Environmental Classification of APIs on Fass.se

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LIF, May 2015

Background to the initiative to publish environmental data for APIs on Fass.se ("the Swedish Prescribing Guide")

- Governmental commission to the Swedish Medical Products Agency (MPA) regarding Pharmaceuticals in the Environment. Report published August 2004. Conclusions:
  - Large data gaps
  - Several substances are environmentally hazardous, but acute environmental risks are limited to ethinyl estradiol and estradiol (sex hormones)
  - An environmental classification scheme cannot be introduced on the Swedish market only. Such an initiative would need an EU wide implementation
  - A voluntary classification scheme could be introduced in Sweden based on an industry initiative monitored by an independent competent body
- The Swedish Minister of the Environment calls for a round-table discussion
  - LIF takes the initiative to develop a system for environmental information on pharmaceutical substances to be introduced on www.fass.se
  - Invites stakeholders of concern to participate in the development of the model

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Swedish Task Force

Sveriges Kommuner och Landsting

The Swedish Association of Local Authorities and Regions

Stockholms läns landsting

Stockholm County Council

Läkemedelsindustriföreningen, LIF
The Swedish Association of the Pharmaceutical Industry

The Swedish Association of the Pharmaceutical Industry

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Medical Products Agency

Apoteket

The National Corporation of Swedish Pharmacies

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International Task Force (original participants)

gsk GlaxoSmithKline

Lilly

Pfizer

Roche

AstraZeneca

MERCK

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Swedish Environmental Classification Scheme for Pharmaceutical Substances

- Launched 2005
- Data and classifications are updated regularly (at least every third year)
- Classifications and data are reviewed by IVL (Swedish Environmental Research Institute)
  - IVL is an impartial body, owned by the foundation SIVL which has a board of directors representing government and industry.
  - IVL reviews the classifications and environmental data in relation to the guidance document (last revision 2012)

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What information is presented?

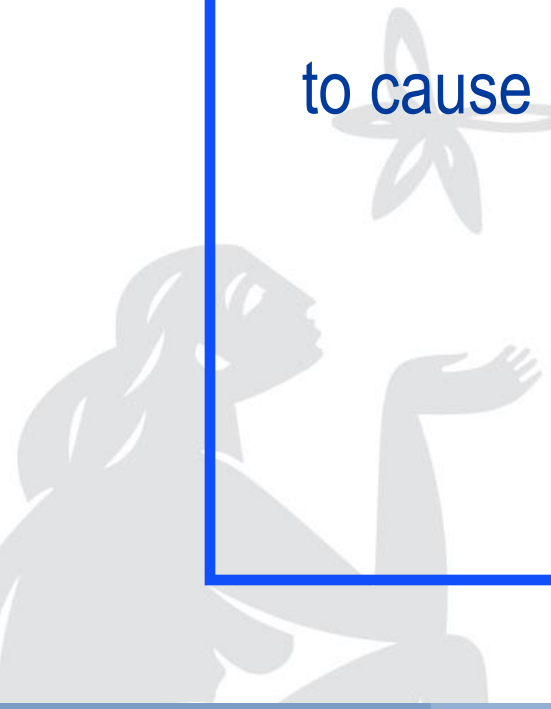
First of all: Distinguish Between Hazard and Risk

Hazard

The inherent capacity to cause harm.

Risk

The probability to cause harm. Without exposure, the hazard does not pose a risk.



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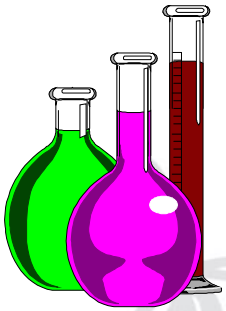
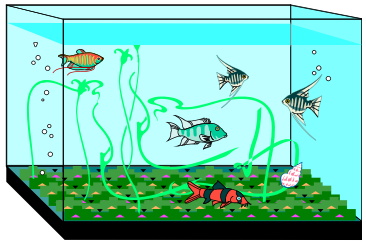
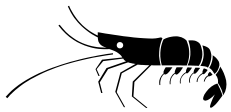
Eco-toxicology

Fate of chemicals in the environment and their effect on eco systems



- Is the substance accumulated in organisms?
- Is it degraded?
- Is it toxic?





Answers the question on HAZARD – the ability of the substance to cause harm

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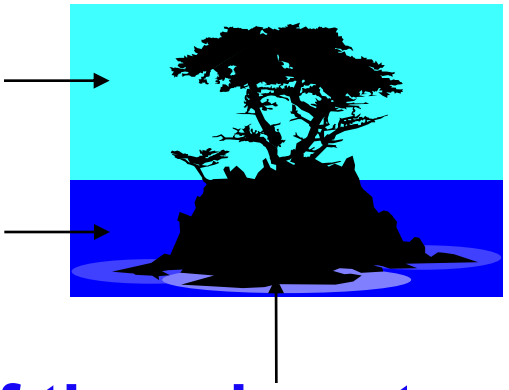
Risk Assessment

To calculate risk, exposure data is needed in addition to hazard:

- **Fate of the substance?**
- **How much ends up in the environment?**



A HAZARD does not pose a RISK, if there is not a potential EXPOSURE

Exposure could be

- ***measured, "occurrence in the environment"***
- ***estimated, e.g. by sales volumes***
- ***estimated, exposure assessment models***

