REPORT

Self-declarations of environmental classification in www.fass.se.

-experiences from the reviewing process

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Report Summary

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Title and subtitle of the report

Experiences from the reviewing process of the self-declarations of environmental classification in www.fass.se.

Summary

In 2005 environmental information was published for two groups of products on www.fass.se to test a new model for classification developed after an initiative from LIF (The Research-Based Pharmaceutical Industry). The initiative was a response to an increasing public demand for environmental information on pharmaceuticals and an attempt to develop a model accepted both by Swedish stakeholders and by the global pharmaceutical industry. Today, all groups of pharmaceuticals in the Swedish medicals product list (Fass) have been subject to environmental risk assessments. The work with the development of the www.fass.se system of self-declarations of environmental classification, and the experiences from the reviewing process are summarised in this report.

Keyword

Pharmaceutical, www.fass.se, environmental classification,

Bibliographic data

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Summary

In 2005 environmental information was published for the first two groups of products on www.fass.se to test a new model for classification developed on the initiative of LIF (The Research-Based Pharmaceutical Industry). The initiative was a response to an increasing public demand for environmental information of pharmaceuticals and an attempt to develop a model accepted both by Swedish stakeholders, but also by the global pharmaceutical industry. The model was developed in collaboration with interested parties in the health care sector, the Stockholm county council, the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency, in conjunction with the international pharmaceutical industry. Today, six years later, all groups of pharmaceuticals in the Swedish medicals product list (Fass) have been subject to environmental risk assessments.

IVL the Swedish Environmental Research Institute and LIF (the owner of the system) defined in an early phase of this work a common project in order to identify and address the pitfalls of such a system. The IVL-LIF project has primarily been structured around the environmental information from pharmaceutical companies published on the www.fass.se -portal.

The advantage of a self-declaration system as the www.fass.se system is that it encourages the involvement of pharmaceutical companies in the process of publically displaying their available environmental data and also to provide data for those substances where there is a data gap. The system becomes however very dependent on the individual actors' voluntary acceptance of guidance, quality assurance and participation. Reviews of the resulting classifications on fass.se have sometimes revealed discrepancies between the results of the review of the environmental data and the actual outcome presented on www.fass.se. This implies that measures need to be taken to achieve a higher quality assurance in the system. One such step has already been taken with more check-points and reminders before environmental data are published in the Fass database.

The project has resulted in methodological guidance regarding the interpretation of the OECD protocol 308, and an evaluation of the suitability of the use of QSAR to predict ecotoxicological effects, when arriving at a Predicted No Effect Concentration (PNEC).

Around 40% of the Active Pharmaceutical Ingredients (APIs) have been assessed for their environmental effect (17% are exempted from classification in accordance with EMA whereas 26% are classified regarding risk, persistence and/or bioaccumulation). For the rest of the APIs data is lacking. Sometimes it may be due to a limited commitment to the system, and sometimes because environmental impact has not yet been studied. 86% of the APIs classified regarding environmental risk end up in the category "insignificant risk".

An overview of the system indicates that Predicted Environmental Concentration (PEC) calculations seem to be in accordance with the precautionary principle.

Environmental information of pharmaceuticals does not yet seem to be an important aspect in the selection of pharmaceuticals. Despite this other studies show that many actors seem to find a value of the system just because of the fact that environmental data on pharmaceuticals are made publically available.

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Introduction

Pharmaceuticals are widely used substances. On the Swedish market there exist approximately 1200 active compounds in about 7600 different products (Swedish Medical Products Agency, 2004). During the last decade pharmaceuticals have become recognized as relevant environmental contaminants (Halling-Sörensen et al., 1998, Kümmerer (ed), 2004).

The inherent bioactivity of pharmaceuticals has manifested itself in the environment in a number of cases such as the adverse effects on reproduction and hormonal disturbances of aquatic organisms due to the presence of a synthetic hormone, ethinylestradiol (MacLatchey et al., 1997, Routledge et al. 1998, Larsson et al., 1999). In South East Asia, the use of the anti-inflammatory drug diclofenac in veterinary medicine has resulted in an almost complete extinction of some species of vultures, feeding on cattle carcasses. These birds have shown to experience acute kidney failure syndrome upon exposure to the drug (Oaks et al., 2004). Concerns have also been raised on the topic of bacterial resistance to antibiotics in sludge from wastewater treatment plants (Alexy et al., 2004).

In 2005 environmental information was published for the first two groups of products on www.fass.se to test a new model for classification developed on the initiative of LIF (The Research-Based Pharmaceutical Industry). The initiative was a response to an increasing public demand for environmental information of pharmaceuticals and an attempt to develop a model accepted both by Swedish stakeholders and by the global pharmaceutical industry. Today, six years later all groups of pharmaceuticals in the Swedish medicals product list (Fass) have been subject for environmental risk assessment.

The aim of the study

IVL the Swedish Environmental Research Institute and LIF (the owner of the system) defined in an early phase of this work a common project to identify and address the pitfalls of such a system. The IVL-LIF project has primarily been structured around the environmental information from pharmaceutical companies published on the www.fass.se -portal. By reviewing the "pre-published data" IVL has taken part in a discussion, led by LIF, with the pharmaceutical companies about how to implement the guideline for environmental risk assessment developed by LIF and their environmental committee. The goal of this reviewing process has been to establish a common praxis for the implementation of the guideline among the different companies and to feed back the experience from the self-declaration process back to the system owners, LIF.

The purpose of this report is to present an overview of the experiences gained in the implementation process. It addresses three major areas; the process of self-declarations on www.fass.se and its quality assurance, the resulting classifications of the system and finally examples of the methodological discussions between pharmaceutical companies and the reviewer/system owner that the system has generated.

Environmental classification of pharmaceuticals at www.fass.se

According to current pharmaceutical legislation an environmental risk assessment is required for the approval of a new medical product (European Medicines Agency, 2006). However the environmental risk will not be considered at the benefit/risk assessment of a new product and can thus not form the basis for a rejection. Legislation around pharmaceuticals is harmonized within EU and thus no national requirements can be made on classification of pharmaceuticals (Swedish Medical Products Agency, 2009).

The Medical Product Agency (MPA) in Sweden was assigned in 2002 to report on the environmental effects of pharmaceuticals. The report presented a situation with too much lack of information to arrive at a viable risk assessment of pharmaceuticals and therefore proposed a voluntary Swedish classification system where the pharmaceutical industry is responsible for obtaining and providing data (the Medical Product Agency, 2004). In 2004, LIF initiated a self-declaration system for pharmaceutical products at the already existing web portal for medical products www.fass.se (Mattson et al., 2007). This was done in collaboration with interested parties in the health care sector, Stockholm county council and the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the MPA. In parallel with the Swedish actors LIF also put together an international task force with internationally recognized environmental expertise from several pharmaceutical companies, i.e. Pfizer, AstraZeneca, Merck, GSK, Lilly, Novartis and Roche.

www.fass.se a type III self-declaration system

The strategy of declaring products environmental properties to the market is commonly referred to as "environmental labelling" or "eco-labelling" and has become more and more important along with a rising environmental awareness among consumers (Gallastegui, 2002). Eco-labelling is in itself no single methodology but is mere a categorization of methodologies used for declaring/communicating the environmental performance of products. The most commonly accepted distinction of different "eco-labelling"- methodologies is probably that of the International Organization for Standardization (ICS 13.020.50: Ecolabelling). According to the ISO-terminology the methodologies commonly known as "eco-labelling" are categorized into Type I, Type II, and Type III-labels.

