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

## Experiences from the reviewing process during 2013

*Linda Örtlund, Petra Wallberg & Jörgen Magnér*

IVL Swedish Environmental Research Institute

**Author:** Linda Örtlund, Petra Wallberg & Jörgen Magnér
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IVL Swedish Environmental Research Institute Ltd.,
P.O Box 210 60, S-100 31 Stockholm, Sweden
Phone: +46-8-598 563 00 Fax: +46-8-598 563 90
www.ivl.se

This report has been reviewed and approved in accordance with IVL's audited and approved management system.

# Foreword

IVL Swedish Environmental Research Institute has since 2005, with the launch of the system of self-declarations of environmental classification in www.fass.se, conducted a project focussed on review of the self-declarations financed by LIF - the Research-Based Pharmaceutical Industry in Sweden and the Foundation for IVL Swedish Environmental Research Institute (SIVL). This report has been prepared with the aim to achieve transparency by explaining the role and the experiences of the reviewer, which may be useful in future development of the system. The main target groups are LIF and its member companies, participating in the system, as well as users of the environmental classifications, e.g. county councils and researchers.

Two previous reports have been published from this project; Lilja et al. (2013) that deals with the experiences from the implementation of the project and Andersson et al. (2013) on experiences from the reviewing process during 2012.

It is of outmost importance that the review is equivalent, irrespective of which persons in the review group that are involved. To facilitate the introduction of new personnel into the group of reviewers it is an on-going task to develop a support system to ensure a common interpretation of the guideline and resulting assessments.

During 2013 the reviewing group at IVL has been changed and a new reviewer and contact person Linda Örtlund, was introduced in the group.

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# Summary

In 2005 environmental information was published for the first two groups of products in www.fass.se, to test a new model for classification, developed on an initiative from LIF (The Research-Based Pharmaceutical Industry in Sweden). The initiative was a response to an increasing public demand for environmental information on pharmaceuticals and an attempt to develop a model accepted by Swedish stakeholders, but also by the global pharmaceutical industry. In 2010, all groups of pharmaceuticals (ATC codes) on the Swedish market had been the subject of an environmental risk assessment.

During the implementation of the environmental classification system IVL Swedish Environmental Research Institute (IVL) performed a project with the aim to identify and address the pitfalls of the system. This project was financed by LIF and the Foundation for IVL Swedish Environmental Research Institute (SIVL). IVL reviewed the pre-published data and took part in a discussion, led by LIF, with the pharmaceutical companies about how to implement the guideline for environmental risk assessment, developed by LIF (LIF Expert Group Environment) in cooperation with stakeholders and the international industry. The goal of this reviewing process was 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 to the system owners, LIF.

The review of pre-published environmental risk assessments and system evaluation is an on-going task and the present report describes the experiences from the review process during the year 2013. With its iterative process, IVL gives feedback to LIF regarding the system as such, both from a scientific perspective as well as from a quality assurance perspective. The following concluding remarks can be made:

- Eight years after the launch of the self-declaration system of environmental classification at www.fass.se, all groups of pharmaceuticals have been the subject of an environmental risk assessment. This has resulted in a unique collection of environmental risk assessments for pharmaceutical substances, accessible to experts, county councils and other purchasing actors, as well as the public.

- IVL has given feedback to LIF regarding the system as such both from a scientific perspective as well as from a quality assurance perspective, providing possibilities to evaluate and improve the system.

- In the review of the classifications IVL has informed the companies, via LIF, on the revision needs, in order for the environmental risk assessments to be conducted according to the principles in the guideline (LIF 2012), in a scientifically acceptable way, thus supporting the quality and credibility of the system.

- 328 risk assessments were reviewed during 2013. About 30 % of these received no remarks and were recommended for publication; a large part of these were however substances exempted for classification. The remaining risk assessments received comments with recommendations for revisions.

- The publication of the new guideline in 2012 (LIF 2012) generated an overhaul of the reviewing process at IVL where effort was placed to generate a common implementation of the new guideline within the group of reviewers. This work has continued in 2013.

- Many risk assessments were reviewed several times before publication in www.fass.se was recommended by the reviewer. This could be an indication of a need for clarifications of the review comments in certain cases. Efforts were thus made to further clarify the comments when risk assessments were being sent for review several times without sufficient revisions in between. This work will continue with the aim to achieve a review process with no unnecessary delay in publication of the updated environmental risk assessments.

- During 2013 IVL conducted literature studies for ibuprofen and diclofenac in order to facilitate the review of the environmental risk assessments of these substances and to enable consistent recommendations of up to date data in the review comments. This is however a field where future research will generate further data and these literature studies will therefore be living documents.

