REPORT

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

- experiences from the reviewing process during 2012

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B 2124
September 2013

The report approved:
2013-09-19

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Report Summary

Project title
Implementation and development of ERA on Fass.se 2012

Project sponsor
LIF the research based pharmaceutical industry

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Title and subtitle of the report

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

- experiences from the reviewing process during 2012

Summary

In parallel to the implementation of the environmental classification system at www.fass.se, IVL has conducted a study of the review process with the aim to identify and address the pitfalls of the system. With experience from the reviewing process, IVL took part in a discussion, led by LIF, with the pharmaceutical companies about how to improve the implementation of the guidelines 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 provide feedback from the experience of 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 2012.

Keyword

Environmental risk assessment, classification, pharmaceuticals, self-declaration system

Bibliographic data

IVL Report

The report can be ordered via

Homepage: www.ivl.se, e-mail: publicationservice@ivl.se, fax+46 (0)8-598 563 90, or via IVL, P.O. Box 21060, SE-100 31 Stockholm Sweden

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, run a project financed by LIF - the Research-Based Pharmaceutical Industry in Sweden and the Foundation for IVL Swedish Environmental Research Institute (SIVL). One part of IVLs role in the project is to, as an independent party, review the self-declarations before publication in www.fass.se. The present report includes a description of the experiences from the reviewing process during 2012, as well as an outlook to 2013 and onwards. The report is published with the aim to achieve a transparency; explaining the role and the experiences of the reviewer. The aim is also to provide insight to the reviewing process, 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.

The background and introduction in the present report is partly based on the report by Lilja et al. (2013).

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.

Under implementeringen av miljöklassningssystemet har IVL Svenska Miljöinstitutet (IVL) genomfört ett projekt finansierat av LIF och stiftelsen IVL (SIVL) med syfte att identifiera och åtgärda fallgropar i systemet. Genom att granska den opublicerade miljöinformationen har IVL deltagit i en diskussion med läkemedelsföretagen, som leds av LIF, om hur man skall implementera den miljöguide som utvecklats av LIF (Expertgrupp Miljö) i samarbete med intressenter och den internationella industrin. Målet har varit 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 2012. För det gångna året har följande sammanfattande kommentarer och slutsatser kunnat göras:

- Sju 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 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; LIF 2007) på ett vetenskapligt godtagbart vis. Detta är viktigt för att stödja kvaliteten och trovärdigheten i systemet.

- 454 riskbedömningar granskades under 2012. Ungefär hälften av dessa fick inga anmärkningar och publicering rekommenderades. Majoriteten av dessa var dock substanser som är undantagna för klassificering. Den andra hälften fick kommentarer med rekommendationer för revidering innan publicering på www.fass.se.

- I och med publiceringen av en ny miljöguide 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.

- Under året ökade också medvetenheten om att många riskbedömningar granskades flera gånger innan publicering på www.fass.se kunde rekommenderas. Detta kan vara en indikation på ett behov av förtydliganden av granskningskommentarerna och ansträngningar gjordes för att ytterligare förtydliga kommentarerna. Detta arbete kommer att fortsätta i syfte att minska risken för onödiga förseningar i publiceringen av miljöriskbedömningarna.

- För en grupp av östrogena ämnen har ny forskning genererat relevanta data för miljöriskbedömning som inte tidigare har beaktats i klassificeringen på www.fass.se. IVL genomförde därför en litteraturstudie som stöd för granskningen av miljöriskbedömningar av dessa ämnen. Denna litteraturstudie möjliggjorde en konsekvent rekommendation av data i granskningskommentarerna. Vi kan förutse att framtida forskning kommer att generera ytterligare relevanta uppgifter, varför litteraturstudien kommer att vara ett levande dokument framöver.

- Det konstaterades att för statistiken av försäljningsmängden av aktiva ingredienser i läkemedel (vilken tillhandahålls av IMS Health), som används i beräkning av Predicted Environmental Concentration (PEC), behövdes ytterligare granskning. En kontroll av den angivna totala försålda mängden ingår därför nu i granskningsrutinen, än så länge med kommentarer ofta 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.

- 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 förbättra kvalitetskontrollen. Som ett led i detta arbete planeras utvecklingen av en databas och ett verktyg för granskningsarbetet.