Type I labels are used by businesses to communicate to the consumer that their products are more environmentally friendly than others. Third-party experts (eco-labellers) are the ones that select product categories and point out, through a set of criteria, the most environmentally preferable products within a given product group. The ISO-standard for Type I labels also prescribes that guidelines/criteria have to consider the entire life cycle of the product. This is not however the same as requiring full life-cycle assessments (LCAs) to be undertaken. The incentive for businesses to eco-label (Type I) their products in the first place is the competitive advantage that the labelling supposedly creates on a given product market. The supposed benefit, from an environmental viewpoint, is attained when the market share of eco-labelled products increases through changed purchase behaviour of the consumer[1]. This also presupposes that the consumers are motivated by environmental concern to change behaviour and at the same time will recognize and trust the label (Harrison 1999). Moreover, if the market share of "green"

[1] This is in a situation where the total quantity of demand for the same type of product remains unchanged meaning that the rebound effect is minimal. This also presuppose that meaningful criteria could be developed that distinguish environmentally preferable products.

products grows it could create pressure for other manufacturers (those actors not involved in eco-labelling on a given product market) to reformulate their own products or processes such that they adopt the eco-label criteria. This is the reason why type 1 eco-labelling schemes also have been hailed as a mean to improve products environmental performance. In other words, eco-labelling prompts firms to engage in a "race to the top" to qualify for the label and thus attract environmentally conscious consumers. The fact that eco-labels rely on pass or fail certification has made some researchers claim that there is not so much to "the top" as to "clear the bar" (Harrison 1999).

Type II labels refer to environmental claims made about goods by their manufacturers, importers or distributors. These declarations may be used to inform customers via advertisements and other communications about the environmental attributes of products. In contrast to Type I labels, Type II labels are not independently verified and do not use predetermined and accepted criteria for reference (UNEP 2005). UNEP (2005) describes Type II-labels to be the least informative of the three types of environmental labels defined by the ISO.

The purpose of Type III labels is to provide relevant, verified and comparable information of a product's environmental impacts throughout its life cycle (Environdec 2010). The best known type three label system is that of an Environmental Product Declaration (EPD). The information categories found in an EPD can be set by an industrial sector or by independent bodies (UNEP 2005). The information found in EPDs is simply presented as it is without making judgment weather the product is environmentally friendly or not. The task is left to the ones receiving the information, i.e. consumers and customers (UNEP, 2005).

The www.fass.se model bares most resemblance with what is commonly referred to as Type III-label (ISO). The www.fass.se model does however take the information published one step further and differentiates the risk posed by the pharmaceuticals in four different categories, insignificant risk, low risk, moderate risk and high risk. The environmental assessment of www.fass.se is displayed at three different levels. For the non-expert user there are two levels with only the chosen risk and hazard phrases. For the expert reader there exist however a third level with all information available that has been the basis for the self-declaration or references to document that have been used. The advantage of this is that any deviation for the basic data set for assessments is displayed and not only the phrases can be compared between different products but also what data that supports the classifications. This differentiates the systems from many other attempts of environmental labelling.

Different parties and their responsibility in the classification process

The quality of the environmental data published on www.fass.se is the sole responsibility of the specific company. The guidelines to what environmental data that supports and differentiate the classification steps has been developed by a Swedish working group led by LIF including representatives from the industry (LIF), the Stockholm county council, the pharmacy chain Apoteket, SKL and the MPA.

Before publication of environmental data on www.fass.se, the risk and hazard assessment is reviewed by IVL. IVL comments on the choice of classification phrase according to what data that supports it and gives a recommendation to LIF whether to allow or stop publication. LIF allows for publication or encourage the company to adjust the classification according to the review. It is however the responsibility of the company to make sure that it is the finally agreed

classification that is actually published on www.fass.se. The system as of today does not permit LIF to inhibit any classifications. To ensure the impartiality of the reviewer there is no direct contact between the company and the reviewer. The partners involved in the quality assurance process and the information flow is presented in Figure1.

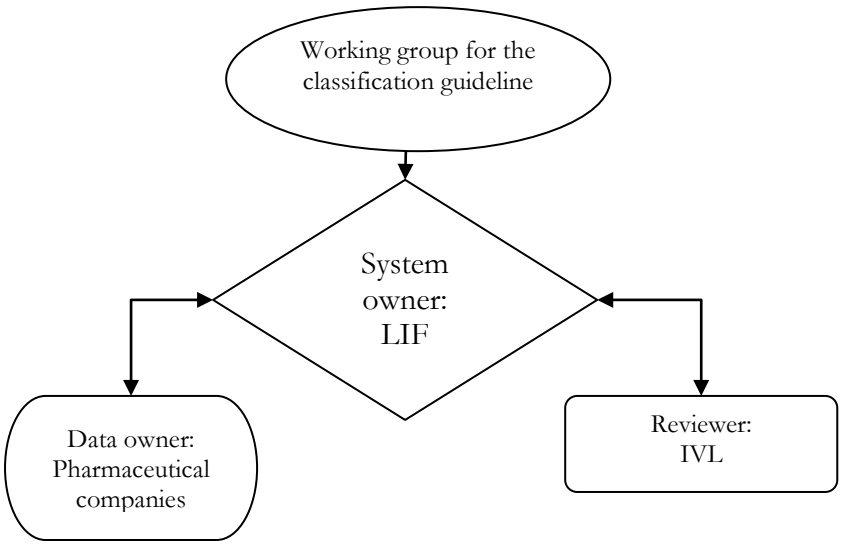

Figure 1. Partners in the quality assurance process of environmental classification on www.fass.se

The guidance document

The guidance document is specifically designed for the Swedish classification system (LIF, 2007). To ensure a sound scientific basis of the system, as well as a large commitment by the pharmaceutical industry, the guidance document is based on already existing guidance tools for environmental risk assessments used in connection with the approval of new medicine such as the European Medicines Agency (EMA) guideline (EMA, 2006) and the European Technical Guidance Document (TGD, 2003). In contrast to the EMA regulation that demands environmental data for new products, and for some marketed products in connection with new market applications, the scope of the Swedish classification system is to include all existing APIs. The EMA guideline also states that APIs with a PEC lower than 0.01 μg/l (and where no other environmental concerns are apparent), can be excluded for risk assessment while APIs with a PEC/PNEC ratio greater than one should undergo extended environmental effect analysis. The www.fass.se system demands the same amount of information for all APIs regardless of volume or risk quotient. To arrive at a situation where risk assessments can be made for all these substances the system acknowledges the use of all existing data and not only data derived from standardized testing. It also allows for the use of short term data when there is a lack of more relevant long term testing (LIF, 2007).

Since 2008 the TGD (2003) have been replaced by the guidance documents for the implementation of REACH. The assessments are thus now done in accordance with the Guidance on information requirements and chemical safety assessment (ECHA, 2008).

Gaps, ambiguities and deficiencies in the guidance document for the Swedish classification system identified during the reviewing process are continuously communicated to LIF and the working group for the classification guideline, and an updated version of the guideline is expected early 2012.

Environmental risk assessment according to www.fass.se

An environmental risk assessment according to www.fass.se is obtained by deriving a ratio between the Predicted Environmental Concentrations (PEC) and the predicted no effect concentration (PNEC). The system has four classification categories:

PEC/PNEC≤ 0.1

Use of the medicine has been considered to result in insignificant environmental risk

0.1< PEC/PNEC ≤ 1

Use of the medicine has been considered to result in low environmental risk

1< PEC/PNEC ≤ 10

Use of the medicine has been considered to result in moderate environmental risk

PEC/PNEC > 10

Use of the medicine has been considered to result in high environmental risk

When there are not sufficient data to arrive at any risk ratio the phrases "Risk of environmental impact cannot be excluded, since no ecotoxicity data are available" or "Risk of environmental impact cannot be excluded however some ecotoxicity data are available" can be used.

The PEC is the total sold amount of API on the Swedish market, taking into account dilution and removal in the sewage treatment plant[2]. If considerations are made concerning metabolism in the human body a full risk assessment is required for the main metabolites. If these data do not exist, the total amount is considered to be excreted as the parent compound.

The PNEC should normally be based on ecotoxicity data from three trophic levels, algae, crustacean and fish. However, if relevant data are available for the species believed to be the most sensitive, e.g. based on an understanding of receptor-mediated effects, there can be an exception to this. Long term data are preferred but when this does not exist short term data will be accepted. The choice of assessment factor should be in accordance with ECHA (2008). Tests are to be performed according to the appropriate guideline, OECD, FDA or similar. Companies are encouraged to use not only their own data but also data from other companies or what can be found in the open scientific literature. Measured data should be used prior to calculated and if estimated data is used the company should justify the scientific rational. Internal or external references should be given in association with all the submitted data.