- It was recognized already in 2012 that the use of the statistics (provided by IMS Health) on the total sales of the Active Pharmaceutical Ingredient (API), for the Predicted Environmental Concentration (PEC) derivation, needed further review. Checking reported usage statistics is now included in the responsibilities of the reviewer, so far with comments generally directed to LIF rather than the companies. Focus was also placed to ensure that it is clear to the reader that the sales data cover total sales of the API, i.e. the amount from all human medicines marketed by different companies containing the same API. These control efforts continued in 2013.

- As the number of substances covered by the system have grown, and therefore also the number of reviews, there is an increasing need to improve the work processes during the review. This has been done with the aim to achieve a robust and transparent system, further improving the quality control. As one part of this work, a database has been developed.

# Sammanfattning

Under 2005 publicerades miljöinformation för de första två grupperna av produkter på www.fass.se, för att testa en ny modell för klassificering, utvecklad på initiativ av LIF - De forskande läkemedelsföretagen. Initiativet var en respons på en ökande efterfrågan på miljöinformation om läkemedel från allmänheten, och ett försök att utveckla en modell som kunde accepteras både av svenska intressenter, men också av den globala läkemedelsindustrin. År 2010 hade miljöriskbedömningar publicerats för alla grupper av läkemedel (ATC-koder) på den svenska marknaden.

När miljöklassningssystemet infördes hade IVL Svenska Miljöinstitutet (IVL) ett projekt finansierat av LIF och stiftelsen IVL (SIVL) med syfte att identifiera och åtgärda fallgropar i systemet. Genom att granska den opublicerade miljöinformationen deltog IVL i en diskussion med läkemedelsföretagen, som leddes av LIF, om hur man skall implementera den miljöguide som utvecklats av LIF (Expertgrupp Miljö) i samarbete med intressenter och den internationella industrin. Målet var att etablera en gemensam praxis för implementering av miljöguiden mellan de olika företagen och att återkoppla erfarenheter från självdeklarationsprocessen tillbaka till systemägaren, LIF.

Granskningen av miljöriskbedömningar innan de publiceras på www.fass.se, och utvärdering av systemet är en kontinuerligt pågående aktivitet och i föreliggande rapport beskrivs erfarenheterna från granskningsarbetet under 2013. För det gångna året har följande sammanfattande kommentarer och slutsatser kunnat göras:

- Åtta år efter lanseringen av självdeklarationssystemet för miljöklassning på www.fass.se, har miljöriskbedömningar genomförts för alla grupper av läkemedel. Detta har resulterat i en unik samling av miljöriskbedömningar för läkemedel, tillgängliga för experter, landsting och andra aktörer inom inköp, liksom för allmänheten.

- IVL har återkopplat till LIF om systemet både ur ett vetenskapligt perspektiv och ur ett kvalitetssäkringsperspektiv, vilket har gett LIF möjligheter att utvärdera och förbättra systemet.

- Genom granskningsarbetet har IVL informerat företagen, via LIF, om behov att revidera miljöinformationen, för att miljöriskbedömningarna skall följa Miljöguiden (LIF 2012) på ett vetenskapligt godtagbart vis. Detta är viktigt för att stödja kvaliteten och trovärdigheten i systemet.

- 328 riskbedömningar granskades under 2013. Ungefär en tredjedel av dessa fick inga anmärkningar och publicering rekommenderades. En stor andel av dessa var dock substanser som är undantagna för klassificering. De övriga riskbedömningarna fick kommentarer med rekommendationer för revidering innan publicering på www.fass.se.

- I och med publiceringen av den senaste versionen av Miljöguiden (LIF 2012) initierades en översyn av granskningsprocessen på IVL, med syfte att utarbeta en gemensam tillämpning av den nya miljöguiden och fastställa ett standardiserat uttryckssätt, så långt möjligt, i kommentarerna om revideringsbehov av miljöriskbedömningarna. Detta arbete har fortsatt under 2013.

- Även under 2013 ökade medvetenheten om att en del riskbedömningar granskades flera gånger innan publicering på www.fass.se kunde rekommenderas. Detta kan vara en indikation på ett behov av bättre tydlighet och ansträngningar gjordes för att ytterligare förtydliga kommentarerna. Detta arbete fortsätter i syfte att minska risken för onödiga förseningar i publiceringen av miljöriskbedömningarna.

- IVL genomförde litteraturstudier för ibuprofen och diklofenak vilka ska fungera som stöd för att kunna ge konsekventa rekommendationer i granskningskommentarerna. Eftersom framtida forskning kommer att generera ytterligare uppgifter, kommer litteraturstudierna att vara levande dokument.

