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Self-declarations of environmental classification at Fass.se

Experiences from the reviewing process during 2015

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

Foreword

IVL Swedish Environmental Research Institute (IVL) has since 2005, with the launch of the system of self-declarations of environmental classification at www.Fass.se, conducted a project focused 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 describes the experiences gained during the review process in year 2015 and 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, as well as users of the environmental classifications, e.g. county councils and researchers.

Four previous reports describing experiences from the reviewing process have been published within the Fass-project. Lilja et al. (2013) describes the implementation of the environmental classifications of pharmaceuticals at Fass.se and the reviewing process from the project start in year 2005 until 2012. The other three reports, Andersson et al. (2013), Örtlund et al. (2014), and Graae et al. (2015), each describe the reviewing process during the year prior to publication.

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Summary

Since 2005 Sweden has a unique environmental classification system for pharmaceutical products. It is a self-declaration system where each pharmaceutical company is responsible for their own environmental information. The environmental risk assessments are published on the web based portal www.Fass.se, which is open to the public. Prior to publication the environmental risk assessments are reviewed by IVL as an independent, external part to make sure that the classifications are based on a scientifically acceptable interpretation of the guidance for the pharmaceutical companies.

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 2014. 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.

In 2015, 400 environmental risk assessments were sent in for review. Of these 41% received the comment no remarks and were recommended to be published. Another 41% received the assessment remark and were recommended to be corrected before publication and 19% needed to be corrected and sent in for another review before publication. The number of times a document is re-sent in for revision has decreased during the last three years. One of the reasons is the development and implementation of the assessment tool, which has improved the review process and clarified the comments sent to the companies. The statistical calculations of the environmental risk assessments in this report are based on documents that were published at Fass.se during 2015. The total number of unique substances was 391 and 19% of these were classified regarding environmental risk. 50% were exempted from classification and 31% were reviewed, but no classification could be made due to lack of data. The work of improving the review system is an on-going process.

Sammanfattning

Sedan 2005 har Sverige ett unikt system för miljöklassificering av läkemedel. Systemet bygger på självdeklaration där varje läkemedelsföretag själva är ansvariga för miljöinformationen för sina produkter. Miljöklassificeringen publiceras på en web-baserad portal, www.Fass.se, som är öppen för allmänheten. Före publiceringen granskas miljödokumenten av IVL, som en oberoende extern part för att säkerställa att klassificeringarna baseras på en vetenskapligt accepterad tolkning av guiden som läkemedelsföretagen utgår ifrån. Utvärdering av systemet är en kontinuerlig pågående aktivitet och i föreliggande rapport beskrivs erfarenheterna från granskningsarbetet under 2015.

Under 2015 sändes 400 miljödokument till IVL för granskning. Av dessa rekommenderades 41 % för direkt publicering. Ytterligare 41 % fick rekommendationer för revidering innan publicering medan 19 % behövde korrigeras och återsändas för ytterligare granskning innan publicering. Antalet gånger ett miljödokument återsänds för granskning har minskat de senaste åren. En förklaring är granskningsverktyget som har utvecklats och implementerats, vilket har förbättrat granskningsprocessen och förtydligat kommentarerna till företagen. De statistiska beräkningarna av miljödokumenten i denna årsrapport baserar sig på de miljödokument som publicerades på Fass.se under år 2015. Totala antalet unika substanser var 391 och 19 % av dessa klassificerades med avseende på miljörisk. 50 % var undantagna från klassificering och 31 % blev granskade, men kunde inte klassificeras på grund av bristande information. Arbetet med att förbättra granskningsprocessen är ständigt pågående.

1 Environmental classification of pharmaceuticals at Fass.se

1.1 Background

Pharmaceutical products are essential for health and wellbeing in our everyday life. Medicines provide enormous benefits, such as improvement in quality of life, and the demand will likely increase in the future due to a growing ageing population, chronic/lifestyle diseases, emerging market expansion, and treatment and technology advances. Unfortunately, benefits of the use of pharmaceuticals may come with an environmental downside. Therefore, pharmaceutical residues in the environment have become a prioritized area within environmental surveillance as well as within environmental risk assessment. It is a focus area in the EU Strategy for the Baltic Sea Region and it is being investigated in a number of national and international projects (see for example Halling-Sörensen B. et al. 1998, Fick J. et al 2011, Kümmerer K. 2004 and The Swedish Medical Agency 2015).