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 of pharmaceuticals and an attempt to develop a model accepted both 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 to an environmental risk assessment.

During the implementation of this environmental classification system IVL Swedish Environmental Research Institute (IVL) has conducted a study aiming 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). In the role of being responsible for reviewing the pre-published data, IVL took part indiscussions 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 provide feed-back on 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 2012. For the past year the following concluding remarks could be made:

- Seven 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 and from a quality assurance perspective, thus providing suggestions on how to evaluate and improve the system.

- In the review of the classifications IVL has informed the companies, via LIF, on the necessary revision, to ensure that the environmental risk assessments are conducted according to the principles in the guideline (LIF 2012), and in a scientifically acceptable way. Thus supporting the quality and credibility of the system.

- 454 risk assessments were reviewed during 2012. About half of these received no remarks and were recommended for publication; the majority of these were however substances exempted for classification. For the remaining compounds comments with recommendations for revisions were provided.

- The publication of a new guideline initiated an overhaul of the reviewing process at IVL where efforts were focussed on generating a common implementation of the new guideline within the group of reviewers and to establish standardized writing, as far as possible, in the comments given by IVL.

- It was also recognized that many risk assessments were being reviewed several times before publication at www.fass.se could be recommended by the reviewer. This could be an indication of a need for clarifications of the review comments in certain cases. Effort was 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 without unnecessary delay in publication of the updated environmental risk assessments.

- For a group of estrogenic substances it was recognized that new research has generated relevant data for environmental risk assessment that was not always taken into consideration in the classifications published at www.fass.se. IVL conducted a literature study to facilitate 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 that this is a field where future research will generate further relevant data the literature study will be a living document.

- It was recognized 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 control. This is now included in the responsibilities of the reviewer, so far with comments often 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.

- As the number of substances covered by the system, and therefore also the number of reviews, have grown, there is an increasing need to improve the procedures of the review. This will be done with the aim to achieve a robust and transparent system, improving the quality control. As one part of this work, the development of a database and review assessment tool is being planned.

Contents

1 Background

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).

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).

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 2012 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 2011 and 2012, removal processes in the sewage treatment plant as well as in the environment have been studied

with the use of multivariate analysis. The results from these studies are reported in Rahmberg & Björk (2012) and Rahmberg et al. (2013).

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 displayed 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 there exist a second level with all information available that has been the basis for the self-declaration, and/or references to documents that have been used. The advantage of this is that any deviation from 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.

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 (after the re-regulation of the pharmacy market in Sweden the dialogue now takes place with the Swedish Pharmacy Association), the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency (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. The quality of the environmental data published on www.fass.se is however the sole responsibility of the specific company. LIF allows for publication or encourage the company to adjust the classification according to the review. Depending on the type of comments, the company may be 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 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 reviewed again before publishing.

It is 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, or IVL, to inhibit any classifications. To ensure the impartiality of the reviewer direct contact between the company and the reviewer is avoided. If direct contact is taken, LIF is always informed.

Each environmental risk assessment is published for three years. Thus, every third year the environmental risk assessment of each substance is updated. The updated risk assessment is sent in for review before publication at www.fass.se.

In the summer of 2012 a new guideline for environmental risk assessment was published by LIF (LIF 2012).

2 Experiences from the reviewing process during 2012

In this chapter brief descriptions of the experiences from the reviewing process during 2012 are given, starting with summary statistics for the year, which is followed by descriptions of the major methodological challenges identified during the year.

2.1 Statistics of the review process during 2012

During 2012, 454 environmental risk assessments, for 406 substances, were reviewed. The majority of the risk assessments were only reviewed once during 2012 (82%)[1]. 13% were reviewed twice, 4% three times, 1% four times and 0.2% 6 times.

The number of reviews during 2012 was 566 and the most common assessment from IVL was to give no remark, i.e. to recommend publication at www.fass.se (Figure 1)[2]. The second most common assessment was however a "major deviation", which means that one or several of the risk and hazard phrases were not correct 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.