[2] PEC (µg/L) = A x 1000000000 x (100-R)/ 365 x P x V x D x 100 where A=(kg/year), R=removal rate, P = number of inhabitants in Sweden = 9 x 10^6, V (l/day) = volume of wastewater per capita and day = 200 (ECHA default) and D = factor for dilution of waste water by surface water flow = 10 (ECHA default)

In addition to the risk assessment, additional information on the persistence and bioavailability is presented and categorized in three and two different categories, respectively:

For persistence:

The medicine is degraded in the environment.

The medicine is slowly degraded in the environment

The medicine is potentially persistent.

Classification related to persistence is primarily based on data from laboratory experiments such as the ready tests (OECD 301), inherent tests (OECD 302) or simulation studies (OECD 303, 307, 308, 309). When non standardized tests are used the data should be supported with enough information on test conditions to allow for comparison with standardized test data. As there exist no exact "trigger" for the persistence phrases this leads to a more case by case classification and reviewing approach.

For bioaccumulation:

Log Dow (at pH7) < 3

No significant bioaccumulation potential; or

Log Dow (at pH7) ≥3

Potential to bioaccumulate

The potential to bioaccumulate is determined by measuring the bioconcentration factor or the log Kow potential e.g. the octanol/water partitioning coefficient.

For substances potentially fulfilling the EU criteria of a Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) chemical, further information on persistence according to ECHA (2008) will be required.

The reviewing procedure

In order to establish a common praxis around the interpretation of the guideline all information available on www.fass.se has been reviewed before publication by a reviewing team at IVL. The reviewing team has checked that the submitted information is in accordance with the basic data requirements for risk assessment according to the guideline. If not, the company has been asked by LIF to complement. The reviewing team has not however had the opportunity to review each specific test protocol. Only in those cases where it has been considered necessary for the interpretation of the test result, the company has been asked to complement with this information.

There have been several cases where companies have chosen to base the risk and hazard assessments on supplementary or alternative data than what was originally asked for by the guidance document. In these situations a case-by-case review has been undertaken, sometimes requiring more profound investigations regarding the scientific or regulatory correct way of handling the issue from a guidance perspective. Any deviation from the guideline has required a motivation. The precautionary principle has been the guiding principle in these case-by-case reviews.

Comments given in the review have been structured in three levels depending on the severity of deviation from the guideline:

- Major deviation – deficiencies in the submitted material lead to an inaccurate classification of risk or/and hazard and needs to be changed before publication on www.fass.se
- Minor deviation - deficiencies in the submitted material that does not lead to an inaccurate classification of risk or/and hazard but still needs to be changed before publication on www.fass.se
- Remarks – minor deficiencies – correction is recommended to be in full compliance with guideline

When the submitted material is in full compliance with the guideline no remarks are given and a recommendation for publication is made to LIF.

In several cases the discussions around classification have led to alterations or clarifications of the guideline (for example the interpretation of OECD 308). In other cases the scientific basis for such alterations has not been sufficiently motivated and the environmental risk assessment for the chosen product has been recommended not to be allowed for publication (for example the use of QSAR).

Non-standard tests are being reviewed in a case by case approach. The company is asked by the reviewer to provide as much information as possible about the test procedure in order to tell the relevance of the test both for the reviewing as such but even more important for the end-user of the data at www.fass.se. A short discussion is demanded along with the test results that argue for the relevance in the classification.

Quality assurance of environmental information on www.fass.se

All published material on the www.fass.se system is the sole responsibility of the specific company. Before publishing the environmental classification a pre-publishing is made in the www.fass.se editor. The pre-published data are reviewed by IVL. The reviewing comments are then passed on to the company by LIF.

The accuracy of the www.fass.se risk assessment was evaluated by Ågerstrand et al. (2010). This evaluation showed large discrepancies between what the guideline required in the form of underlying data for risk assessment and what the actual outcome on the www.fass.se webpage was. A revisit by the reviewer of these substances showed that there existed a gap between the actual outcome of the review and what was actually published on the www.fass.se. The issue of quality assurance is addressed by LIF. All information on the web portal of www.fass.se is owned by the companies and the participation in the reviewing process is optional. However, most companies do stick to the principles in the guideline, and do not publish until the reviewer has approved the data.

The evaluation by Ågerstrand et al. (2010) also pointed out that there was a low tendency among the pharmaceutical companies to incorporate data from the open scientific literature into the risk assessments. The bias towards using company owned data had according to the authors resulted in an under classification for the environmental risk for 10 out of the 48 assessments scrutinized (Ågerstrand et al., 2010). The suggestion by the authors to deal with this problem was to make

the incorporation of all available environmental data for the API mandatory in the risk assessment. This calls for a more detailed guideline not only on reporting different methods of assessing the toxicity but also on how to deal with non-standardized data. As of today regulatory demands for the introduction of new APIs does not give any guidance on the issue. The challenge on how to reach a shared approach to this within the industry therefore remains.

Methodological challenges when interpreting the guideline

A great challenge when developing a guideline for voluntary participation in a classification system such as the www.fass.se system is to find a balance between comparability between compounds and flexibility for the use of the most relevant data in every specific case. The guideline of www.fass.se leaves many openings for the companies to use non-standardized data and methods they find the most appropriate for their products. This can either be in-house or external non-standardized test data. In several cases there has been an interest from experts within the industry also to suggest new data and methods. These cases have led to a case by case reviewing approach. On certain occasions there has also been a need for a more profound discussion between the reviewers at IVL, the pharmaceutical companies and the environmental committee of LIF. Examples of such cases are the use of QSAR-modelling, and specifically the ECOSAR model (US Environmental Protection Agency, 2011) for predicting eco-toxicity and the interpretation of the OECD Protocol 308 in relation to the classification categories of persistence within the www.fass.se system. These two examples are further described below.

Validation of the ECOSAR modelling package with respect to pharmaceuticals

The use of QSAR-modelling, and specifically the ECOSAR model for predicting eco-toxicity was assessed and the result of this process was presented at Knappe (Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters) conference in Nîmes 2008. It was also addressed to the pharmaceutical industry as a letter from LIF. To see the full evaluation and the letter to LIF, please visit appendix1.

As an attempt to fill the data gap for ecotoxicity, QSAR (Quantitative Structure-Activity Relationship) modelling was suggested as tool to derive a PNEC for several APIs. The QSAR-package attempted for this was ECOSAR, a computerized predictive system that estimates the aquatic toxicity of industrial chemicals (US Environmental Protection Agency, 2011). However, ECOSAR has never been validated in the context of pharmaceuticals. In a brief evaluation, 39 ecotoxicological end points from 22 different pharmaceuticals (corresponding to the therapeutic main classes of *A, C, G, J, M, N, P* and *S*) were retrieved both from experimental data at www.fass.se and estimated by using the QSAR-modelling package ECOSAR.

The evaluation showed that the toxicity of pharmaceuticals was in several cases underestimated. Further, the prediction error of the used QSAR was very different between different organism groups (fish, daphnia, algae). For instance, the toxicity of tetracycline towards algae and daphnia was underestimated by the model while the corresponding toxicity towards fish was overestimated.

From this brief study of predictions of ecotoxicity retrieved using the ECOSAR QSAR package, it was obvious that the QSAR models of ECOSAR (ECOWIN v.0.99g) were not suitable to be used for the environmental risk assessment of pharmaceuticals. The overall prediction error was too large, the correlation too low, and often the depicted ecotoxicological data retrieved from the QSAR was not including the most sensitive species or end-point (see table in Appendix 1, last column "NOEC www.fass.se"). These objections to the unrestricted use of ECOSAR in the context of pharmaceuticals stems thus largely from the fact that ECOSAR was not developed with the intention to be used for the prediction of the ecotoxicological properties of pharmaceuticals. The conclusion from the reviewing team and the LIF environmental committee was therefore not to allow the use of such a model to fill the data gap without a sound scientific rationale included.

Interpretation of the OECD 308-protocol

In November 2008 an addendum to the existing guideline was designed to provide guidance to pharmaceutical companies on the use of data from the simulation study on degradation, OECD 308, in the www.www.fass.se environmental classification scheme. The OECD 308 guideline describes a laboratory test method to assess aerobic and anaerobic fate of organic chemicals in aquatic sediment systems. OECD 308 data are now being generated to support regulatory submissions in Europe, hence it is considered appropriate, where such data exist, to use these to support the environmental classification.