In 2005 environmental information was published at 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 on 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 had been conducted for all groups of pharmaceuticals (ATC codes) on the Swedish market.

The model was developed by a Swedish Working Group consisting of LIF, the Stockholm county council, and the pharmacy chain Apoteket, the Swedish association of local authorities and regions (SKL) and the Swedish Medical Products Agency (MPA), in conjunction with the international pharmaceutical industry. During the implementation of this environmental classification system IVL Swedish Environmental Research Institute (IVL) runs projects with the aim to identify and address the pitfalls of the system. The Fass project is financed by LIF and the Foundation for IVL Swedish Environmental Research Institute (SIVL).

The results from the environmental classifications of pharmaceuticals are being presented at Fass.se, a web based pharmaceutical portal that includes information on all approved pharmaceuticals on the Swedish market. The information is accessible not only to experts, county councils and other purchasing actors, but open to the public as well. On the Swedish market today there are approximately 1900 APIs (The Swedish Medical Agency, January 2015, personal communication (Hillver S-E)).

The environmental classification at Fass.se is a self-declaration system meaning that each pharmaceutical company is responsible for the environmental information published at Fass.se. Prior to publication the classifications are reviewed by IVL as an independent, external part to make sure that the classifications are based on a scientifically acceptable interpretation of the guidance for the pharmaceutical companies. The reviewing process ensures a common praxis for the implementation of the guideline among the different companies and feeds back experience from the self-declaration process to the system owners, LIF. At the same time 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 classifications are, according to the principles of the system, to be updated and reviewed every three years. In the reviewing process, issues in need for further investigation are continuously coming up. This is due to availability of new data or knowledge in the field as well as possibilities of comparisons to be made across different pharmaceuticals with the same active ingredients. In order to keep its credibility it is thus of outermost importance that the system is continuously reviewed and improved. The work on the review of the environmental risk assessments at Fass.se is conducted in close connection with related research studies, which form the bases for the development of the reviewing process.

The overall aim of the Fass-project during 2015 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.

1.2 How the classifications are made

In the environmental classification of pharmaceuticals at 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 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 including a list of references to documents that have been used.

1.3 The guideline and the reviewing process

The guidelines to what environmental data that support and differentiate the classification steps were developed by the LIF-secretariat and the LIF Expert Group on Sustainable Development, including representatives from the industry, the Stockholm county council, the pharmacy chain Apoteket, SKL and 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 a revised document was presented in June 2012.

Before publication of environmental data at Fass.se, the risk and hazard assessments are reviewed by IVL. IVL comments on the choice of classification phrase based on the 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 four 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 at 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 at Fass.se
- **Remarks** – minor deficiencies, correction is recommended (although not mandatory) to be in full compliance with guideline
- **No remarks** – no deficiencies found in the submitted material and the document is recommended for publication.

2 Experiences from the reviewing process during 2015

2.1 Statistics of the review process during 2015

The total number of reviews during 2015 was 400 and the most common assessment from IVL was to give remark or no remarks (41 % each). During 2015, 327 environmental risk assessments with unique substance/pharmaceutical company-combinations were submitted for review. The highest grade of comment that each company received for their risk assessments for a specific substance is illustrated in Figure 1. The majority (81%) of the environmental risk assessments got the comments "no remarks" or "remark". Only a minor part (19%) got a comment that needed to be corrected before publication, which is a major improvement compared with 2014 when 49% of the risk assessments needed to be corrected before publication. In total, risk assessments for 299 substances were reviewed during 2015.