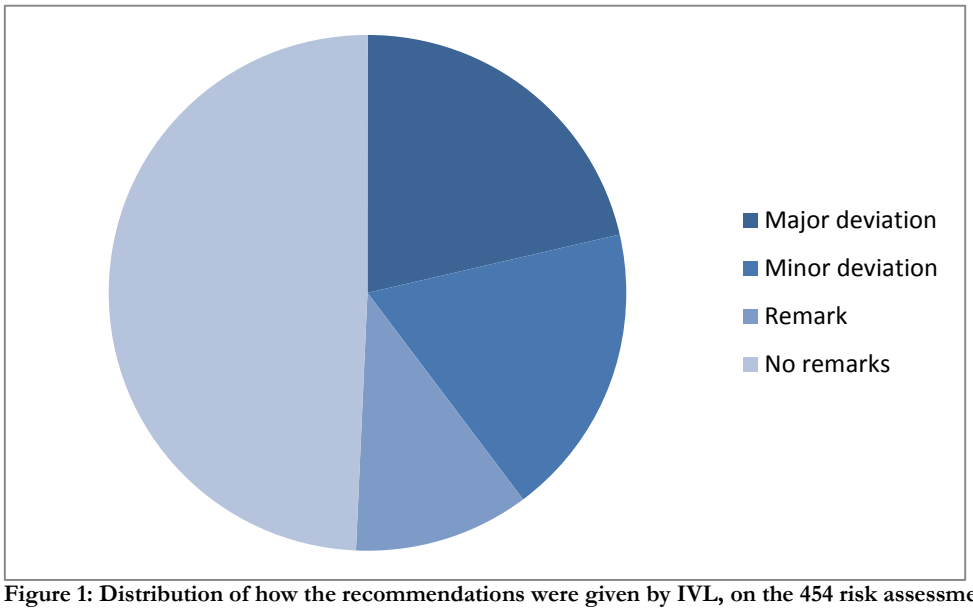

Figure 1: Distribution of how the recommendations were given by IVL, on the 454 risk assessments sent for review during 2012. The figure is based on the total number of reviews, i.e. 566. The figure shows the highest grade of comment for each risk assessment during that review, i.e. in the order major deviation, minor deviation, remark and no remarks.

[1] These statistics cover only 2012, which mean that for some substances the review process (first review of the environmental risk assessment) might have started before 2012 and for some substances the review process continues in 2013.
[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.

2.2 New guideline

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). However, in the new guideline several sections are further clarified and it gives a more detailed description on how the risk assessment should be conducted.

Examples of updates important for the review of the environmental risk assessments are:

- The chapter on exempted substances has been elaborated and the phrases assigned to an exempted substance updated. The new guideline does also open up to exempt other substances than those listed by EMA (vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids), and for the reviewer to request full environmental information even if the substances are exempted according to the EMA guideline (EMA 2006).

- How references should be given has been clarified; all submitted data should be referenced and all references included in a list at the end of the document. Furthermore the use of external data, e.g. scientific publications, is more pronouncedly encouraged.

- In the new guideline the former addendum on how to interpret the results from the OECD 308, on aerobic and anaerobic transformation in aquatic sediment systems, has been incorporated and to some extent simplified.

- The threshold for assessment of bioaccumulation potential has been changed. In the previous version of the guideline a substance was assessed as having a significant bioaccumulation potential if the partition coefficient between water and octanol, the logK_{ow}, was over three (logK_{ow} > 3). In the new guideline this threshold was changed to a log K_{ow} of four (log K_{ow} > 4). The reason for this change is to adapt to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS), where the trigger is log K_{ow} > 4 to indicate a potential for bioaccumulation (www.unece.org). The naming of the hazard phrases have been changed from “no significant bioaccumulation potential”/”potential to accumulate in aquatic organisms” to “the substance has low potential for bioaccumulation”/”the substance has high potential for bioaccumulation”. Furthermore, in the new guideline, clarifications have been made regarding the threshold for how a bioconcentration factor (BCF) shall be used.

- In appendix 1of the new guideline a recommended structure of the risk assessment document has been included

The more detailed guideline provides, to some extent, basis for a more detailed review. Examples of changes in the review process since the new guideline was published are:

- Request of additional information for a number of substances suggested to be classified as exemptions.
- The use of external data is now more strongly requested in the review, if such data are known to be available.
- The outline given in the appendix is recommended to follow for unstructured documents.

