

Sweden's Voluntary Environmental Drug Classification System

Bengt Mattson, Inger Näsman and Jan Ström explain Sweden's industry-led system for gathering and publishing environmental risk data on pharmaceuticals.

The level of debate on various potential environmental hazards differs among countries and over time. Sweden has for the past few decades had a very lively debate on environmental issues and the general public's interest is high, as evidenced by active government legislation in different fields of environmental protection.

In 2004, the potential effects of residues of pharmaceutical products in the water supply became a media issue in Sweden. Several reports on the appearance of active pharmaceutical ingredients (APIs) in the environment had been published, among which were several very high-profile news reports on national television. Such alerts can reach a pitch where science suffers, and industry as a consequence finds itself fighting an uphill PR and legislative battle. The Swedish County Councils, which are responsible for managing and financing healthcare including reimbursement of prescription medicines, increasingly suggested that environmental effects should in future be included in the factors that the regional drug committees took into account when making recommendations to doctors on which medicines to prescribe. It was also suggested that environmental data should be one of the factors taken into account when county councils applied for tenders on pharmaceutical products.

Risk assessment is a difficult subject in a general debate with laymen, but nonetheless it has to be taken seriously. The fact that pharmaceutical compounds are biologically active substances, albeit with many unknown factors and with the science constantly developing, gives industry the possibility to provide factual information about the state of current knowledge. Industry will never be able to defend its products if scare reports of unknown side effects in, for example, lakes and the water supply are not balanced with information about persistence, bioaccumulation and the amount of residue that actually reaches the water. We call this "the danger versus risk paradox".

Taken separately, a case could be made for a given product being "dangerous", or more commonly "hazardous", if you look solely at the inherent toxic effects of the substance in question, irrespective of the concentration in which such a dangerous effect can occur, and if such an effect is at all possible with the amount of substance used and excreted.

The "risk assessment" is something different: it looks at the substance and its characteristics, but also takes into account metabolism, biodegradability and the total amount used, and compares this with best available knowledge of the limits above which negative effects can occur.

The environmental debate

The problem for the industry – and this is why we call it a difficult subject – is that the environmental debate usually takes place in an arena where concerns for the patient and for the needs of the healthcare system are not at all taken into account, and where possible dangers can make titillating headline material, and industry by default is put on the defensive as a producer of these "dangerous substances". In the end, this raises the risk of new constraints in the form of regulations imposed on industry by legislative bodies.

This is not to disrespect the concerns of environmental proponents, most of whom indeed have an extremely serious interest in the subject. But we have noted that the special characteristics of pharmaceutical products, and the complicated way in which residues may reach the water stream, in some cases lead to disregard for scientific facts, mostly because of lack of knowledge of the processes involved.

Industry also has to acknowledge that even we do not know everything about the possible environmental effects of our products. If we let it go at that, and do not supply the best information we have, then legislation will be passed as a result of concern among the electorate about risks, and we will be too late to influence it. Any responsible branch of industry needs to get its facts straight so that it can defend its position in a debate on the environment. If industry accuses others of not taking the full picture into account, it is up to us to present that full picture. We have the best knowledge; it is our responsibility to disseminate it.

This is the background for the environmental drug classification project, and in this article we

Environmental dangers of pharmaceutical substances have been the subject of increased political and media attention

Industry cannot defend its products if scare reports are not balanced with information about the amount of residue that actually reaches the water

The environmental debate raises the risk of new constraints being imposed on industry

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will present an overview of the process in Sweden that brought this project into existence, and how the project is arranged, managed and presented. We will also evaluate the pros and cons of the process now that it is up and running and has gone a long way towards the goal of publishing environmental information on all approved pharmaceutical products in Sweden, and has been the subject of considerable interest in Sweden and abroad.