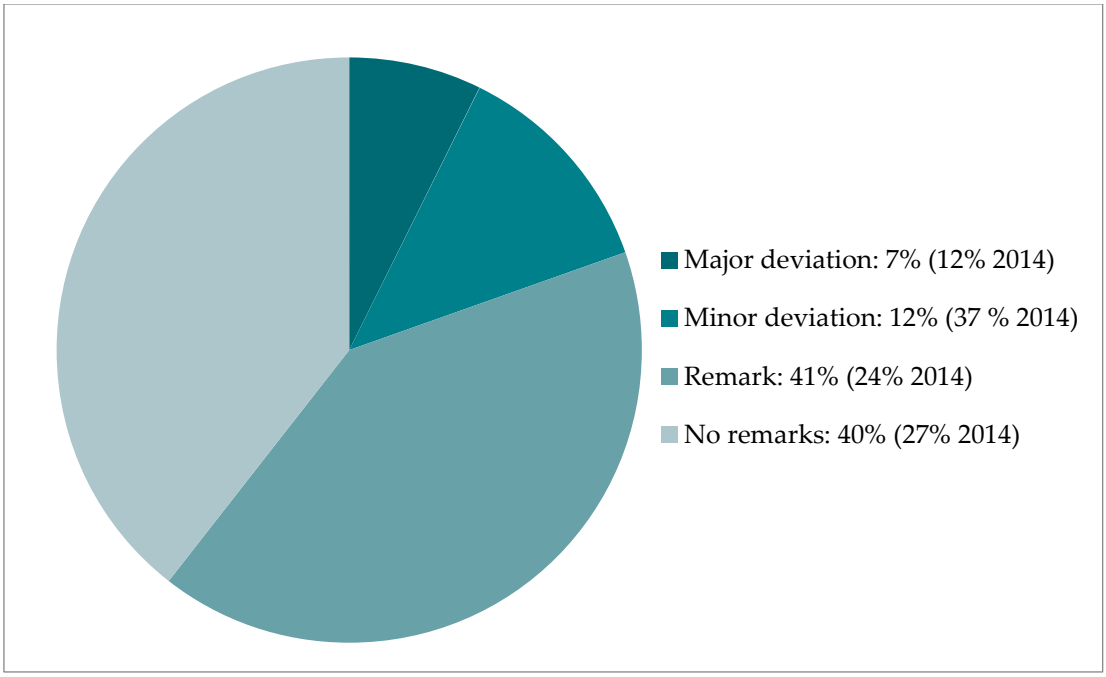

Figure 1: Distribution of the highest grade of recommendations that each company received for a specific substance that was sent in for review during 2015. The figure is based on the total number of reviews, i.e. 400 and the figure shows the highest grade of comment for each risk assessment during the year in the order: major deviation > minor deviation > remark > no remarks.

2.2 Statistics comparing the last three year period

The number of substances with environmental risk assessments has grown substantially since the start (2005) and the number of sets of reviewing comments is continuously growing as the risk assessments undergo three year revisions. In addition, in June 2012 a new guideline for environmental risk assessments was launched (LIF 2012). This initiated discussions both within the reviewing team at IVL and with LIF to update the reviewing process and find a common interpretation of the guideline. In line with this, a database and review assessment tool was developed during 2013 in order to facilitate the review process, support the quality assurance procedures and ensure that the environmental risk assessment undergoes equivalent review, independent of the reviewer. One of the improvements was to clarify the comments as well as the format of the comments provided to the pharmaceutical companies and thereby decrease the time before publication. In addition the assessment tool provides IVL valuable support in identifying where more elaborate comments may be needed. The review process was completely transferred to the new system in August 2014.

The statistics of the review process from the last three years, i.e. between 2013 (when the new guideline was fully implemented) and 2015 (when the assessment tool was fully implemented) have been compared. Figure 2 illustrates the highest grade of comment that each company received for their risk assessments for a specific substance for each of the three years. In 2015 only 19% of the risk assessments needed revision before publication (i.e. received the comments major or minor deviation) compared to 49% in year 2014 and 47% in 2013.

One possible explanation to the decreasing number of revisions could have been an unusually high load of environmental documents for exempted substances in year 2015, since these documents rarely receive major or minor deviation as comments to their risk assessments. However, the number of exempted substances has only increased marginally over the last three years. In year 2015 50% of all the documents belonged to the group of exempted substances, whereas it was 49% in year 2014 and 41% in year 2013. Therefore this hardly accounts for the large decrease in number of revisions during these three years.