With the new guideline also the reviewing process needed to be updated and the first months with the new guideline in use, effort was put to find a common interpretation of the guideline, both within the reviewing team and also with LIF. To achieve this, a number of discussion points were identified by IVL and these were discussed with LIF at project meetings designated to discuss the reviewing process. These discussion points concerned the full guideline and not necessarily only the updates. In a few cases LIF informed the companies participating in the www.fass.se system, of the outcome of a specific discussion and how it affected their work with the risk assessments.

2.3 Improved reviewing process

During 2012 IVL has made some changes in the work procedure to strive towards greater extent of continuity in the reviewing process, aiming for a faster process from the time the unpublished data are sent to IVL until the company receives IVL's comments. The group of reviewers has been expanded and the delivery of environmental risk assessments for review is now sent from LIF to IVL with regular intervals. These new arrangements aimed to minimize the risk that documents for review accumulate at IVL, and thus to shorten the time from when the document is sent for review until the comments are received.

The introduction of new personnel into the group of reviewers is however a challenging task, as it is of outmost importance that the review is equivalent, irrespective of which persons in the review group that are involved. Therefore it is an on-going task to ensure a common interpretation of the guideline as well as similar way of expression in the comments, and thus equal review independent on the reviewer.

Another attempt to achieve a faster process, with less iterations of a review and thus revisions, has been to clarify the review comments further when a risk assessment was sent in for review again without the necessary revisions. The aim of course being to achieve a revision of the risk assessment, which would result in a material that IVL can recommend for publishing.

As the system grows with its continuous existence, the need for a database, to store the outcomes of the review, has become apparent. The number of substances with

environmental risk assessments has grown substantially since the start (2005), and the number of sets of reviewing comments grows continuously as the risk assessments undergo three year revisions. The iterative process of review of the risk assessments need to be stored in a format where it is easy to search for the full review history of a substance, for a specific company. This would not only support the quality assurance procedures, ensuring that the environmental risk assessment undergoes equivalent review, independent of the reviewer, but also provide IVL valuable support in identifying where more elaborate comments may be needed. The latter also supports the work towards a faster reviewing process.

2.4 Literature study on estrogenic substances

During 2012 a literature review on estrogenic substances was conducted, as it was recognized by LIF that several of these substances had different classification between different companies. It was also recognized by both LIF and IVL that not all of the risk assessments on the estrogenic substances took into consideration recent research in the field, which was considered important.

The literature review focused on estradiol and ethinylestradiol and covered ecotoxicology, degradability and bioaccumulation. No definite recommendation on the use of Predicted No Effect Concentration (PNEC), degradation rates or bioaccumulation factors were brought forward but the literature review was a valuable tool to support the review of the environmental risk assessments for these substances as it made it possible to identify important data gaps in the environmental information presented by the companies. This literature review will be a living document as new research is conducted and results made available in the scientific literature.

2.5 Improved control of sales data

During 2012 LIF did also 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). 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 to ensure correct use of the data. The review comment was often directed to LIF to highlight the possibilities of an error, instead of being directed directly to the company. The reason for this was that the statistics from 2011 in some cases was difficult to interpret and thus errors not always obvious.

Focus was 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

Statistics from www.fass.se (2013-03-01[3]) show that 23% of the unique substances at www.fass.se were classified regarding environmental risk, 40% of the substances were exempted from classification and 38% were reviewed but due to lack of data no classification could be made (either no data at all or not sufficient data). The statistics are based on environmental risk assessments published on www.fass.se, i.e. risk assessments that were published and reviewed within the last three year period (not only 2012).

The total number of unique substances with environmental information on www.fass.se was 882 and for these substances 1161 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. A few APIs are however only included in products manufactured by companies which are not part of the www.fass.se collaboration and thus they cannot take part in the environmental classification system.

