant	• Removal efficiency > 70% by activated sludge	(Choubert et al., 2012)

Ketoprofen	Analgesic, antipyretic and anti-inflammatory	• Removal efficiency between 30 and 70% by activated sludge	(Choubert et al., 2012)
Metoprolol	Analgesic, antipyretic and anti-inflammatory	• Removal efficiency > 70% by activated sludge Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
	β-blocker	• Removal efficiency between 30 and 70% by activated sludge Removal efficiency between 50 and 100% per bed planted with macrophytes • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012; Gabet-Giraud et al., 2010)
Nadolol	β-blocker	• Removal efficiency > 70% by activated sludge • Removal efficiency by tertiary treatment > 70% for reverse osmosis and ozonation, between 30 and 70% for the activated carbon filtration	(Choubert et al., 2012)
Naproxen	Analgesic, antipyretic and anti-inflammatory	• Removal efficiency > 70% by activated sludge	(Choubert et al., 2012)
Nordiazepam	Antidepressant	• Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Oxprenolol	β-blocker	• Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Paracetamol	Analgesic and antipyretic	• Removal efficiency > 70% by activated sludge Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Paroxetin	Antidepressant	• Cytotoxic effect of the fluoxetine / paroxetin combination	(Porte et al., 2009)

Propranolol **Roxithromycin**	β-blocker	• Removal efficiency < 30% by activated sludge • Removal efficiency between 50 and 100% per bed planted with macrophytes • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012; Gabet-Giraud et al., 2010)
Salbutamol	Antibiotic	• Removal efficiency between 30 and 70% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Sotalol	Bronchodilator	• Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
	β-blocker	• Removal efficiency < 30% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Choubert et al., 2012)
Sulfamethoxazole	Antibiotic	• Growth inhibitory effect of the trimethoprim / sulfamethoxazole combination • Removal efficiency between 30 and 70% by activated sludge • Removal efficiency by tertiary treatment > 70%	(Eguchi et al., 2004; Choubert et al., 2012)
Terbutaline	Bronchodilator	• Removal efficiency < 30% by activated sludge	(Choubert et al., 2012)
Timolol	β-blocker	• Removal efficiency between 30 and 70% by activated sludge • Removal efficiency by tertiary treatment > 70% for reverse osmosis and ozonation, between 30 and 70% for the activated carbon filtration	(Choubert et al., 2012)
Tonalide	Musc synthétique	• Cytotoxic effect of the tonalide / celestonide combination	(Porte et al., 2009)
Trimethoprim	Antibiotic	• Growth inhibitory effect of the triméthorpim/sulfaméthoxazole combination	(Eguchi et al., 2004)

Annex 1: Summary Table of molecules studied in the bibliographic synthesis

Pharmaceutical classes	Substances	Reverse osmosis	Ozonation	Activated carbon filtration
Analgesics and anti-inflammatory	Diclofenac, Paracetamol, Kétoprofen	> 70%	> 70%	> 70%
	Aspirin	> 70%	< 30%	> 70%
Antibiotics	Sulfamethoxazole, Roxithromycin	> 70%	> 70%	> 70%
Antidepressants	Bromazepam, Amitriptyline, Fluoxetine, Carbamazepine, Diazepam, Nordiazepam, Alprazolam	> 70%	> 70%	> 70%
Lipid-lowering agents	Gemfibrozil	> 70%	> 70%	> 70%
Bronchodilators	Salbutamol	> 70%	> 70%	> 70%
B-blockers	Acebutolol, Bisoprolol, Metoprolol, Atenolol, Oxprenolol, Propranolol, Sotalol	> 70%	> 70%	> 70%
	Nadolol, Timolol	> 70%	> 70%	Entre 30 et 70%
Hormones	Estrone, EE2	Entre 30 et 70%	> 70%	> 70%