- Det konstaterades redan 2012 att statistiken av försäljningsmängden av aktiva ingredienser i läkemedel (vilken tillhandahålls av IMS Health), som används i beräkning av ”Predicted Environmental Concentration” (PEC), behövde granskas. En kontroll av den angivna totala försålda mängden ingår därför nu i granskningsrutinen, men än så länge med kommentarer främst riktade till LIF och inte direkt till företagen. Fokus har även legat på att tydliggöra att försäljningsdata täcker den totala försäljningen av den aktiva ingrediensen, d.v.s. från alla humanläkemedel som marknadsförs av olika företag. Detta arbete har fortsatt under 2013.

- I och med att antalet ämnen som omfattas av systemet och därmed antalet granskningar har ökat finns det ett ökat behov av att förbättra arbetsprocesserna för granskningen. Syftet är att uppnå ett robust och transparent system, och ytterligare förbättra kvalitetskontrollen. Som ett led i detta arbete har en databas och ett verktyg för granskningsarbetet utvecklats under 2013 som sätts i drift under 2014.

# 1 Background

Pharmaceuticals are widely used substances. At the start of this project, approximately 1200 active compounds in about 7600 different products existed on the Swedish market (Swedish Medical Products Agency, 2004). During the last decades pharmaceuticals have become recognized as relevant environmental contaminants (Halling-Sörensen et al., 1998, Kümmerer (ed), 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 by LIF - The Research-Based Pharmaceutical Industry in Sweden. 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. In 2010, environmental risk assessment has been conducted for all groups of pharmaceuticals (ATC codes) on the Swedish market.

During the implementation of this environmental classification system IVL Swedish Environmental Research Institute (IVL) run a project with the aim to identify and address the pitfalls of the system. This project was financed by LIF and the Foundation for IVL Swedish Environmental Research Institute (SIVL).

By reviewing the pre-published data IVL took 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 expert group on environment. The goal of this reviewing process was 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 outcome of the first part of the project was described in a report by Lilja et al. (2013).

At present the project continues with review of pre-published data and system evaluation, and IVL as an independent reviewer. With its iterative process, the project gives feedback to LIF regarding the system as such, both from a scientific perspective as well as from a quality assurance perspective. The review of the classifications informs the companies on the needs in order for the environmental risk assessments to be conducted according to the principles in the guideline (LIF 2012), in a scientifically acceptable way, thus supporting the quality and credibility of the system.

The overall aim of the project 2013 was to continue to develop and strengthen the Swedish environmental classification system in order to make it a powerful tool on a national level and to raise acceptance and interest on an international level. This included continued review of the companies' interpretation of the guideline, with in depth discussions with LIF in cases where more guidance than the guideline contains was needed.

In addition to this continuous review, as part of the project during 2013, a database and review assessment tool has been developed. The aim of this work was to achieve a robust and transparent system which will further improve the work processes and

quality control during the review and thereby clarify the format of the comments provided to the pharmaceutical companies.

## 1.1 Environmental classification of pharmaceuticals at www.fass.se

### 1.1.1 How the classifications are made

In the environmental classification of pharmaceuticals at www.fass.se, the risk posed by the pharmaceuticals is differentiated in four different categories, insignificant risk, low risk, moderate risk and high risk. In addition to the risk phrase, which concerns the risk of ecotoxicological effects, each substance is assigned hazard phrases for bioaccumulation and persistence. A substance can be exempted from classification, in accordance with the European Medicines Agency (EMA) Guideline (EMA 2006), if they are unlikely to result in significant risk to the environment, e.g. proteins, vitamins and electrolytes.

The environmental assessment at www.fass.se is presented at two different levels. For the non-expert user there is a level with summary phrases describing the classifications regarding environmental risk, degradation and bioaccumulation, assigned to the substance. For the expert reader a second level includes all information that has been the basis for the self-declaration, and/or references to documents that have been used.

### 1.1.2 The guideline and the reviewing process

The guidelines to what environmental data that support and differentiate the classification steps were developed by a Swedish working group led by LIF, including representatives from the industry, the Stockholm county council, the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency (MPA). After the deregulation of the pharmacy market in Sweden the pharmacy chain Apoteket has been replaced by the Swedish Pharmacy Association in the dialog. The first guideline was published in 2007 and revised document was presented in June 2012.

Before publication of environmental data on www.fass.se, the risk and hazard assessments are reviewed by IVL. IVL comments on the choice of classification phrase based on supporting data and gives recommendations to LIF whether or not revision is needed by the company before publication. If revision is needed, the company is encouraged to send the risk assessment for another review before publication.

The review by IVL results in comments in three categories:

- **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 (although not mandatory) to be in full compliance with guideline

One or more major or minor deviations mean that IVL recommends revision of the risk assessment and new check in for review before publishing on www.fass.se. If remarks are given, revisions according to the remark are recommended but the risk assessment need not be checked in for a new review before publishing. The environmental risk assessment of each substance is published for three years and will thereafter be updated after a new review by IVL.