Another explanation is instead the change in classification that occurred during the autumn 2014. Until the end of November 2014 environmental documents with "lack of data" could receive the comments minor or major deviation. From December 2014 and forward these documents instead only receive the classification remark. Prior to the change there were unusually many documents (116 documents between May and November 2014) with "lack of data", which accounts for about 22% of the reviewed risk assessments in 2014. These documents thus constitute a large part of the shift seen in comments from minor and major deviation to remark or no remarks between year 2014 and 2015.

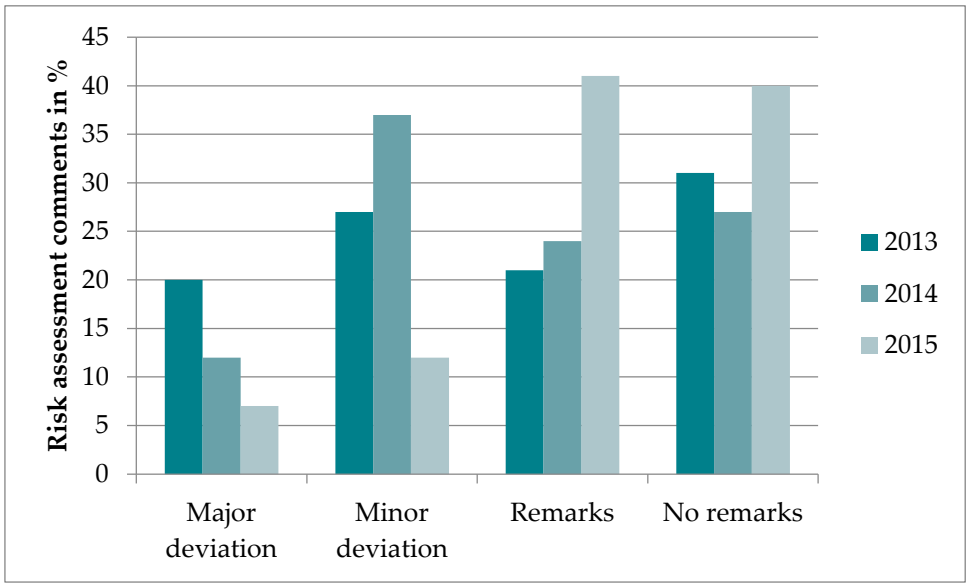

Figure 2: Distribution of the highest grade of recommendations that each company received for a specific substance that was sent in for review during 2013, 2014 and 2015. The figure is based on the total number of reviews during each year.

In line with this there is also a decrease in number of times a document was sent for review to IVL before publication. In 2015 only 19% of the documents needed more than one revision, whereas it was 25% of the documents in 2014 and 39% in 2013 that needed more than one revision, see Figure 3.