Fundamentally, the data generated from an OECD 308 study does not lend itself to the generation of independent half-lives for water and sediment since the test system represents a dynamic interaction between the two compartments. Furthermore, the presence of bound (unextractable) sediment residues often makes determination of half-lives in sediment impossible in practice. Consequently, the concept of a total system half-life has been introduced to support this classification scheme.

The following criteria were proposed for the different degradation phrases:

Degradation phrase	**t½ (DT50 from an OECD 308 study)**
The medicine is degraded in the environment	DT50<16d in freshwater and DT50<48d in sediment, or DT50<32d for the total system.
The medicine is slowly degraded in the environment	16d>DT50>40d in freshwater, or 48d>DT50>120d in sediment, or 32>DT50>60d for the total system.
The medicine is potentially persistent	DT50>40d in freshwater, or DT50>120d in sediment, or DT50>60d for the total system.

Additional requirements on test results to be fulfilled in order to use the criteria presented above are presented in the addendum. It is important to note that the addendum represents a novel approach to using DT50 data from OECD 308 studies for classification purposes. OECD guidelines do not provide any definitive fail/pass criteria for the OECD 308 test and there is no regulatory precedent for the values used in this scheme. As with all other aspects of the

'Guidance for Industry', this approach will be reviewed in an on-going basis and may be subject to future refinement based on developing scientific principles, new data and regulatory guidance.

Final results of the classification

A compilation of the performed risk assessments have been assembled (September 2011). In the following statistics the strictest classification was used in case one substance had different classifications. Of the 1200 substances at www.fass.se;

- 194 substances (16%) have been classified regarding environmental risk
- 252 substances (21%) have been classified regarding persistence
- 310 substances (26%) have been classified regarding bioaccumulation

In total, only 26 % of the substances published on www.fass.se have enough environmental information to be classified regarding risk, persistence and/or bioaccumulation, according to the guideline (Figure 2). This highly limits the potential of the system to be used as a comparative tool when selecting pharmaceuticals. However, 17 % of the substances on www.fass.se are regarded as exemptions in accordance with the EMA guideline, since they are unlikely to result in significant risk to the environment (e.g. electrolytes and proteins). 23 % of the substances have gone through the reviewing process, but due to lack of data they cannot be classified. For 34 % no information regarding classification was presented. One reason to this outcome could be that the reviewing process for exempted substances has changed during the development of the system. During the first years, this category was not subject to the full review process, and a significant proportion of the substances lacking classification appear to belong to this category.

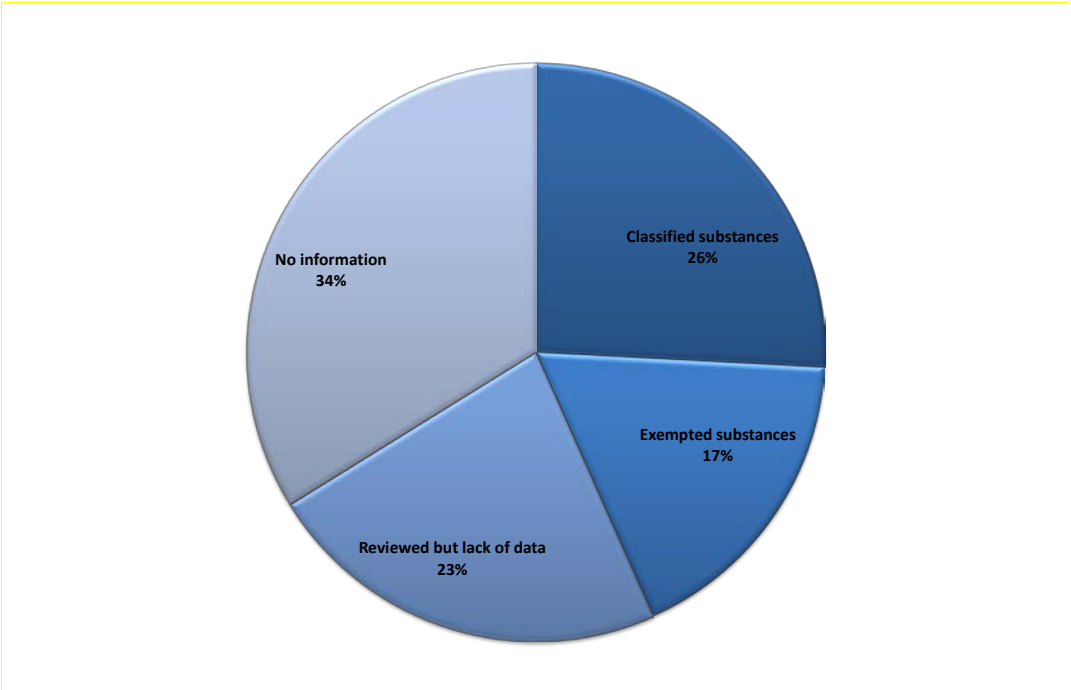

Figure 2. Outcome in terms of environmental classification of substances on www.fass.se (n=1200)

Of the pharmaceuticals classified according to risk (16% of the substances at www.fass.se) the majority (86%) end up in the classification category of "insignificant risk" e.g. the PEC/PNEC ≤ 0.1 (see Figure 3). The only compound ending up in the category of high risk was the hormone ethinylestradiol. In the category of moderate risk the substances acetylsalicylic acid, the penicillin amoxicillin, the hormone estradiol, the immune suppressors; mycofenolatmofetile and potassiummycophenolate, the beta-receptor blocker; propranolol and the selective serotonin reuptake inhibitor (SSRI) ingredient sertraline could be found. In the category of low risk the following substances could be found; the antibacterial substance ceftazidime, the antidepressant duloxetine, the antipsychotic klozapine, the antibiotics erythromycine, sulfamethoxazole, tetracycline and pivmecillinam, the potassium antagonist felodipine, the SSRI substance fluoxetine, galantamine used to treat dementia, the antimycotic ketoconazole, the non-steroidal anti-inflammatory (NSAID) drugs dexibuprofen and naproxen, the analgesic paracetamol, the anesthetic propofol, the anti-oestrogen fulvestrant, the kinase inhibitor sorafenib and the anticoagulant warfarin.

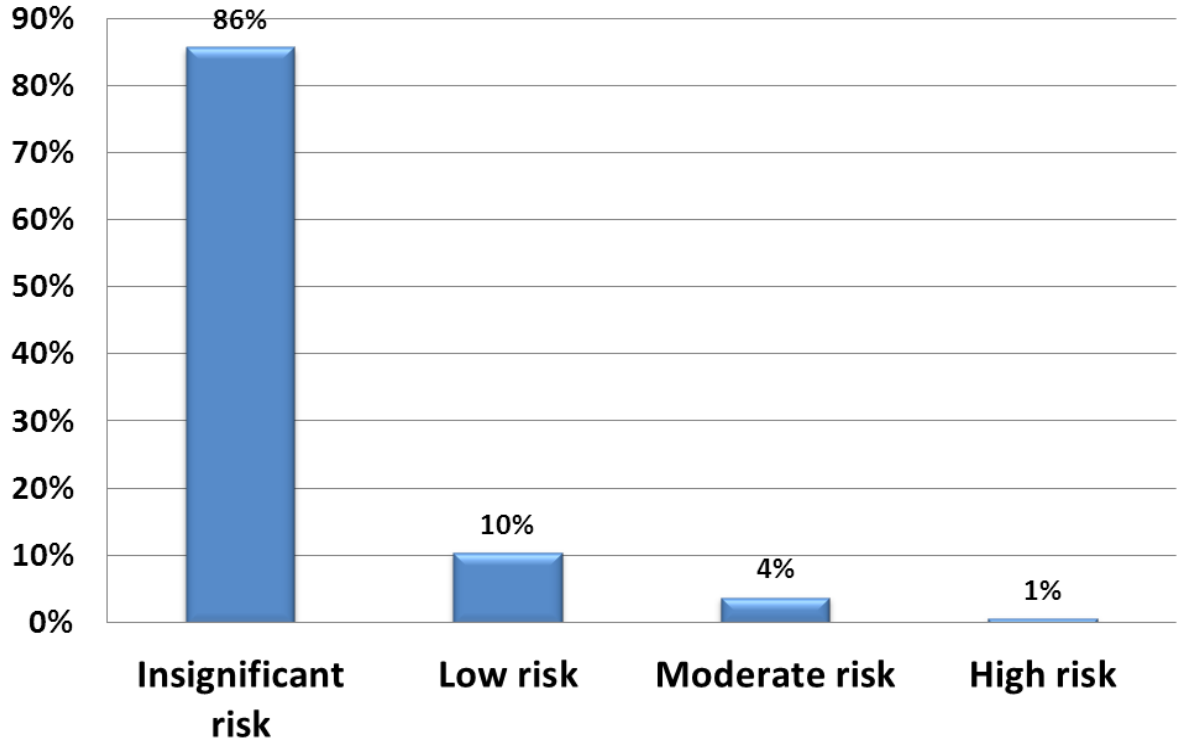

Figure 3. The outcome of the environmental risk assessments of pharmaceuticals in www.fass.se.