An MPA report said that it is not legally possible to implement a mandatory environmental classification and labelling system in Sweden

In response to the greater attention paid in Sweden to the potential hazards of APIs in the environment, the Swedish Medical Products Agency (MPA) was instructed by the government to carry out a commission on the state of knowledge and examine whether it was possible to put in place a mandatory environmental classification and labelling system in Sweden. A report was presented in August 2004, entitled "Environmental impact from pharmaceuticals as well as cosmetics and hygiene articles". The full report is only available in Swedish as "Miljöpåverkan från läkemedel samt kosmetiska och hygieniska produkter"¹. However, some comments and conclusions from the report are outlined below:

- environmental data are missing for a considerable number of substances, especially older ones developed before there were requirements for environmental risk assessments upon regulatory filing, ie substances from the 1980s and before;
- out of 30 APIs which were selected for environmental risk assessment, there were sufficient data for only 12. The selection of the 30 APIs was based on volume of sales on the Swedish market (eg paracetamol) or suspected potential to affect the environment (eg ethinylestradiol);
- nine of these 12 substances were found to be environmentally hazardous. However, only in the case of sex hormones, ie estradiol and ethinylestradiol, was the concentration in the environment high enough to present a potential risk;
- no environmental risk related to excipients or pharmaceutical packaging materials could be identified. For cosmetics and hygiene articles it was not possible to perform any assessment because verifiable data on volumes were not available; and
- the MPA concluded in the report that European Union (EU) rules applied and that it was not legally possible to implement a mandatory environmental classification and labelling system in Sweden.

The press and environmental groups claimed the MPA report offered no practical suggestions on tackling the perceived problem

The reaction in the press and from environmental groups to the MPA report was clearly negative. The report was said to be "bland" and was deemed to have no relevant or practical suggestions as to how the perceived problem could be tackled. It was symptomatic of the level of environmental interest in political circles in Sweden that within days of the report's publication, the then minister for environmental affairs, Lena Sommestad, called a round table meeting with stakeholders. In that meeting the minister made it very clear that she expected rapid action on developing an environmental classification scheme, and if EU laws prohibited a mandatory classification system then such a system should be on a voluntary basis.

There was already a basis for such a voluntary system because two players in the Swedish health sector – the Stockholm County Council and the Swedish Pharmacy chain Apoteket – had started to develop a classification scheme for substances. The system was to be used to differentiate the potential hazards of an API relative to those of another API.

The industry association LIF developed a voluntary classification scheme with a range of shareholders

In response to the request by Ms Sommestad, LIF took the initiative to develop a voluntary system together with interested parties in the healthcare sector. In addition to the Stockholm County Council and Apoteket, the Swedish Association of Local Authorities and Regions (SKL) and the MPA participated in collaboration with LIF on the task. In parallel with the Swedish task force, LIF also put together an international task force with internationally recognised environmental expertise from several pharmaceutical companies, ie Pfizer, AstraZeneca, Merck, GSK, Lilly and Roche. Finally, a reference group was formed with stakeholders from the academies, governmental agencies, and representatives of patients and physicians.

On 10 October 2005, information on the first two groups of products (proton pump inhibitor anti-ulcers and SSRI antidepressants) was published on www.fass.se (Fass.se), which is the Swedish medical products list, managed by LIF. The two groups were included in the pilot test of the new model.

Model for presenting data on environmental impact

Information on the environmental impact of pharmaceutical substances is presented on three levels. Level 1 describes the environmental risk of the API, while Level 2 supplements the risk with information on the degradability of the substance and the potential for bioaccumulation. On Level 3 all background data for the assessment of risk, degradability and bioaccumulation are presented in depth. An explanation of the system with its three levels is shown below.

Level 1

This level of information is intended to answer questions by the general public or patients on the potential for environmental effects of pharmaceuticals. It comprises the basic level of information on *Fass.se* for patients. The environmental risk assessment is based on the ratio between the predicted concentration of the substance in Swedish water systems (predicted environmental concentration, or PEC) and the concentration that is predicted to be safe for organisms and plants living in them (predicted no effect concentration, or PNEC). If the concentration in the environment is lower than the concentration that, based on tests, is regarded as safe for organisms, – in other words, if the PEC/PNEC ratio is lower than 1 – the risk of environmental impact is low or negligible. If, on the other hand, PEC is higher than PNEC, ie the PEC/PNEC ratio is higher than 1, there is a risk of impact on the environment. The model on *Fass.se* uses different standard phrases depending on the PEC/PNEC ratio:

- $PEC/PNEC \leq 0.1$: Use of the medicine has been considered to result in insignificant environmental risk;
- $0.1 < PEC/PNEC \leq 1$: Use of the medicine has been considered to result in low environmental risk;
- $1 < PEC/PNEC \leq 10$: Use of the medicine has been considered to result in moderate environmental risk; and
- $PEC/PNEC > 10$: Use of the medicine has been considered to result in high environmental risk.