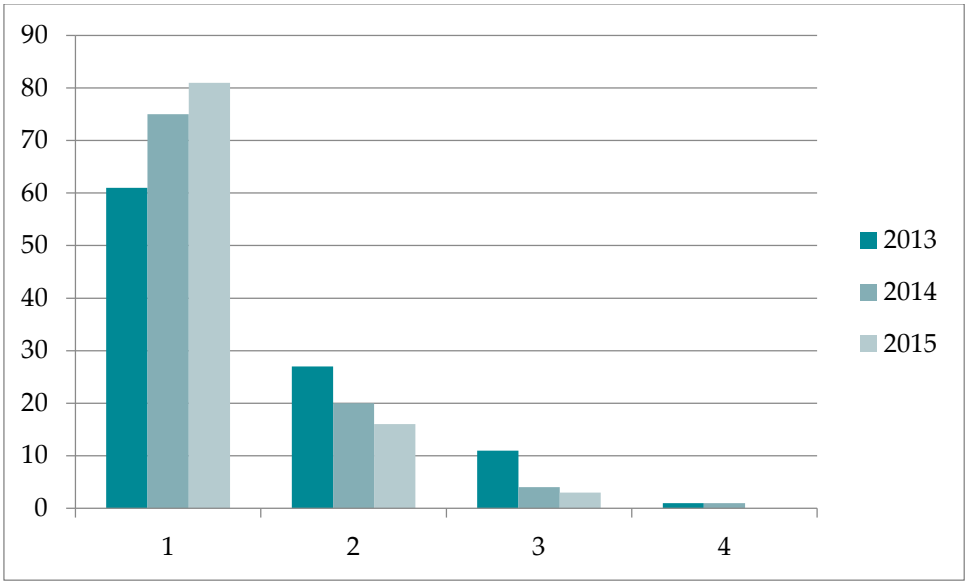

Figure 3: Distribution of the number of times a risk assessment was sent in for review to IVL before publication at Fass.se.

2.3 Fate of pharmaceutical residues in sewage treatment and on farmlands fertilized with sludge

Within the context as third party reviewer, IVL also performs research to increase the knowledge of pharmaceuticals in the environment to improve the reviewing process. The focus of the research during 2014-2015 was to investigate the distribution and removal of a selection of pharmaceuticals within a sewage treatment plant (STP) and their final fate in the environment.

For unclear reasons pharmaceutical residues are often represented in higher concentrations in the effluent wastewater compared to the influent, which limits correct conclusions to be made regarding their removal during sewage treatment. Several studies on matrix effects and metabolism were performed to test different hypotheses that could explain the phenomena and to be able to estimate the "true" concentrations of pharmaceuticals within a STP. A mass balance was also performed to further study the pharmaceutical distribution. To assess the dispersion and fate of pharmaceuticals in the environment a farmland fertilized with sludge from the investigated STP were studied. Soil and sludge samples were analyzed as well as soil water collected by lysimeter techniques. In addition laboratory based soil sorption tests of the farmland soil exposed to pharmaceutical and sewage sludge were performed. The study is presented in a separate report published in 2016 (Magnér J. et al. 2016).

3 Final results of the classification

3.1 Environmental risk assessments included in the statistics

The statistics are based on data from a document, generated by LIF, showing a snapshot of all the risk assessments that are published at Fass.se at the time the document is generated. The data is retrieved as close to the end of every year as possible in order to ease comparisons between each year's statistic calculations.

Previous years the statistics have been based on all the environmental risk assessments shown at Fass.se within the last three year period from when the statistic document was generated. An environmental risk assessment at Fass.se is valid for three years and will thereafter be updated by the company. However, the company is free to remove or update the risk assessment before the end of these three years. This have the consequence that statistics covering the three year period 2012–2014 and 2013–2015 will not have the same number of documents representing year 2013 or 2014 even though they are said to cover the same period. Since the deviations on published documents increases with increasing time, IVL decided to base the statistics on environmental risk assessments published within the last year instead of the last three years. Thus, the statistics in this report include all the environmental risk assessments that had been published during 2015 (instead of 2013–2015) and that could be viewed at Fass.se at 2016-01-07 (the date when the document was generated).

3.2 Environmental classification of substances

The total number of unique substances that was published at Fass.se during 2015 was 391, which corresponds to 460 environmental risk assessments. 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. 19% of the 391 unique substances were classified regarding environmental risk, 50% were exempted substances and another 31% were reviewed, but no classification could be made (either no data at all or not sufficient data). The distribution of the unique substances is illustrated in Figure 4, below.