A fifth (22%) of the compounds classified regarding bioaccumulation potential (26% of the substances at www.fass.se) are considered as having the potential to bioaccumulate (Figure 4). This result could be expected as most pharmaceuticals are designed to be hydrophilic in order to enhance transport in the body. Many pharmaceuticals are also bio-transformed in the body which may lead to further enhanced water solubility when excreted.

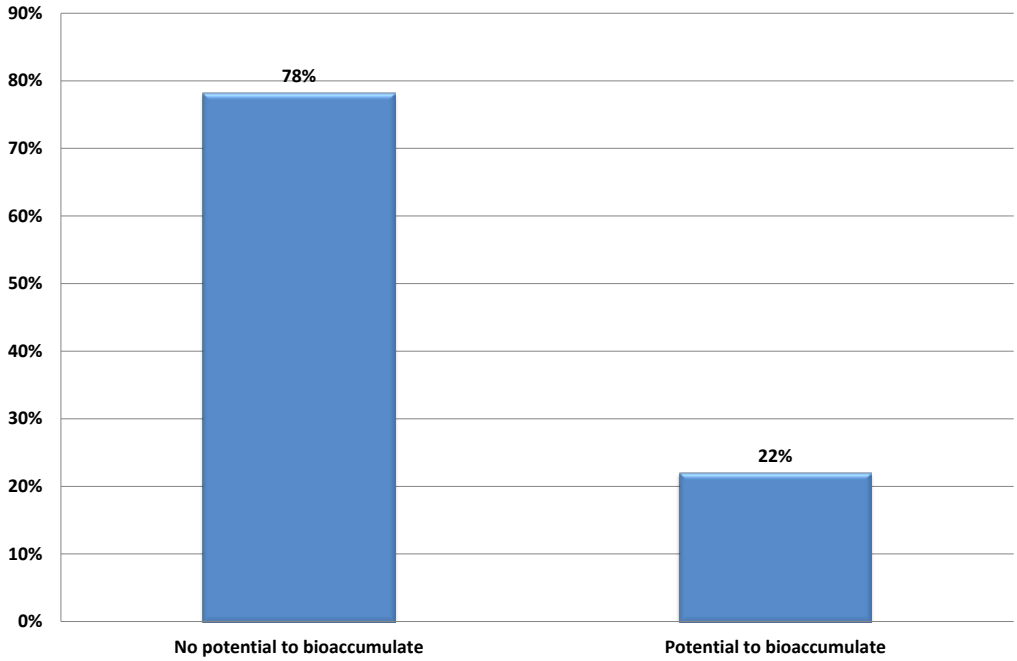

Figure 4. The outcome of the environmental classification of bioaccumulation on level 2 in www.fass.se.

The majority of the APIs classified on www.fass.se are in the category "potentially persistent" (Figure 5). This does not necessarily mean that they cannot be degraded in the environment, only that evidence for degradation is lacking. Substances within this category have failed a ready degradation test and /or the criteria proposed for the OECD 308 test. To end up in the category of "degradable "the substances need to pass any of these two tests. To further distinguish between those substances that do not pass the criteria for the category "degradable" there exists two categories for persistence. Substances that show inherent degradability, pass criteria proposed for the OECD 308 test, or show significant abiotic degradation are categorized as "slowly degradable".

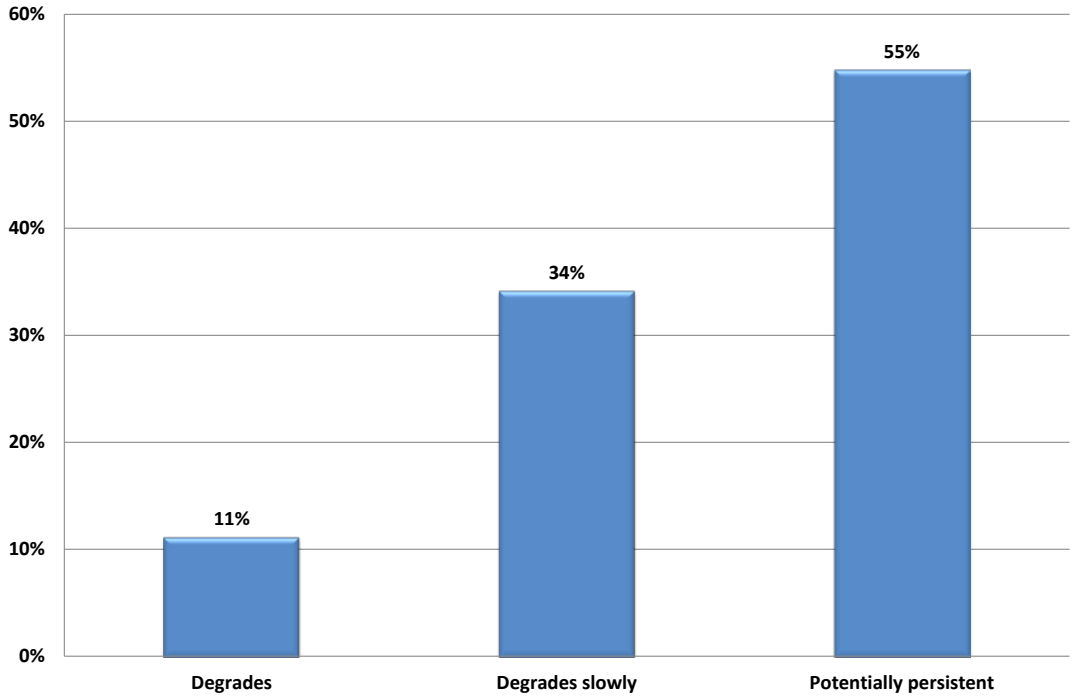

Figure 5. The outcome of the environmental classification of degradation on level 2 in www.fass.se

PEC vs. MEC in Sewage Treatment Plant (STP) effluents

A comparison of data from screening studies in the Swedish environment performed by IVL (Andersson et al., 2006; Woldegiorgis et al., 2007), including over 50 STPs throughout Sweden shows that the use of PEC based on sales data does not seem to underestimate the environmental risk for the aquatic environment (Table 1). PEC based on sales data are 1.5-150 times higher compared to environmental concentrations calculated based on measured average concentrations in effluent water (MEC in the table). Given a minimum of 10 times dilution in the recipient, the PEC calculation method used in www.fass.se thus seems to be in accordance with the precautionary principle. It should however be noticed that this is based on average measured concentrations in effluent water.

Table 1. Comparison of measured environmental concentrations based on average concentrations in effluent from Swedish STPs (MEC), and PEC presented at www.fass.se (Poster presented at Knappe Conference, 2008).