The quality of the published environmental data is the responsibility of the company and to make sure that it is the agreed classification that is published on www.fass.se. The system as of today does not permit LIF, or IVL, to inhibit any classifications. To ensure the impartiality of the reviewer there is generally no direct contact between the company and the reviewer.

# 2 Experiences from the reviewing process during 2013

In this chapter brief descriptions of the experiences from the reviewing process during 2013 are given, starting with summary statistics for the year, followed by descriptions of the major methodological challenges identified during the year.

## 2.1 Statistics of the review process during 2013

During 2013, 328 environmental risk assessments, for 302 substances, were reviewed. The majority of the risk assessments were only reviewed once (61 %)[1], 27 % were reviewed twice, 11 % three times and less than 1 % four times. The total number of reviews was 494 and the most common assessment from IVL was to give no remark and to recommend publication at www.fass.se (Figure 1)[2]. The second most common assessment was a "minor deviation". This means that the classifications of risk or/and hazard are correct but there are deficiencies in the submitted material that needs to be changed before publication, and thus a revision of the risk assessment was recommended. A large part of the risk assessments given no remarks were for exempted substances, which are not being classified for risk or hazard.

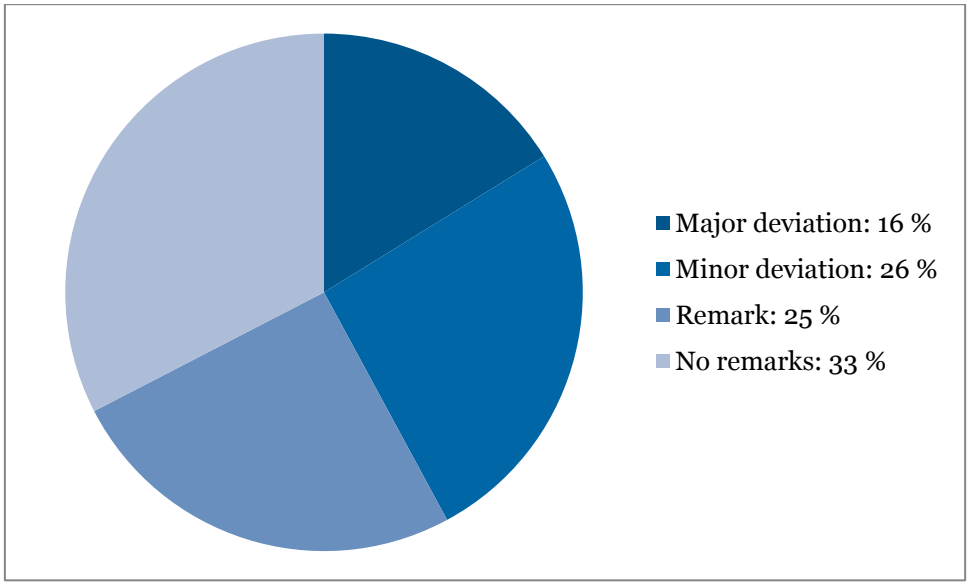


**Figure 1: Distribution of how the recommendations were given by IVL, on the 328 risk assessments sent for review during 2013. The figure is based on the total number of reviews, i.e. 494. The figure shows the highest grade of comment for each risk assessment during that review, i.e. in the order major deviation, minor deviation, remark and no remarks.**

[1] These statistics cover only 2013, which mean that for some substances the review process (first review of the environmental risk assessment) might have started before 2013 and for some substances the review process continues in 2014.
[2] Note that these statistics contain all reviews during the year, i.e. often more than one per environmental risk assessment. Normally the revision of the environmental risk assessment leads to less severe comments in the next review, and eventually only remarks or no remarks.

The new guideline for environmental risk assessment (LIF 2012) follows the same principles as the previous version of the guideline, published in 2007 (LIF 2007). In the revised guideline for environmental risk assessment several sections are further extended and give a more detailed description on how the risk assessment should be conducted. Examples of changes in the review process since the revised guideline was published are:

- Request of additional information for a number of substances suggested to be classified as exemptions.
- Complete reference lists are requested if such lists are missing.
- The use of external data is now more strongly requested in the review, if such data are known to be available.
- Recommendations to follow the suggested outline of the document presented in the appendix.

More examples of updates important for the review of the environmental risk assessments are given in our report of the experiences from the review process during 2012.

After the revived guideline was launched in June 2012 the reviewing process also needed to be updated. Discussions were initiated in 2012 and continued in 2013 to find a common interpretation of the guideline, both within the reviewing team and with LIF.