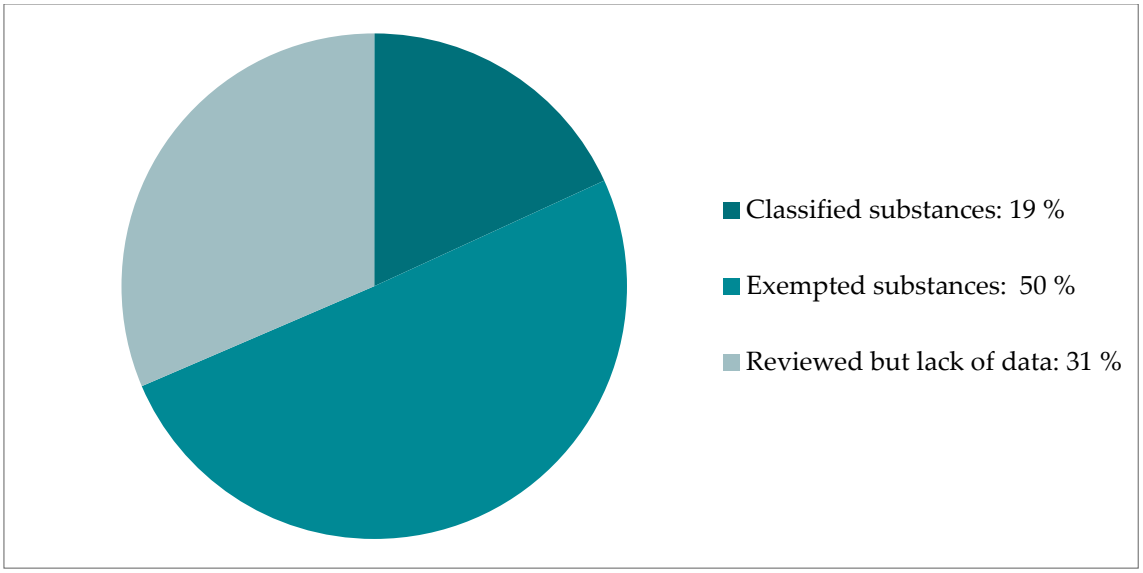

Figure 4: Outcome in terms of environmental classification of substances at Fass.se (n = 391). The figure covers classification of environmental risk, i.e. not potential for degradation or bioaccumulation.

3.3 Environmental risk

Of the 71 (19%) substances classified according to environmental risk the vast majority were classified as posing an insignificant risk (82%), 11% were classified as low risk, 3% as moderate risk, 3% as high risk, and 1% as hazardous (Figure 5). 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. When the PEC/PNEC <1, but the substance is flagged as a potential PBT (Persistent, Bioaccumulative, and Toxic) or vPvB (very Persistent and very Bioaccumulative), the substance is classified as having hazardous environmental properties. The number of substances classified as posing a moderate risk decreased from 6% to 3% whereas substances classified as high risk increased from 1% to 3% in 2015 compared to the statistics based on documents published during 2012-2014.

In 2015 one substance, Bedaquiline, an antibiotic drug used for multi-drug-resistant tuberculosis, received the risk assessment hazardous. Two substances were classified as posing a high risk: Abirateron, an anti-hormone substance used as treatment for testicular cancer, and Levonorgestrel, a hormone used as contraceptive agents. Two substances were classified as posing a moderate risk: Amoxicillin, a penicillin used for bacterial infections in duodenum or infections in the stomach caused by *Helicobacter pylori*, and Chlorhexidine, an antibacterial used as an antiseptic ingredient in mouthwash.