Name	# STPs	Detection frequency	Average Conc (µg/l)	MEC* (µg/l)	PEC (fass.se) ((µg/l)	PEC/MEC
Ibuprofene	**52**	**51(52)**	**1.6**	**0.16**	**16.7**	**105**
Naproxene	**52**	**52(52)**	**1.9**	**0.19**	**1.74**	**9**
Ketoprofene	**52**	**52(52)**	**1.1**	**0.11**	**0.51**	**4**
Diclofenac	**52**	**51(52)**	**0.25**	**0.025**	**0.63**	**25**
Oxytetracycline	**52**	**4(52)**	**0.10**	**0.010**	**0.04**	**4**
Tetracycline	**52**	**11(52)**	**0.07**	**0.007**	**0.13**	**18**
Estriol	**51**	**8(51)**	**0.032**	**0.0032**	**0.005**	**1.5**
Estradiol	**51**	**3(51)**	**0.013**	**0.0013**	**0.002**	**1.6**
Ethinylestradiol	**51**	**1(51)**	**0.004**	**0.0004**	**0.011**	**28**
Norethindrone	**49**	**21(49)**	**0.003**	**0.0003**	**0.006**	**20**

Progesterone	**49**	**42(49)**	**0.021**	**0.0021**	**0.008**	**3.6**
Propofol	**28**	**17(28)**	**0.059**	**0.0059**	**No DDDs**	**-**
Fentanyl	**28**	**0(28)**	**-**	**-**	**0.0006**	**-**
Dextropropoxyphene	**28**	**0(28)**	**-**	**-**	**0.3**	**-**
Bromocritptine	**28**	**0(28)**	**-**	**-**	**0.0009**	**-**
Clozapine	**28**	**0(28)**	**-**	**-**	**0.09**	**-**
Risperidone	**28**	**3(28)**	**0.0063**	**0.00063**	**0.003**	**4.8**
Zolpidem	**28**	**6(28)**	**0.0092**	**0.00092**	**0.06**	**65**
Sertraline	**28**	**0(28)**	**-**	**-**	**0.375**	**-**
Fluoxetine	**28**	**9(28)**	**0.035**	**0.0035**	**0.045**	**13**
Flunitazepam	**28**	**0(28)**	**-**	**-**	**0.0015**	**-**
Diazepam	**28**	**0(28)**	**-**	**-**	**0.0255**	**-**
Oxazepam	**28**	**28(28)**	**0.57**	**0.057**	**0.096**	**1.7**
Paroxetine	**28**	**12(28)**	**0.029**	**0.0029**	**0.039**	**14**
Citalopram	**28**	**28(28)**	**0.073**	**0.0073**	**0.255**	**35**
Zoplicone	**28**	**0(28)**	**-**	**-**	**0.075**	**-**

*MEC = Measured average concentrations in effluent water divided by a dilution factor of 10.

The potential impact of ERA at www.fass.se to reduce the environmental load of pharmaceuticals

The purpose of assessing the environmental risk of pharmaceuticals is to increase knowledge, understand any risks, and to be able to reduce any possible impacts in the environment. For the development of new pharmaceuticals, reduction of potential risks may be possible already when designing the molecules, e.g. by involving the pharmaceutical industry in what is called green pharmacy or benign by design (Kümmerer, 2009). For existing pharmaceuticals of environmental concern, reduction of potential risks instead could be done by reducing the content of APIs in the effluent streams from the STPs.

Integrating www.fass.se in the selection process at county level

Many counties in Sweden have pointed out the importance of potential environmental impacts of pharmaceuticals in their environmental programmes. The Swedish Environmental Management council has outlined a strategy for public procurement that states that all suppliers of pharmaceuticals should be encouraged to deliver relevant and third party reviewed data for the API, e.g. via www.fass.se. It should be clearly stated where this data is to be found. If no data can be presented the reason why should be explicitly communicated. This environmental data could be produced and presented by the company separately or it could be presented at www.fass.se (The Swedish Environmental Management Council, 2011).

One example of when published environmental data has been integrated in the selection process of pharmaceuticals is the Stockholm County Council's "Wise List". The Wise List is a recommendation for pharmaceuticals for common diseases based on scientific documentation regarding efficacy and safety, best practice and cost. Environmental information is however only taken into consideration when the pharmaceutical effect and the safety of two or more products are of equivalent importance (SCC, 2011).

In addition to the environmental risk assessment at www.fass.se, the Stockholm County Council has developed a model where each different classification category for toxicity, persistence and

bioaccumulation gives a value between 0-3, and when these values are added together the substance arrives at a final PBT-index (Persistence, Bioaccumulation and Toxicity) between 0-9. This PBT-index together with the risk is used when environmental concern is integrated in the selection process of pharmaceuticals (SCC, 2011).

Uppsala County Council has outspoken strategies for decreased use of compounds with high risks (Uppsala County Council, 2010), while others, like region Västra Götaland, have chosen not to integrate ERAs in their selection process since the assessments made in the system are not considered to be viable enough (Region Västra Götaland, 2011).

Environmental improvement or "business as usual"

The benefit of voluntary systems is that they can be put in place faster and more cost efficient than regulatory constraints. The effectiveness of voluntary systems have however been questioned (OECD, 2003). While some mean that voluntary initiatives are a flexible way to arrive at environmental targets at low costs others mean that the only value is "good will" for the industry. If the voluntary approach does not lead to any improved environmental targets but instead only reflects "business as usual" this could even lead to a "regulatory capture" (OECD, 2003).

Ågerstrand et al. (2009) pointed out in a stakeholder survey that few actors believe that the www.fass.se model would have any major impact on the prescription of medicines. Despite this many of the persons interviewed still believed that there is a value of the model just by the fact that information about pharmaceuticals is made available.

As long as ERAs have no impact in the approval process of a pharmaceutical, the socio-economic value of further exploring the issue of ERA regarding pharmaceuticals could be questioned. The benefit of the patient has always precedence even when unacceptable environmental risks are outlined (Straub, 2002). When substitution or removal is no longer an option, mitigation and precautionary safety measures are the only alternatives remaining.

An interview study of prescribing physicians in Sweden revealed that despite the choice to publish the environmental information in the well-known and frequently used web portal of www.fass.se, few physicians knew about the information (Citec, 2009). They also had little knowledge or interest in how to integrate the environmental impact when prescribing a pharmaceutical.

General conclusions and recommendations

The advantage of a self-declaration system as the www.fass.se system is that it encourages the involvement of pharmaceutical companies in the process of publically displaying their available environmental data and also to provide data for those substances where there is a data gap. Another advantage is that the information publically displayed is owned by the company which increases the chances that it will be updated along with changes in the product or when there are changes in the guidance process.

The difficulties with a self-declaration system are however that the assessments are made by several different actors on the market, with different level of expertise and different level of commitment to the system. This means that despite the fact that the system attempts to make

classifications of presented data on different levels depending on the knowledge of the users, the ambition to include as many products and as much data as possible makes these classifications difficult to compare for the non-qualified user.

The system also becomes dependent on the individual actors; voluntary acceptance of guidance, quality assurance and participation. Reviews of the resulting classifications on fass.se have revealed that there needs to be measures taken in order for the system to achieve a higher quality assurance.

The system seems to be in accordance with the precautionary principle regarding the PEC-calculations. However there have been discussions about the fact that it does not, in all cases, incorporate all available data on environmental effects. The area of using non-standardised data has to be addressed with new guidance on how to make this data integrated and comparable.

As 14 % of the pharmaceuticals were classified in the category low, moderate or high risk for the environment (as opposed to insignificant risk; see Figure 3), the area of environmental risk assessments for pharmaceuticals and the voluntary participation from the industry to publically display environmental data is of much interest and importance as ever.

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Appendix 1. Letter to the Industry (produced by Andreas Woldegiorgis, IVL)

Läkemedelsindustriföreningen, LIF

The Swedish Association of the Pharmaceutical Industry

May 3, 2007

Regarding the use of QSAR-models as a base for environmental risk assessments of pharmaceutical substances

The utilisation of QSAR (Quantitative Structure-Activity Relationships) have been introduced by a number of companies as a possible route to environmental risk assessment in the classification system on pharmaceutical substances as introduced by the Swedish Association of the Pharmaceutical Industry (LIF) in Sweden. Primarily, QSAR is used in data gap-filling for substances where necessary data for risk assessment is lacking.