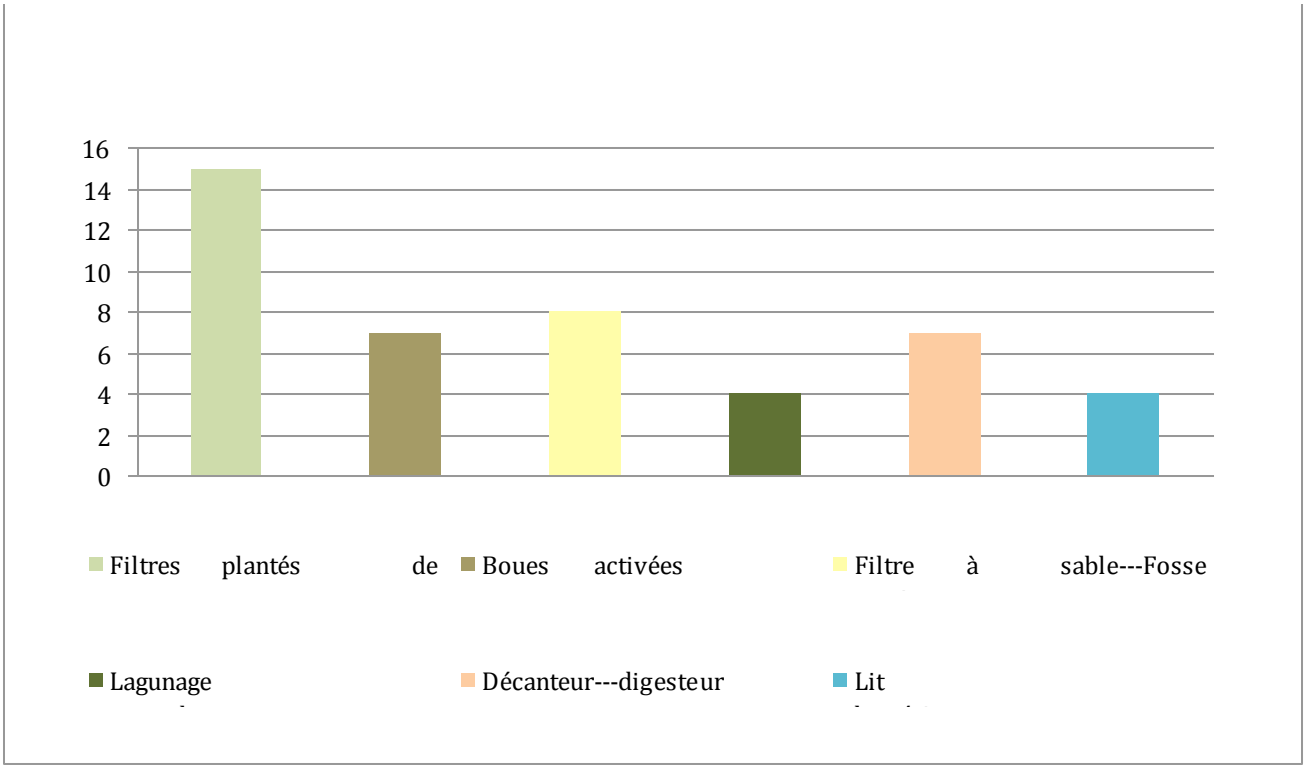
Annex 2: Removal efficiency of tertiary treatment processes (Choubert et al., 2012)

Town	WWTP	Capacity (PE)	Assessment of the SATESE
Aix-en-Diois	Bed planted with macrophytes	300	Good
Allex-Grane	Activated sludge	13000	Good
Aurel	Bed planted with macrophytes	300	Good
Autichamp	Sand filter	100	Good
Barnave	Bed planted with macrophytes	320	Bad
Beaufort-sur-Gervanne	Biofilter	700	Good
Beaumont-en-Diois	Septic tank + spreading	270	Not visited
Beaurières	Lagunage naturel	225	Good
Boulc-en-Diois	Bed planted with macrophytes	80 et 40	Good

Chastel Arnaud	Septic tank + spreading	200 à 2000	Not visited
Châtillon-en-Diois	Lagoon	2100	Medium
Cobonne	Bed planted with macrophytes	100	Good
Crest	Activated sludge + tertiary	19000	Good
Die	Activated sludge + tertiary	32300	Not visited
Divajeu	Decanter-digester	1 à 200	Good
Eurre	Decanter-digester	1 à 200	Not visited
Glandage	Decanter-digester	100	Not visited
Laval d'Aix	Septic tank + Bad spreading	115	
Le Chaffal	Decanter-digester	150	Bad
Livron-sur-Drôme	Activated sludge	15000	Good
Loriol-sur-Drôme	Activated sludge	12000	Good
Luc-en-Diois	Lagoon	1600	Medium
Marignac-en-Dios	Bed planted with macrophytes	200	Good
Menglon	Bed planted with macrophytes	500	Good
Miscon	Bed planted with macrophytes	200	Good
Montclar-sur-Gervanne	Decanter-digester	120	Bad
Montmaur-en-Dios	Septic tank	300	Medium
Omblèze – les boutons et les Arbods	Septic tank	120 et 50	Medium
Omblèze - Moulin	Decanter-digester	75	Bad
Pennes le Sec	Septic tank + spreading	20	Medium
Plan de Baix	Activated sludge	350	Medium
Plan de Baix	Bed planted with macrophytes	80	Good
Recourbeau Jensac	Biofilter	450	Bad
Rimon et Savel	Bed planted with macrophytes	15	Not visited
Rimon et Savel	Epandage	10	Not visited
Romeyer	Bed planted with macrophytes	300 et 100	Good
Saillans	Activated sludge + tertiary	2700	Good

Saint Roman	Bed planted with macrophytes	290	Good
Saou	Biofilter	600	Medium
Suze sur Crest	Bed planted with macrophytes	150	Good
Valdrôme	Septic tank + spreading	400	Medium
Val Maravel	Biofilter	100	Good
Vanaveys-la-Rochette	Lagoon	300	Medium
Vercheny	Decanter-digester	440	Not visited

Annex 3: List of WWTP on the territory of SAGE Drôme (SATESE, 2011)



Annex 4: Number of WWTP by sector on the territory of SAGE Drôme

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