In those cases where insufficient data are available to calculate the PEC and/or PNEC values, one of the following standard phrases is used in the model: “Risk of environmental impact cannot be excluded due to lack of data”, or “Risk of environmental impact cannot be excluded, although some ecotoxicity data are available” (from 2007).

Level 2

The information on this level, where the environmental risk is combined with information about characteristics of the substance with regard to persistence and the potential for bioaccumulation, is intended for professional users and constitutes basic information on *Fass.se* for prescribers.

A substance that shows persistence, ie degrades only with difficulty, and/or has the potential for bioaccumulation, ie the substance accumulates in aquatic organisms and thereby gradually increases in concentration higher up in the food chain, could mean that exposure increases over time as the concentration would increase over time in the environment. This in turn could enhance the environmental risk over time.

The model uses different standard phrases depending on specific characteristics. In the case of persistence, they are as follows: “The medicine is degraded in the environment,” “The medicine is slowly degraded in the environment” or “The medicine is potentially persistent” (from 2007). If there are insufficient data to characterise the potential for degradation, the following statement will be used: “The potential for persistence cannot be excluded due to lack of data” (from 2007).

For bioaccumulation the following phrases are used: “No significant bioaccumulation potential” or “Potential to bioaccumulate in aquatic organisms”. If there is insufficient data to characterise the potential for bioaccumulation, the following statement will be used: “The potential for bioaccumulation cannot be excluded due to lack of data” (from 2007).

If the pharmaceutical fulfils the criteria for PBT (persistent, bioaccumulative and toxic) and/or vPvB (very persistent and very bioaccumulative), the following phrase should be added: “According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.”

Level 3

The information on Level 3 should include all relevant background data to verify the calculations upon which the classifications on Levels 1 and 2 are based. Examples of relevant information are:

- PEC/PNEC calculation;
- results from degradation studies;
- partition coefficient octanol/water to estimate bioaccumulation (Kow);
- bio concentration factor (BCF);
- results from ecotoxicology studies – a preferred set of data included results from three trophic levels, ie algae, daphnia and fish;
- information about metabolism; and
- total amount in kg of substance sold per year on the Swedish market (should include all products with the same API) .

The risk assessment looks at the ratio between the predicted environmental concentration and the predicted no effect concentration

Level 2 information is intended for professional users

Level 3 information should include all relevant background data to verify classifications underpinning Levels 1 and 2

Data is compiled by the companies, but reviewed by the independent Swedish Environmental Institute

More detailed information in English on how the calculations are made and the trigger values for the different standard phrases can be found in the *Guidance Document for Companies*, which is available on *Fass.se*², as well as a general portal in English on the whole project³.

Before the information is published on *Fass.se* it is reviewed by an independent party, the Swedish Environmental Institute (IVL). The IVL reviews the assessments and classifications for the different substances and hence ensures that companies comply with requirements in the guidance document. The IVL also collaborates with LIF in the ongoing development of the model as it can deliver feedback on common misunderstandings, areas where the science evolves, and so on.

The importance of the quality control that the IVL provides for the end result and the way that industry's openness is perceived cannot be overestimated. It is also in line with the high quality and impartiality that are fundamental for the continuing success of the web portal. The basis for the listings of pharmaceutical products in general on *Fass.se* is the summary of product characteristics and the patient information leaflet, while quality control of the more general information is provided by the MPA. A further positive effect of the environmental project is that it strengthens the position of *Fass.se* as the most comprehensive database in Sweden on all relevant information about pharmaceuticals. The availability of *Fass.se* as a well-established and reliable source of pharmaceutical information and classification has been critical for the launch of the environmental classification scheme in Sweden. Other countries should identify their most appropriate communication channel before implementing a similar system.