As stated in the guidance document for the classification scheme (*Environmental classification of pharmaceuticals in www.www.fass.se – guidance for pharmaceutical companies 2007*) estimated data could be used as a substitute for experimental data if the latter is missing. However, the companies who chose to do so need to present the scientific rational for the estimations:

> "*It is preferred to use experimental data rather than estimated data (e.g. measured ecotoxicity/K_{ow} vs QSAR). If estimated data are used, the company should justify the scientific rationale. In some cases the reviewer may request additional information from companies to ensure consistency in the approaches used*."

The discussion on the following pages show that there are good reasons to question the use of QSAR-models for the estimation of eco-tox data utilized in environmental risk assessments. Several experts both internally and externally to the industry have expressed their concern regarding an "unrestricted usage" of QSAR-models. ***Therefore LIF, supported by our reviewing body for the classification system, IVL, would urge you to provide stronger support for the suitability of the chosen QSAR-model***. How was the model validated for pharmaceutical substances, are pharmaceuticals at all part of the predictive space of the model? How do we know that the model results in data that decently mirrors the "real world"? Is it possible to estimate the prediction error of the used QSAR model in terms of a RMSEP (Root Mean Square Error of Prediction) or RMSEC (Root Mean Square Error of Calibration)?

If no supporting rational for the use of the QSAR-models can be provided, it is instead recommended that you chose the statement:

> **Risk of environmental impact cannot be excluded, since no ecotoxicity data are available**

In Swedish: **Risk för miljöpåverkan kan inte uteslutas då ekotoxikologiska data saknas**

On behalf of LIF and IVL;

One of the QSAR-packages that have been used in submissions to the Swedish Classification System is ECOSAR. However, ECOSAR has never been validated in the context of pharmaceuticals. In a brief study, 39 ecotoxicological end points from 22 different pharmaceuticals (corresponding to the therapeutic main classes of *A*, *C*, *G*, *J*, *M*, *N*, *P* and *S*) were retrieved both from experimental data at www.fass.se and estimated by using the QSAR-modelling package ECOSAR. The results have been evaluated in a pair-wise manner (Figure 1-2) and a full compilation of the data is given in Table 1 below.

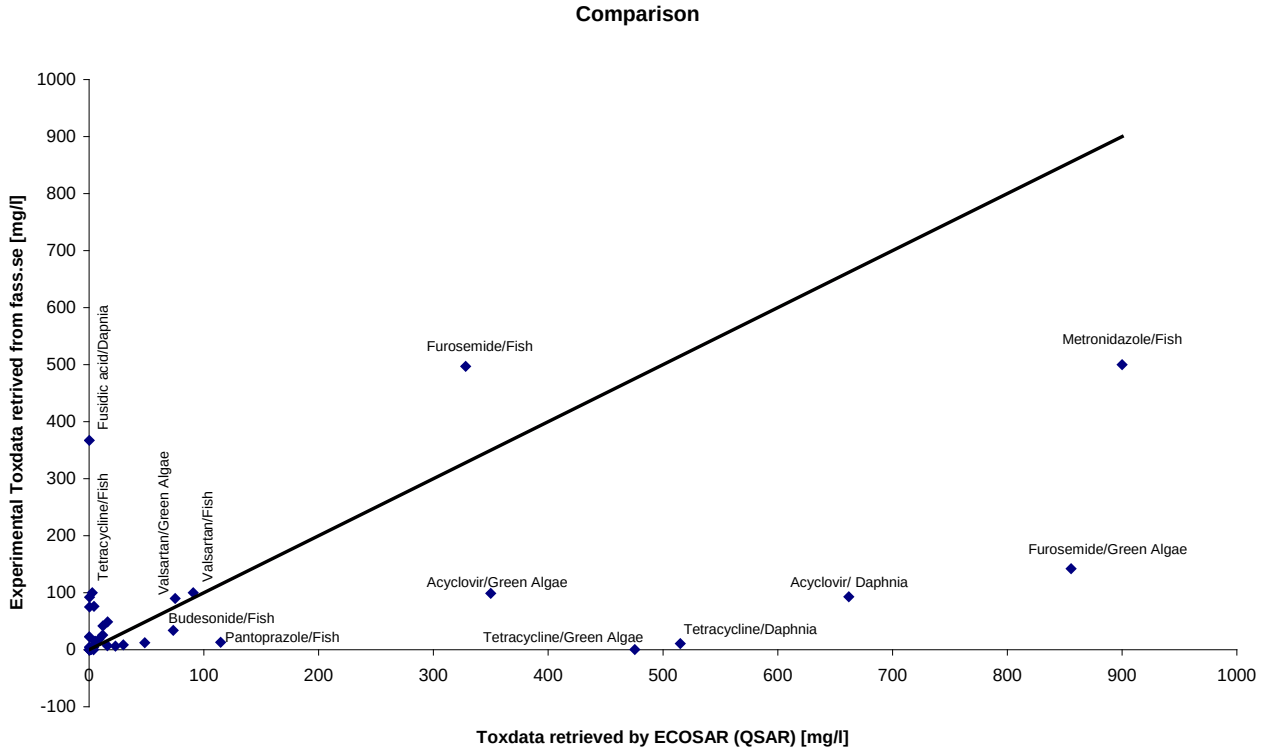

Figure 1. *Y*-axis corresponds to experimental ecotoxicological data retrieved from the www.fass.se-database while the *X*-axis corresponds to predict ecotoxicity data retrieved using different QSARs from the ECOSAR package. The solid line represents the ideal case where the predicted data is in 100 % agreement with the experimental values, while points positioned below the line represents cases where the used QSAR clearly underestimates the toxicity of the corresponding pharmaceutical. In cases where the chosen QSAR overestimates the toxicity of the drug, the point is situated above the solid line.

A can be seen in figure 1 several cases where the toxicity of a pharmaceutical is significantly underestimated are identified. Also alarming is the fact that for a given pharmaceutical different species (fish, daphnia and algae) the prediction error of the used QSAR is very different. For instance, the toxicity of tetracycline towards algae and daphnia is grossly underestimated by the model while the corresponding toxicity of tetracycline towards fish is overestimated. This type of results renders it even more difficult to use ECOSAR as a tool for environmental risk assessment (PEC/PNEC-approach) of pharmaceuticals.

When the data is re-plotted on a logarithmic scale (in order to increase resolution) also the prediction error of the most toxic compounds is visible (figure 2).