It is possible to identify deviations in the statistics of 2013 (Figure 1), compared to the statistics from previous years, that could be explained by the introduction of a revised guideline. A comparison between data from 2012 and 2013 reveals a change in the proportion of assessments given by IVL. The most common assessment from IVL in both 2012 and 2013 was *No remarks*. However, in relation to the total number of assessments the proportion decreased from approximately 50% to 33% from 2012 to 2013. Instead the proportion of documents receiving a *Remark* as the most severe comment from IVL has increased. The total percentage of *Major* and *Minor deviations* during 2013 is approximately the same as during 2012 but with a shift towards a greater proportion of *Minor deviations* instead of *Major deviations*.

## 2.2 Literature studies on ibuprofen and diclofenac

During 2013 literature reviews on ibuprofen and diclofenac were conducted. In 2012, a literature study on estrogenic substances was performed as it was recognized by LIF that several of these substances had different classification between different companies as described in the report by Andersson et al. (2013). A similar problem was suspected for ibuprofen since it is a pharmaceutical sold by more than one company in Sweden. It was therefore considered important to take recent research into account in the reviewing process. As the literature search on ibuprofen proceeded, interesting information was simultaneously found regarding diclofenac that also was assembled. Diclofenac is of interest as it is included in the watch list of the Water Framework Directive and as a consequence a lot of new information has become available.

The focus of the review was primarily to gather new data on Predicted No Effect Concentration (PNEC) but also data concerning degradation rates or bioaccumulation factors assembled. The reviews will be living documents and updated when found needed.

## 2.3 Continued control of sales data

During 2012 LIF did recognize the need to review that the correct data on total sales of the Active Pharmaceutical Ingredient (API) were used in the calculation of the Predicted Environmental Concentration (PEC). The reason for this was that the statistics from 2011 in some cases was difficult to interpret and thus unintentional errors may occur. Therefore IVL now receives the yearly statistics collected by IMS Health, and checks that the correct amount is used for each API. If needed LIF is consulted regarding the interpretation of the statistics and LIF may forward the question to IMS Health or to the company, to ensure correct use of the data.

Focus is also placed on how the sales data were described and referenced; assuring that the reader of the environmental information understands that data cover total sales of the API in Sweden for a specific year, i.e. the amount from all human medicines marketed by different companies containing the same API, as well as the source of the data.

# 3 Final results of the classification

The statistics are based on environmental risk assessments published on www.fass.se 2013-12-18[3], and thus, it includes all risk assessments that have been published and reviewed within the last three year period (2011-2013). The statistics show that 22 % of the unique substances were classified regarding environmental risk, 41 % were exempted from classification and 37 % were reviewed but due to lack of data no classification could be made (either no data at all or not sufficient data).

The total number of unique substance was 875 and for these substances 1156 environmental risk assessments were published. The larger number of risk assessments in comparison to the number of unique substances was due to the fact that one substance can be marketed and, thus, risk assessed by more than one company.

On the Swedish market today there are currently approximately 1200 APIs. The majority of these APIs are covered by the www.fass.se collaboration and the companies marketing these have the possibility to take part in the environmental classification system.

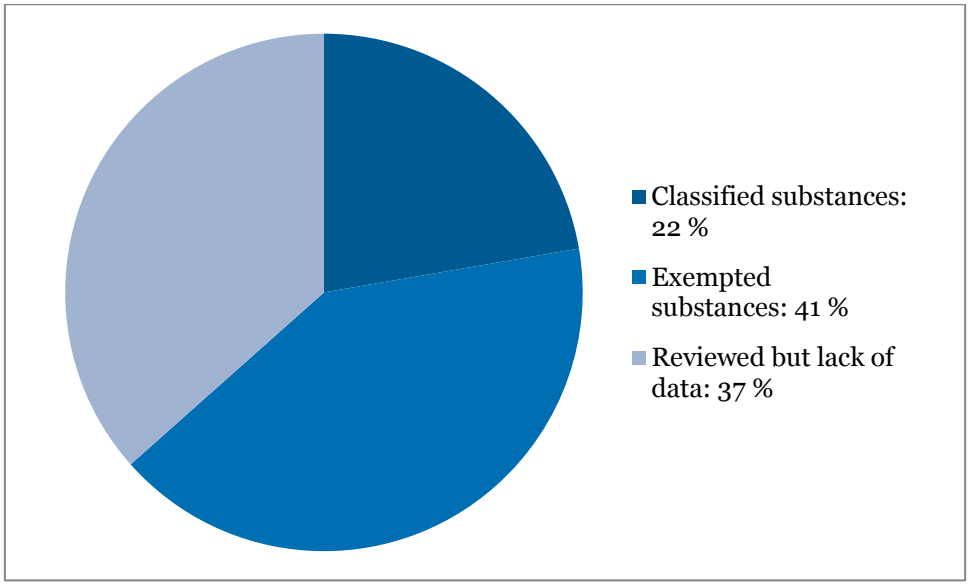


**Figure 2: Outcome in terms of environmental classification of substances on www.fass.se (n = 875). The figure covers classification of environmental risk, i.e. not potential for degradation or bioaccumulation.**