The process so far

Information on substances from the therapeutic areas of anti-infectives, sex hormones and antihypertensives was added in 2006

In addition to the 11 substances published in October 2005 (PPIs and SSRIs), information on 113 substances from the therapeutic areas of anti-infectives and sex hormones was published on 13 March 2006, and information on 40 antihypertensive substances on 17 May 2006. The information on all 164 substances is summarised in Tables 1-3. Table 1 shows the results from the environmental risk assessments, Table 2 includes information on degradation, and Table 3 shows information published on *Fass.se* on bioaccumulation.

Table 1. Environmental risk assessments: results

Risk phrase	PPI	SSRI	Anti-infectives	Sex hormones	Anti-hyper-tensives	Total	% of total	% excluding "lack of data"
Insignificant	4	4	39	2	20	69	42.1%	85.2%
Low	-	1	2	2	1	6	3.7%	7.4%
Moderate	-	1	2	1	1	5	3.0%	6.2%
High	-	-	-	1	-	1	0.6%	1.2%
Lack of data	1	-	50	14	18	83	50.6%	-
Total	5	6	93	20	40	164	100%	100%

Table 2. Degradation information

Degradation phrase	PPI	SSRI	Anti-infectives	Sex hormones	Anti-hyper-tensives	Total	% of total	% excluding "lack of data"
Degraded	-	-	2	1	1	4	2.4%	3.8%
Slowly degraded	4	6	54	7	31	102	62.2%	96.2%
Lack of data	1	-	37	12	8	58	35.4%	-
Total	5	6	93	20	40	164	100%	100%

Table 3. Bioaccumulation information

Bioaccumulation phrase	PPI	SSRI	Anti-infectives	Sex hormones	Anti-hyper-tensives	Total	% of total	% excluding "lack of data"
No potential	4	4	50	1	28	87	53.0%	81.3%
Potential for bioaccumulation	-	2	7	7	4	20	12.2%	18.7%
Lack of data	1	-	36	12	8	57	34.8%	-
Total	5	6	93	20	40	164	100%	100%

Since these tables were compiled, information was published on more products in the therapeutic areas of asthma and cough as well as lipid-lowering agents and antidepressants (except SSRIs), the latest in February 2007, which brings the number of substances to 267. This corresponds to just over 620 products on *Fass.se*. In April 2007 information on products for musculoskeletal diseases will be published.

The results presented in Table 1 show that the model succeeds in differentiating between substances. There is a fairly good spread of the substances in the different PEC/PNEC levels, with a strong predominance for "insignificant impact", ie PEC/PNEC being below 0.1 as expected. Estradiol and ethinylestradiol are the only substances that fall into the "high impact" level, which was also not really surprising. The potential environmental impact of these two related compounds has been widely discussed in recent years.

Table 2, however, shows a deficiency with the model. It does not manage to distinguish between different substances when it comes to persistence. Over 96% of the substances with available data have been classified as "slowly degraded in the environment". An adjustment of the model was proposed in order to differentiate substances that are "slowly degraded" from those that are "potentially persistent". LIF has therefore reviewed the criteria for the classification and updated the model accordingly with the new classification, "The medicine is potentially persistent".

Table 3 presents results on bioaccumulation which in general terms were according to LIF's expectations. Roughly 80% of the substances with available data do not show potential to bioaccumulate.

LIF's aim is to have an environmental classification published on all substances that are available on the Swedish market within five years of the system's launch in October 2005. The substances are published based on their ATC (Anatomical Therapeutic Chemical) codes on *Fass.se*, and the ATC groups are prioritised based upon the size of the group and perceived interest.

LIF has worked to develop an information gathering system that is easy and secure for companies to work with. We use a web interface where authorised personnel in the member companies file their reports, thereby limiting the time lag and the risk of unauthorised input. A streamlined process is necessary to restrict the number of steps each individual company has to go through in order to deliver their input to LIF and IVL. Guidelines have been developed and a number of seminars and courses have been held for employees of member companies.

The result of this effort, and more importantly that of the member companies themselves, is that the process is running smoothly and that we are ahead of our own schedule. We have delivered a large amount of data and there is no perceived danger that the process will come to a halt.