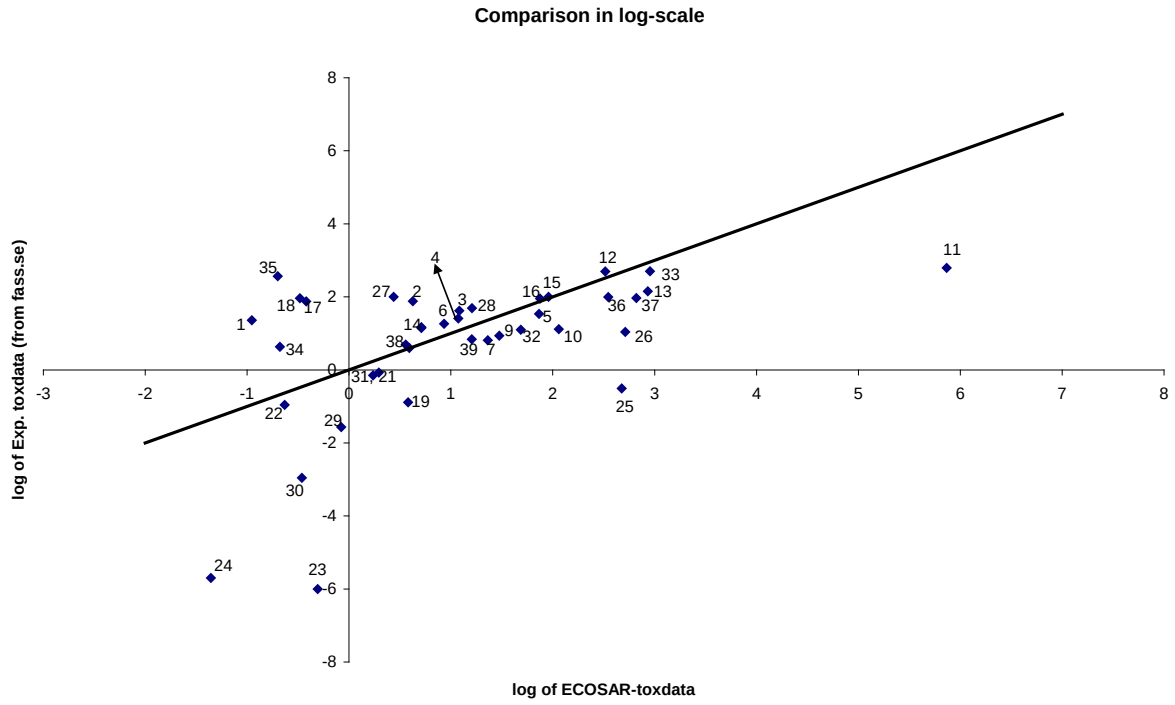

Figure 2. The same data as in figure 1 but plotted with logarithmic scales on both axes. The numbers indicate the corresponding pharmaceutical, species and toxicity end point. A unit step in the log scale corresponds to a difference in toxicity by a factor of 10. Points situated below the solid line correspond to cases (*pharmaceutical, species, end point*) where the chosen QSAR underestimates the toxicity. The point nr 20, representing the toxicity of Ezetimibe towards Green algae (96 h EC_{50}) falls exactly on the solid line, indicating in this rare case an excellent agreement between QSAR and experimental data.

Conclusion

From this brief study of predictions of ecotoxicity retrieved using the ECOSAR QSAR package, it is obvious that the QSAR models of ECOSAR (*ECOWIN v.0.99g*) are not suitable to use for the environmental risk assessment of pharmaceuticals. The overall prediction error is too large, the correlation too low, and often the depicted ecotoxicological data retrieved from the QSAR is not including the most sensitive species or end point (see table 1, last column "NOEC www.fass.se"). Noteworthy is the fact that for some of the results retrieved from ECOSAR, the end point concentration may very well be above the water solubility of the pharmaceutical (*Furosemide, Cromolyn sodium*).

These objections to the unrestricted use of ECOSAR in the context of pharmaceuticals stems thus largely from the fact that ECOSAR was not developed and 'trained' with the intention to be used for the prediction of the ecotoxicological properties of pharmaceuticals.

# Fig. 2	Pharmaceutical	ATC-code	Species ECOSAR	End point ECOSAR	End point Exp.	QSAR ECOSAR	ECOSAR [mg/l]	Experimental [mg/l]	Difference [mg/l]	NOEC www.fass.se [mg/l]
1	Simvastatin	C10AA01	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Ester'*	0.111	22.8	-22.689	9.6
2	Diclofenac	M01AB05	Daphnia	16 d, EC_{50}	48 h EC_{50}	*'Neutral org. acids'*	4.24	76	-71.76	10
3	Omeprazole	A02BC01	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Imidazoles'*	12.1	41.9	-29.8	23.2
4	Pantoprazole	A02BC02	Green algae	96 h, EC_{50}	OECD 201, EC_{50}	*'Imidazoles'*	11.81	25.75	-13.94	-
5	Pantoprazole	A02BC02	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Imidazoles'*	73.35	34	39.35	25.7
6	Lansoprazole	A02BC03	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Imidazoles'*	8.56	18.3	-9.74	6.2
7	Rabeprazole	A02BC04	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Imidazoles'*	23.02	6.5	16.52	2.7
8	Rabeprazole	A02BC04	Green algae	96 h, EC_{50}	72 h, EbC_{50}	*'Imidazoles'*	5.128	14	-8.872	3.3
9	Budesonide	A07EA06	Green algae	96 h, EC_{50}	72 h, EbC_{50}	*'Vinyl/Allyl ketones'*	29.8	8.6	21.2	5.6
10	Budesonide	A07EA06	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Vinyl/Allyl ketones'*	114.6	13	101.6	-
11	[3]Cromolyn sodium	A07EB01	Daphnia	48 h, LC_{50}	48 h, EC_{50}	*'Vinyl/Allyl Ethers-acid'*	$7.36*10^{5}$	620	735380	-
12	Furosemide	C03CA01	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Neutral org. acids'*	328	497	-169	-
13	Furosemide	C03CA01	Green algae	96 h, EC_{50}	OECD 201, EC_{50}	*'Neutral org. acids'*	855.6	142	713.6	-
14	Carvedilol	C07AG02	Green algae	96 h, EC_{50}	72 h, EbC_{50}	*'Aliphatic Amines'*	5.14	14.8	-9.66	0.5-1

[3] Chronic toxicity of Cromolyn Sodium towards Daphina corresponds to 74802 mg/l acc. ECOSAR

15	Valsartan	C09CA03	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Neutral org. acids'*	90.8	100	-9.2	-
16	Valsartan	C09CA03	Green algae	96 h, EC_{50}	72 h, IC_{50}	74.9	74.9	90	-15.1	58
17	Atorvastatin	C10AA05	Green algae	96 h, EC_{50}	72 h, EbC_{50}	*'Neutral org. acids'*	0.38	75	-74.62	24
18	Atorvastatin	C10AA05	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Neutral org. acids'*	0.33	92	-91.67	92
19	Ezetimibe	C10AX09	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Phenols'*	3.8	0.13	3.67	0.13
20	Ezetimibe	C10AX09	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Phenols'*	3.9	4	-0.1	4
21	Ethinyl Estradiol	G03AB03	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Phenols'*	1.96	0.84	1.12	0.000001
22	Ethinyl Estradiol	G03AB03	Daphnia	21 d, chronic	21 d, EC_{50}	*'Phenols'*	0.234	0.11	0.124	0.000001
23	Ethinyl Estradiol	G03AB03	Fish	Chronic	Early life stages, chronic	*'Propargyl Alc-hindered'*	0.493	0.000001	0.493	0.000001
24	Estradiol	G03CA03	Fish	90 d, chronic	Early life stages, chronic	*'Phenols'*	0.044	0.000002	0.044	0.000002
25	Tetracycline	J01AA07	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Aliphatic Amines'*	475.4	0.31	475.09	0.1
26	Tetracycline	J01AA07	Daphnia	48 h, LC_{50}	48 h, LC_{50}	*'Benzyl Alcohols'*	515	11	504	2
27	Tetracycline	J01AA07	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Vinyl/Allyl Alcohols'*	2.74	100	-97.26	100
28	Abacavir	J05AR02	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Imidazoles'*	16.1	49	-32.9	26
29	Fluoxetine	N06AB03	Green algae	96 h, EC_{50}	$EC_{50,}$ TAD4.01	*'Aliphatic Amines'*	0.84	0.027	0.813	0.0011
30	Fluoxetine	N06AB03	Green algae	96 h, Chronic	14 d, NOEC	*'Aliphatic Amines'*	0.345	0.0011	0.344	0.0011
31	Fluoxetine	N06AB03	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Aliphatic Amines'*	1.72	0.71	1.01	0.005

32	Metronidazole	P01AB01	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Imidazoles'*	48.5	12.5	36	-
33	Metronidazole	P01AB01	Fish	96 h, LC_{50}	NOEC	*'Imidazoles'*	900	500	400	-
34	Fusidic acid	S01AA13	Green algae	96 h, EC_{50}	EC_{50}	*'Esters-acid'*	0.21	4.3	-4.09	-
35	Fusidic acid	S01AA13	Daphnia	48 h, LC_{50}	48 h, EC_{50}	*'Esters-acid'*	0.2	367	-366.8	-
36	Acyclovir	S01AD03	Green algae	96 h, EC_{50}	72 h, EC_{50}	*'Imidazoles'*	350	99	251	99
37	Acyclovir	S01AD03	Daphnia	48 h, LC_{50}	48 h, EC_{50}	*'Imidazoles'*	662	93	569	93
38	Mirtazapine*	N06AX11	Green algae	96 h, EC_{50}	NOEL	*'Aliphatic Amines'*	3.6	4.9	-1.3	4.9
39	Mirtazapine*	N06AX11	Fish	96 h, LC_{50}	96 h, LC_{50}	*'Aliphatic Amines'*	16	6.92	9.08	1.27

* Most sensitive NOEC reported in www.fass.se for Mirtazapine corresponds to 0.24 mg/l for Daphnia, 21 d semi-static test.