## 3.1 Environmental risk

Of the 195 (22 %) substances classified according to environmental risk the vast majority were classified as posing an insignificant risk (82 %), 13 % were classified as

[3] In case a substance has more than one classification a conservative approach was used and the most severe classification for that substance was used in the statistics

low risk, 5 % as moderate risk and only 1 % as high risk (Figure 3). A classification of an insignificant risk means that the PEC/PNEC ≤ 0.1, low risk 0.1< PEC/PNEC ≤ 1, moderate risk 1< PEC/PNEC ≤ 10 and high risk PEC/PNEC > 10.

The substance classified as posing a high risk was the hormone ethinylestradiol and the substances classified as posing a moderate risk were the penicillin amoxicillin, the acne reducing benzoyl peroxide, the antibacterial substance ciprofloxacin, the hormone estradiol, the immune suppressors mycophenolate mofetil and mycophenolate sodium, the proton pump inhibitor and parasiticidum permethrin, the beta-receptor blocker propranolol, the antidepressant (selective serotonin reuptake inhibitor, SSRI) sertraline and the antifungal terbinafine.

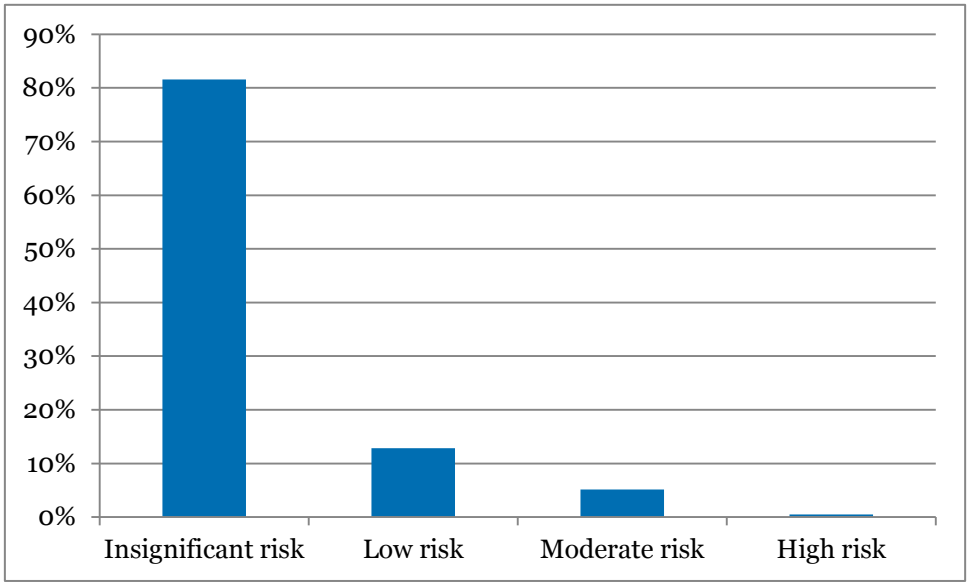


**Figure 3: The outcome of the environmental risk assessments of pharmaceuticals in www.fass.se (n = 195).**

## 3.2 Potential to bioaccumulate

Depending on when the risk assessment was conducted the environmental risk assessments currently published at www.fass.se are classified according to either criterion for bioaccumulation from the guideline of 2007, i.e. cut off for potential bioaccumulation is log $K_{ow}$ >3 or 2012 where log $K_{ow}$ >4 indicates potential for bioaccumulation (see section 1.1.2). Thus, some of the substances in the category "high potential to bioaccumulate" may have a log $K_{ow}$ between 3 and 4 (Figure 4).

Of the 875 substances at www.fass.se, 319 (36 %) were assessed for bioaccumulation potential. For 185 substances (21 %) data to make an assessment were not available and for 371 substances (42 %) a hazard phrase was not assigned. The majority of the latter were exempted substances, for which an assessment of bioaccumulation potential was not made.

As shown in Figure 4, the vast majority of the substances with a classification of the bioaccumulation potential were assigned a hazard phrase indicating a low potential to bioaccumulate. For pharmaceuticals, often designed to be hydrophilic to enhance transportation in the body, this is to be expected. Many substances do also undergo metabolism to more hydrophilic forms in the human body.