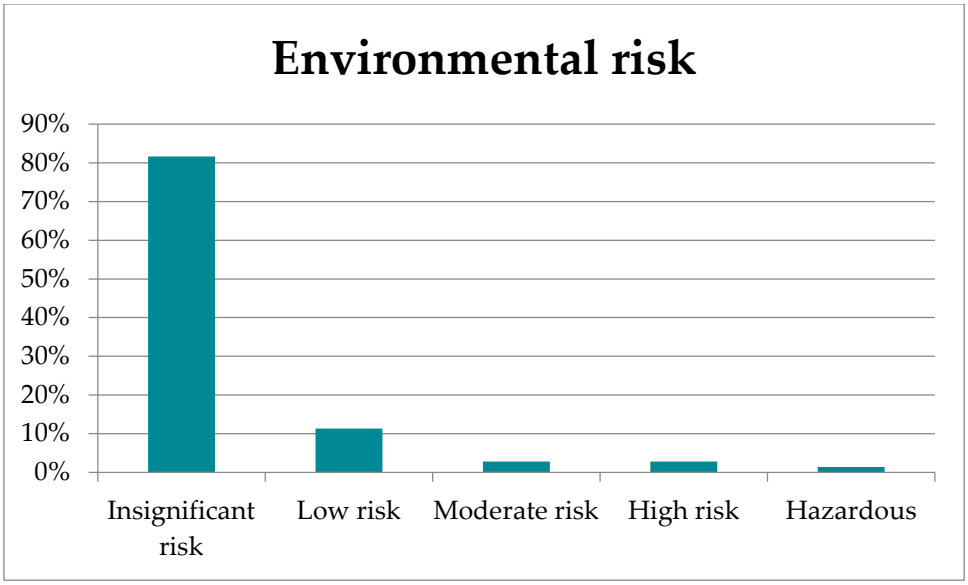

Figure 5: The outcome of the environmental risk assessments of pharmaceuticals at Fass.se (n = 71).

3.4 Potential to bioaccumulate

Depending on when the risk assessment was conducted the environmental risk assessments currently published at 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. Thus, some of the substances in the category "high potential to bioaccumulate" may have a log K_{ow} between 3 and 4 (Figure 6).

Of the 391 unique substances published at Fass.se during 2015, 113 (29%) were assessed for bioaccumulation potential. For 80 substances (20%) data to make an assessment were not available and for 198 substances (51%) 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 6, the vast majority of the substances with a classification of the bioaccumulation potential were assigned a hazard phrase indicating a low potential to bioaccumulate (90%). 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.

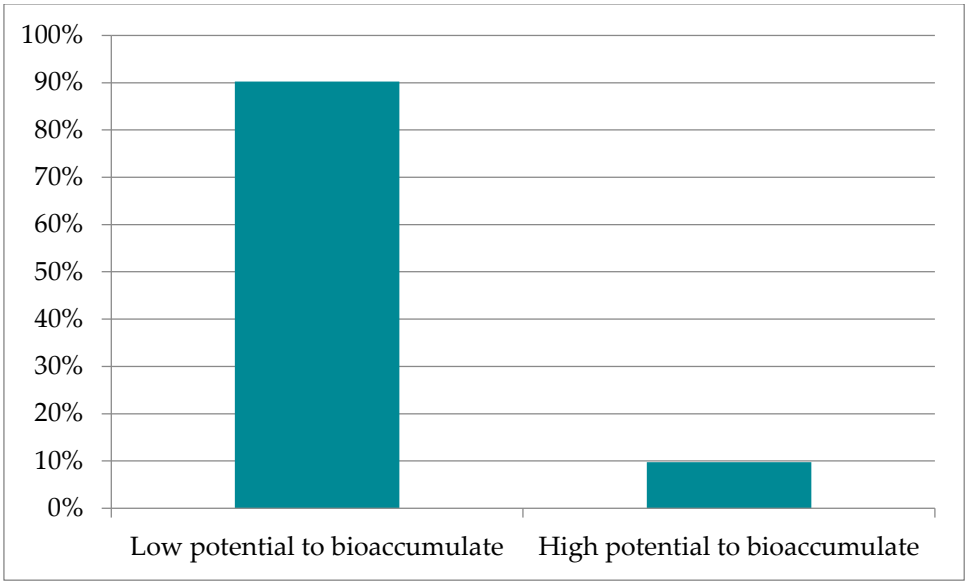

Figure 6: The outcome of the classification of bioaccumulation at Fass.se (n = 113).

3.5 Persistence

Of the 391 unique substances published at Fass.se during 2015, 74 substances were classified for degradation (19%), data for classification were lacking for 119 substances (30%) and for 198 substances (51%), 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 (72%) (Figure 7). Substances are classified as degradable e.g. if they have passed a 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.