The task force on the Swedish initiative

It was clear very early in the process of starting and developing the initiative that it was crucial to have an understanding within the global industry of the driving forces for the initiative and an acceptance of the classification scheme. Therefore, the creation of the international task force on the Swedish initiative, with highly respected experts, was a key factor for success. The different drafts were discussed in parallel with the Swedish group (MPA, Stockholm County Council, the pharmacists' association, the association of Swedish communities and counties, and LIF) and the reference group (including, but not limited to, academy representatives, environmental and chemical agencies, representatives from patient groups and physicians) in order to secure full buy-in from both the industry and all critical stakeholders.

Several topics were discussed at these meetings: the details of the design of the scheme in itself, of course, but also issues such as:

- the amount of resources needed within the industry to fulfil the commitment to gather, compile, compute and publish environmental data on all products;
- loss of "confidentiality" for information such as environmental risk assessments that are today only accessible through/by medical products agencies; and
- ensuring comparability between background data for classifications made by different companies.

This last point was addressed via the quality control provided by the IVL. Although the initiative is fairly resource-intensive both for pharmaceutical companies and LIF, and confidentiality is lost when the data are made public, most of the industry agreed very early in the process that the positives outweighed the potential negatives. Industry needs to participate actively in the discussions within society on potential environmental impacts of pharmaceutical substances, and

The model does not distinguish between different substances with regard to persistence

The aim is to have classifications published on all substances within five years of the October 2005 launch

A key factor for success was the creation of the international task force on the Swedish initiative

Confidentiality is lost when the data are made public

it has the best possibility to perform risk assessments and classifications based on the science, competence and knowledge available in the various companies. Industry builds credibility by sharing all data, both “good” and “bad”, with all its stakeholders. As long as critical intellectual properties are not lost, the loss of confidentiality of environmental and risk assessment data does not pose a risk to the industry but offers important information to stakeholders.

The industry is now regarded as a serious and collaborative partner by the stakeholders in environmental discussions

The initiative has so far been very successful. The global industry has been supportive and stakeholders have responded very positively. The industry is now regarded as a serious and collaborative partner by the stakeholders in environmental discussions. It has gained trust by being transparent and open with its knowledge – and in some cases its lack of data and knowledge.

But, with hindsight and with the published results as background, it is important to examine further whether the whole exercise has been worthwhile. Since the only examples of “high environmental impact” in over 620 products are the already known closely related sex hormones, estradiol and ethinylestradiol, isn't the whole thing futile? Have we added any real new knowledge or are we just doing a lot of work for no reason? Furthermore, have we really gained a better understanding of what is arguably still a not very well known subject? We feel that the following points summarise our conclusions on these subjects.

The fact that we can show that most of our products clearly are either not accumulated at all or have a very low environmental impact is in itself a major step. Industry is not just saying this – we have hard facts and numbers to verify it, and we publish them openly.

A similar project launched in 2004 was not welcomed by LIF and its member companies because some data would have been misleading

In Sweden another project started in 2004 with the same aim of gathering and publishing environmental data on pharmaceuticals. LIF and member companies were not entirely happy with the proposed layout of that project. For example, the level of metabolism in any given substance was not taken into account, so the amounts of the original substance that eventually reached the water supply would have been misleading. With industry's and LIF's resources combined with those of other stakeholders, we could offer a more relevant model that gave a fuller picture and more accurate results. There is definitely an argument that if you get all stakeholders together to jointly agree on a scientifically valid way of assembling and computing data, you put yourself in a better position than trying after the fact to argue against a data set that someone else has published.

This model, jointly agreed by all stakeholders, also means that if and when environmental data become part of the county councils' tender conditions for pharmaceuticals, then the *Fass.se* classification is the sole accepted source of such data for active ingredients.

Moreover, we have contributed to strengthening the “science first, legislation later” process. It is true that the science of the environmental impact of pharmaceuticals is still in its infancy. Difficult problems might well arise in the coming years with regard to the issue of possible harmful effects on the environment and specifically the water supply. But we are now a relevant, and dare we say trusted, stakeholder in these discussions. That will put us in a better position if such problems arise.

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