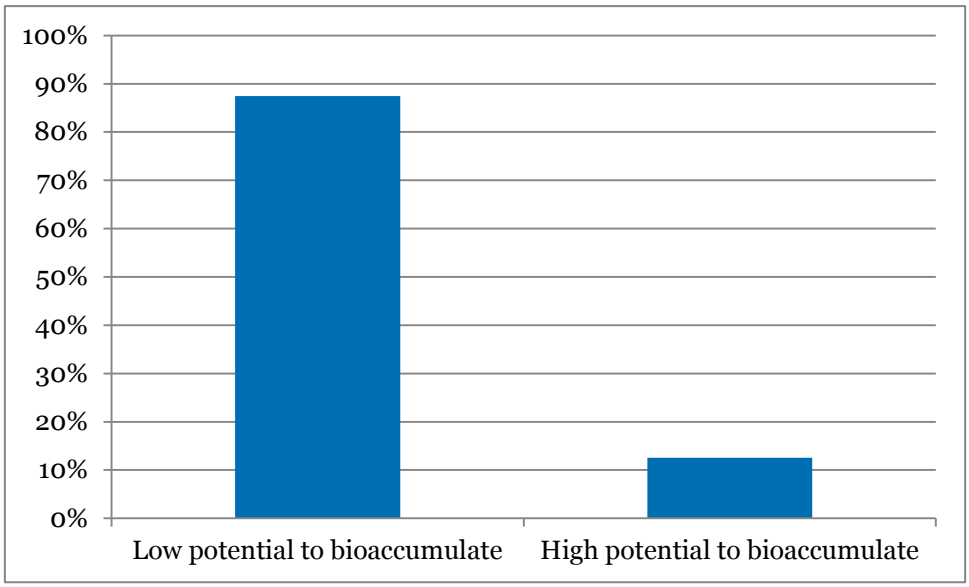


**Figure 4: The outcome of the classification of bioaccumulation in www.fass.se (n = 319). Some of the substances in the category "high potential to bioaccumulate" may have a log Kow between three and four as the statistics cover assessments of bioaccumulation from before and after the publication of the new guideline.**

## 3.3 Persistence

Of the 875 substances at www.fass.se, 240 substances were classified for degradation (27 %), data for classification were lacking for 263 substances (30 %) and for 372 substances (43 %), of which the majority were exempted substances, no hazard phrase was assigned.

In the assessment of degradability the majority of the substances classified for degradation were assigned the phrase indicating that the substance is potentially persistent (59 %). Substances are classified as degradable e.g. if they have passed the ready biodegradability test (e.g. OECD 301) or sufficiently low dissipation half-lives are achieved in the OECD 308 test. Slowly degradable substances show e.g. inherent degradability (e.g. OECD 302), pass the criteria set up for the OECD 308 test or show significant biotic or abiotic degradation in other tests. However, a classification that the substance is potentially persistent does not necessarily mean that it cannot be degraded in the environment, but that lack of sufficient data result in the classification persistence or that persistence cannot be excluded. Substances within this category have failed a ready and /or inherent degradation test and /or the criteria proposed for

the OECD 308 test. Substances within this category could also have been indicated to be potentially persistent, based on other standard or non-standard data.

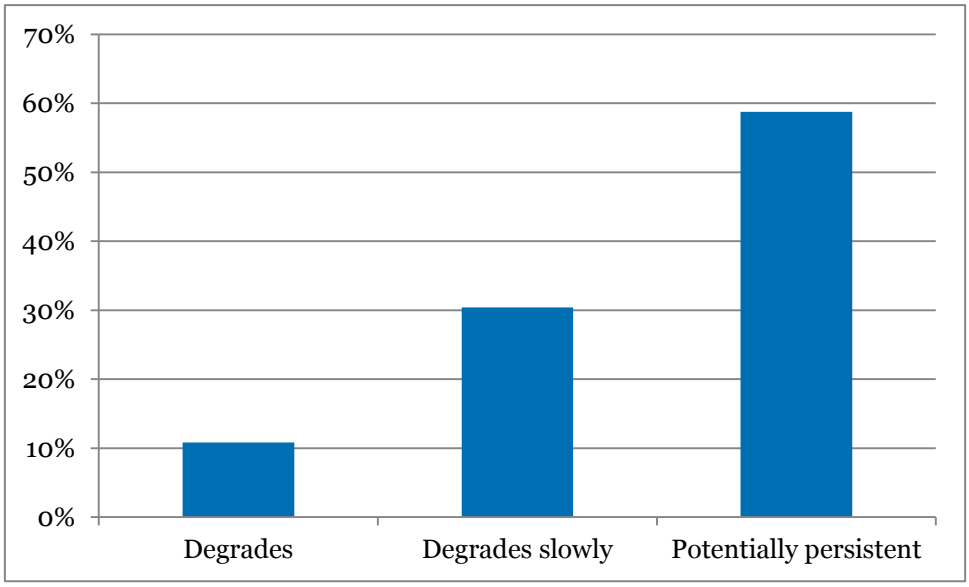


**Figure 5: The outcome of the classification of degradation in www.fass.se (n = 240).**

In the previous report by Lilja et al. (2013), with corresponding statistics from September 2011, the outcome of classification was in general very similar to what is presented here. The substances that were included in the highest risk categories had changed to some extent, showing that although the general picture of the outcome was similar, the underlying data had changed.