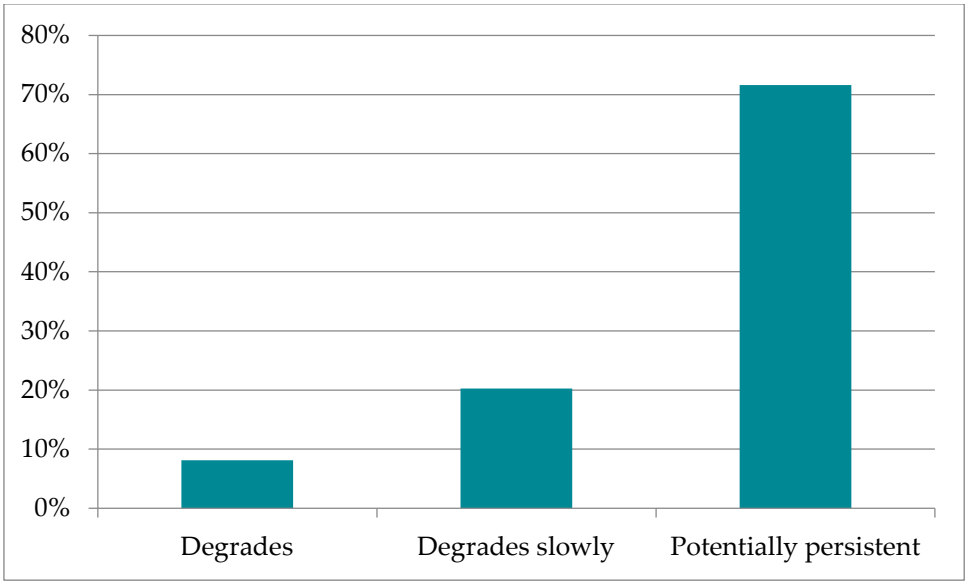

Figure 7: The outcome of the classification of degradation at Fass.se for documents published during 2015 (n = 74).

4 Future outlook

During 2016 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:

1. 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.

2. Publishing of a peer-reviewed article and organizing a dialog meeting. In the peer-reviewed article the experiences gained from the reviewing process during the ten years the Fass-project will be evaluated and discussed. This will not only increase transparency and traceability of the classification process both national and international, but also give feedback to improve future guidelines for the self-declaration system of pharmaceuticals. At the dialog meeting recent research and on-going projects in the field will be presented and experiences from the Fass-review process will be discussed together with invited scientists, stakeholders and representatives from the industry.

5 Concluding remarks

- The Fass-project has now been on-going for ten years and 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 via the web-based portal www.Fass.se.
- 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.
- 400 risk assessments (pre-published) were checked in for review during 2015. 41% 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.
- One of the aims of the development of the assessment tool in 2013 was to facilitate the review process and thereby decrease the time before publication. One of the improvements was to clarify the comments given to the pharmaceutical companies. The work with improving the review process will continue with the aim to achieve a review process with no unnecessary delay in publication of the updated environmental risk assessments.
- The statistic calculations on the environmental risk assessments are based on documents published at Fass.se during 2015 instead of previous years when the statistics have been based on documents published within the last thee-year period. The reason is that documents may be removed from the web-portal at any time and the remaining documents representing a year will thus change. Since the deviation increases with time, the statistic calculations will be more robust if only the last year is considered compared to the last three years.
- Risk assessments for 391 unique substances were published at Fass.se during 2015. 19% of the unique substances (n = 71) published at Fass.se at 2016-01-07 were classified regarding environmental risk; 50% were exempted from classification and 31% were reviewed, but no classification could be made due to lack of data.
- One substance, Bedaquiline, received the risk assessment hazardous; two substances were classified as posing a high risk (Abirateron and Levonorgestrel) and two were classified as posing a moderate risk (Amoxicillin and Chlorhexidine). A majority of the classified substances (82%) received the assessment insignificant risk.
- 29% of the unique substances (n = 113) were assessed for bioaccumulation potential. 90% of these were assigned a hazard phrase indicating low potential to bioaccumulate (i.e. log K_{ow} < 3 or 4).
- 19% of the unique substances (n = 74) were assessed for degradation. 72% of these were assigned a phrase indicating that the substance is potentially persistent.
- The study conducted in 2014–2015 has been completed and will be published in a separate report during 2016 (Magnér J. et al. 2016). The study investigated the distribution and removal of a selection of pharmaceuticals within STPs as well as their final fate in the environment.

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