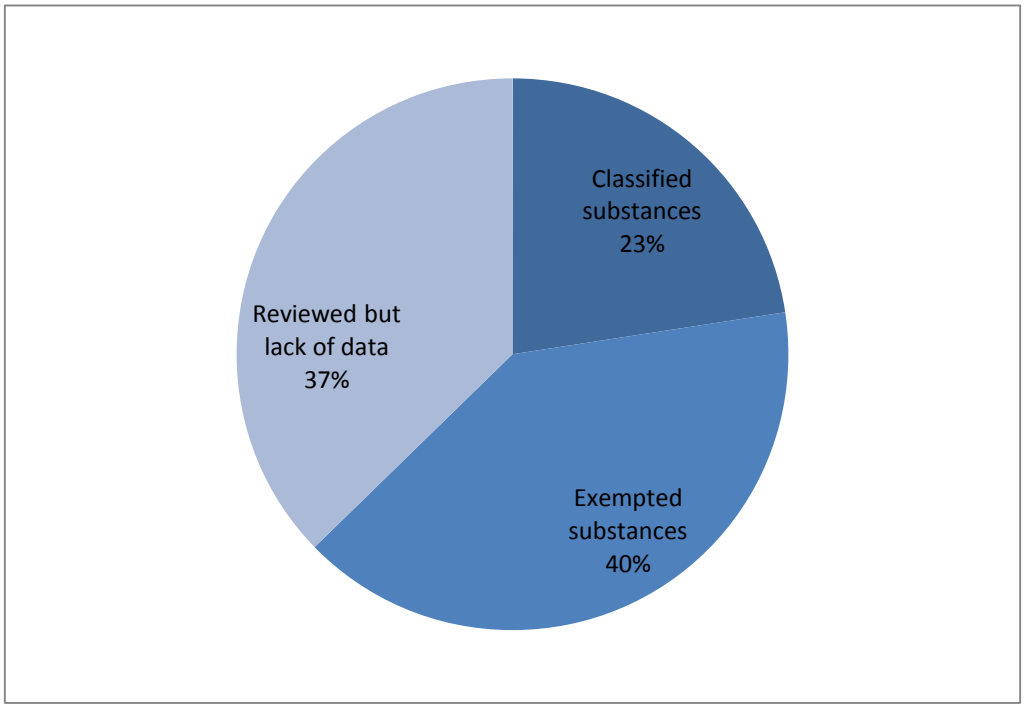

Figure 2: Outcome in terms of environmental classification of substances on www.fass.se (n=882). The figure covers classification of environmental risk, i.e. not potential for degradation or bioaccumulation.

[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

3.1 Environmental risk

Of the 199 (23%) substances classified according to environmental risk the vast majority were classified as posing an insignificant risk (83%), 12% were classified as low risk, 5% as moderate risk and only 1% as high risk, see 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 substance benzoyl peroxide, the antibacterial substance ciprofloxacin, the hormone estradiol, the immune suppressors mycophenolate mofetil and mycophenolic acid, the proton pump inhibitor and parasiticidum permethrin, the beta-receptor blocker propranolol and the antidepressant (selective serotonin reuptake inhibitor, SSRI) sertraline.

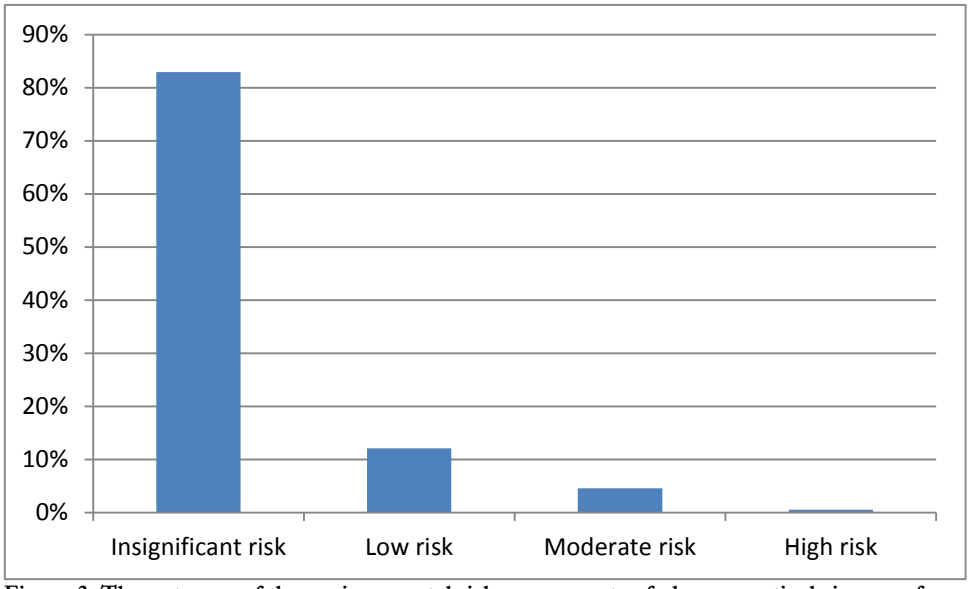

Figure 3: The outcome of the environmental risk assessments of pharmaceuticals in www.fass.se (n=199).