# 4 Outlook towards 2014 and onwards

One of the major tasks forward is to improve the reviewing process with the aim to minimize the number of iterations. This would speed up the process considerably as some of the risk assessments are checked in for review several times. This should be possible to achieve with a combination of activities.

The database has been designed and developed during 2013 and the testing phase has commenced. The database is fed by a data stream triggered by the user of the application, where the not yet reviewed environmental risk assessments are available. The database and review assessment tool is ready to become operational with start in spring 2014.

During the start-up period effort will continue to be placed to further clarify the comments when risk assessments are being checked in for review several times without sufficient revisions in between. The database will give a much better possibility for overview of the reviewing process of a specific substance, and improved possibilities to identify where further clarifications in the review comments may be needed in order for successful revision of the risk assessment.

During 2014 and 2015 the Fass.se-project will continue to develop and strengthen the Swedish environmental classification system in order to make it a powerful tool on a national level and to raise acceptance and interest on an international level. This will be achieved by two separate activities:

- Continued review of the companies' interpretation of the guideline, with in depth discussions with LIF in cases where more guidance than the guideline contains is needed. During the review process the content and implementation of the guideline (LIF 2012) is continuously evaluated and discussed within the review team at IVL and between LIF and IVL. The results of these discussions could be one of the inputs when the guideline is eventually once again updated.

- Improve the knowledge about the reduction of pharmaceuticals in a waste water treatment plant (WWTP) and the degradation in the environment to better support environmental classifications.

# 5 Concluding remarks

- Eight years after the launch of the self-declaration system of environmental classification at www.fass.se, environmental risk assessments have been conducted for all groups of pharmaceuticals. This has resulted in a unique collection of environmental risk assessments for pharmaceutical substances, accessible to experts, county councils and other purchasing actors, as well as the public.

- IVL has given feedback to LIF regarding the system as such, both from a scientific perspective as well as from a quality assurance perspective, providing possibilities to evaluate and improve the system.

- In the review of the classifications IVL has informed the companies, via LIF, on the revision needs, in order for the environmental risk assessments to be conducted according to the principles in the guideline (LIF 2012), in a scientifically acceptable way, thus supporting the quality and credibility of the system.

- 328 risk assessments (pre-published) were checked in for review during 2013. About 30% of these received no remarks and were recommended to be published; a large part of these were however substances exempted for classification. The remaining risk assessments received comments with recommendations for revisions.

- The publication of a new guideline in 2012 generated an overhaul of the reviewing process at IVL where effort was made to generate a common implementation of the new guideline within the group of reviewers. This work has continued in 2013.

- It was also recognized that many risk assessments were being checked in for review several times before publication at www.fass.se. This could be an indication of a need for clarifications of the review comments in certain cases. Effort was, thus, placed to further clarify the comments when risk assessments were being checked in for review several times without sufficient revisions in between. This work will continue with the aim to achieve a review process with no unnecessary delay in publication of the updated environmental risk assessments.

- IVL conducted literature studies for ibuprofen and diclofenac as it was recognized that new research concerning these substances had generated relevant data for environmental risk assessment that was not always taken into consideration in the classifications at www.fass.se. These literature studies facilitated the review of the environmental risk assessments of these substances, enabling consistent recommendation of up to date data in the review comments. As we can foresee, this is a field where future

research will generate further data, why the literature studies will be living documents.

- It was recognized already in 2012 that the use of the statistics on the total sales of the API (provided by IMS Health), used in the PEC derivation, needed further follow-up. This is now included in the responsibilities of the reviewer, so far with comments generally directed to LIF rather than the companies. Focus was also placed to ensure that it is clear to the reader that the sales data cover total sales of the API, i.e. the amount from all human medicines marketed by different companies containing the same API. These control efforts continued in 2013.

- As the number of substances covered by the system, and therefore also the number of reviews, has grown, there is an increasing need to improve the work processes during the review. This has been done with the aim to achieve a robust and transparent system, improving the quality control. As one part of this work a database has been developed and will become operational with start in spring 2014.

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IVL Swedish Environmental Research Institute Ltd., P.O. Box 210 60,
S-100 31 Stockholm, Sweden
Phone: +46-8-598 563 00 Fax: +46-8-598 563 90
www.ivl.se