3.2 Potential to bioaccumulate

The environmental risk assessments currently published on www.fass.se are classified according to either criterion for bioaccumulation, from the guideline of 2007 or 2012, depending on when the risk assessment was conducted (see Chapter 2.2). In the Figure 4 below the hazard phrases from the new guideline are used but the statistics also cover assessments of bioaccumulation from before the publication of the new guideline. Thus, some of the substances in the category "high potential to bioaccumulate" may have a log K_{ow} between three and four.

Of the 882 substances at www.fass.se, 307 (35%) were assessed for bioaccumulation potential. For 209 substances (24%) data to make an assessment were not available and for

366 substances (41%) 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. To some extent the latter may be mirrored in this statistics as the main excreted active form is recommended to be included in the assessment.

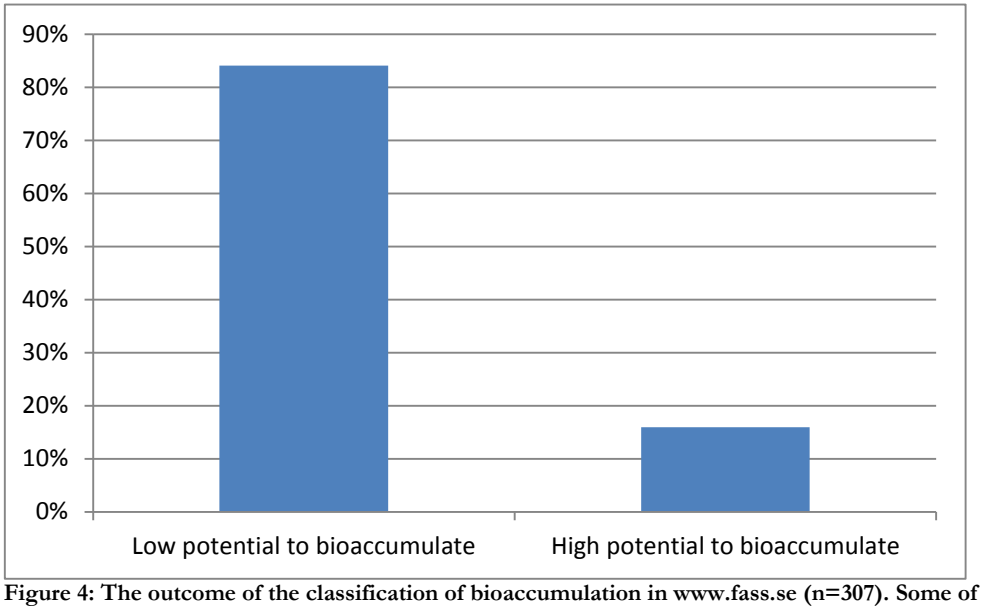

Figure 4: The outcome of the classification of bioaccumulation in www.fass.se (n=307). Some of the substances in the category "high potential to bioaccumulate" may have a log Kow between three and four as the statistics cover assessments of bioaccumulation from before and after the publication of the new guideline.

3.3 Persistence

Of the 882 substances at www.fass.se, 250 substances were classified for degradation (28%), data for classification were lacking for 266 substances (30%) and for 366 substances (41%), 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%). However, a classification that the substance is potentially persistent does not necessarily mean that it cannot be degraded in the environment, but that available data indicate persistence or cannot exclude persistence. 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. Substances are classified as

degradable e.g. if they have passed the ready biodegradability test or sufficiently low dissipation half-lives are achieved in the OECD 308 test. Slowly degradable substances show e.g. inherent degradability, pass the criteria set up for the OECD 308 test or show significant biotic or abiotic degradation in other tests.

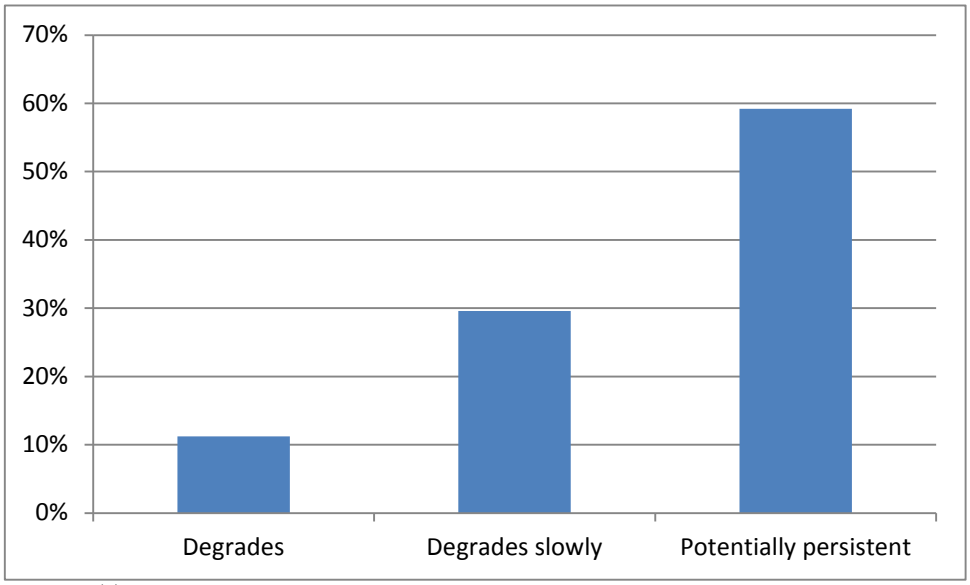

Figure 5: The outcome of the classification of degradation in www.fass.se (n=250).

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 2013 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 many of the risk assessments are checked in for review several times. This should be possible to achieve with a combination of activities. The main activity could be the development of a database and assessment tool for the reviewing process. This would give the reviewers 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. The purpose of minimizing the number of iterations and speeding up the review process is to publish as up to date environmental information as possible at www.fass.se. A database and review assessment tool as described above is planned to be developed, with a start in 2013. During the development, effort will continue to be placed to further clarify the comments when risk assessments are being sent in for review several times without sufficient revisions in between.

In 2011 LIF identified a number of substances for which the classifications in the environmental risk assessments, of the same substance, differed between companies. IVL reviewed the environmental information and the classifications and reported to LIF why the classifications were different and, where possible, recommended further actions to achieve equivalent classification. As of today IVL cannot easily compare classifications of substances under review. To minimize the occurrence of these "double messages" at www.fass.se a future part of the reviewing process could be to control other companies' classifications of the same substance, both in pre-published and published risk assessments. To do so it would be preferable to also be able to easily control classifications of substances for which the risk assessment has not yet been published, i.e. risk assessments under current review. A future database and assessment tool could therefore contain a function to make it easy to make such controls, even if it might not be within the scope of the database being developed in 2013.

During the review process the content and implementation of the guideline (LIF 2012) is continuously evaluated. Discussions regarding the need for clarifications, either to the companies or from LIF to IVL, are regularly held between LIF and IVL. This should continue as it supports an equal implementation of the guideline at the different companies and by IVL. The results of these discussions should also be one of the inputs when the guideline is eventually once again updated.

5 Concluding remarks

- Seven 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.

- 454 risk assessments (pre-published) were reviewed during 2012. About half of these received no remarks and were recommended to be published; the majority of these were however substances exempted for classification. The other half received comments with recommendations for revisions.

- The publication of a new guideline 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 and to establish standardized writing, as far as possible, in the comments given by IVL.

- It was also recognized that many risk assessments were reviewed several times before publication at www.fass.se could be recommended by the reviewer. 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 sent 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.

- For a group of estrogenic substances it was recognized that new research has generated relevant data for environmental risk assessment that was not always taken into consideration in the classifications at www.fass.se. IVL conducted a literature study to facilitate 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 that this is a field where future research will generate further relevant data, the literature study will be a living document.

- It was recognized that the use of the statistics on the total sales of the API (provided by IMS Health), used in the PEC derivation, needed further control. This is now included in the responsibilities of the reviewer, so far with comments often

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.

- 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 will be done with the aim to achieve a robust and transparent system, improving the quality control. As one part of this work the development of a database and review assessment tool is being planned.

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