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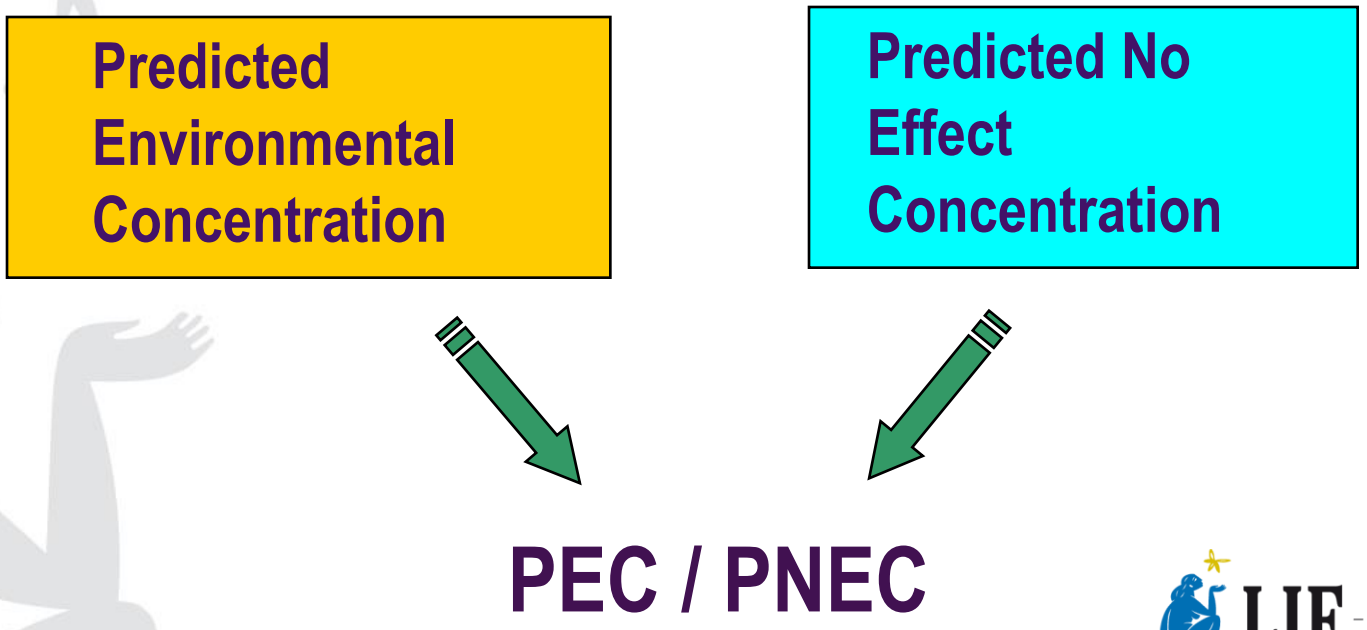
Basic Principle Used in Environmental Risk Assessments (ERA)

Predicted concentration of the substance in the environment is related to the toxicity of organisms living in the environment



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Generation of PEC

Predicted Environmental Concentration

Quantity on market

- Provided by LIF

Excretion and metabolism in man

Urine Faeces

Parent compound
Metabolites
(pharmacological activity)

Fate during sewage treatment

- Does it degrade or adsorb to sludge?

PEC

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Calculation of PNEC

Predicted No Effect Concentration

Ecotoxicity to fish

Ecotoxicity to *Daphnia*

PNEC

Ecotoxicity to algae

Assessment factors

The most sensitive species is used.

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Is there an Environmental Risk?

Based on the PEC/PNEC ratio

- PEC/PNEC < 1
  - No significant risk identified, no risk management action needed
- PEC/PNEC ≥ 1
  - Potential risk identified, precautionary and safety measures required, e.g.:
    - **Restricted clinical use, e.g. hospitals only**
    - **Product labelling**
      - **E.g. return the unused medicine to the pharmacy**

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Environmental Risk, as presented on www.fass.se

PEC/PNEC ≤ 0,1

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

0,1 < PEC/PNEC ≤ 1

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

1 < PEC/PNEC ≤ 10

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

PEC/PNEC > 10

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

No data:

→ **Risk of environmental impact cannot be excluded due to lack of data**

→ **Risk of environmental impact cannot be excluded, however some ecotoxicity data are available**

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Environmental Hazard, as presented on www.fass.se

Persistence: **The medicine is degraded in the environment** *or* **The medicine is slowly degraded in the environment** *or* **The medicine is potentially persistent**

Bioaccumulation: **No significant bioaccumulation potential** *or* **Potential to bioaccumulate in aquatic organisms**

If the pharmaceutical fulfills 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.

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Detailed Environmental Information, e.g.

- PEC/PNEC, PEC and PNEC calculations
- Total amount of sold API (kg) and year
- Results from degradation tests
- Partition coefficient octanol/water (bioaccumulation)
- Results from ecotoxicological studies
- Information about excreted forms of the API; parent compound and/or metabolites
  - Pharmacological activity of the metabolites

Exemptions

According to the EU EMEA guideline for environmental risk assessment of APIs the following exemptions are listed:

- Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids

These groups of medicines can use the following standard phrase in fass.se:

Use of xx has been considered to result in insignificant environmental impact.

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Swedish Classification of Pharmaceutical Substances - SUMMARY

- Roughly 95% of the substances, with sufficient data for classification, have been considered to have insignificant impact, only 2% have a high or moderate risk for environmental impact
- Roughly 90% do not have a potential for bioaccumulation
- More than 90% of the substances are slowly degraded or potentially persistent in the environment

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Environmental Classification of APIs on Fass.se, May 2015

- More than 1000 documents published
- Covering over 800 different pharmaceutical substances

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Environmental Risk

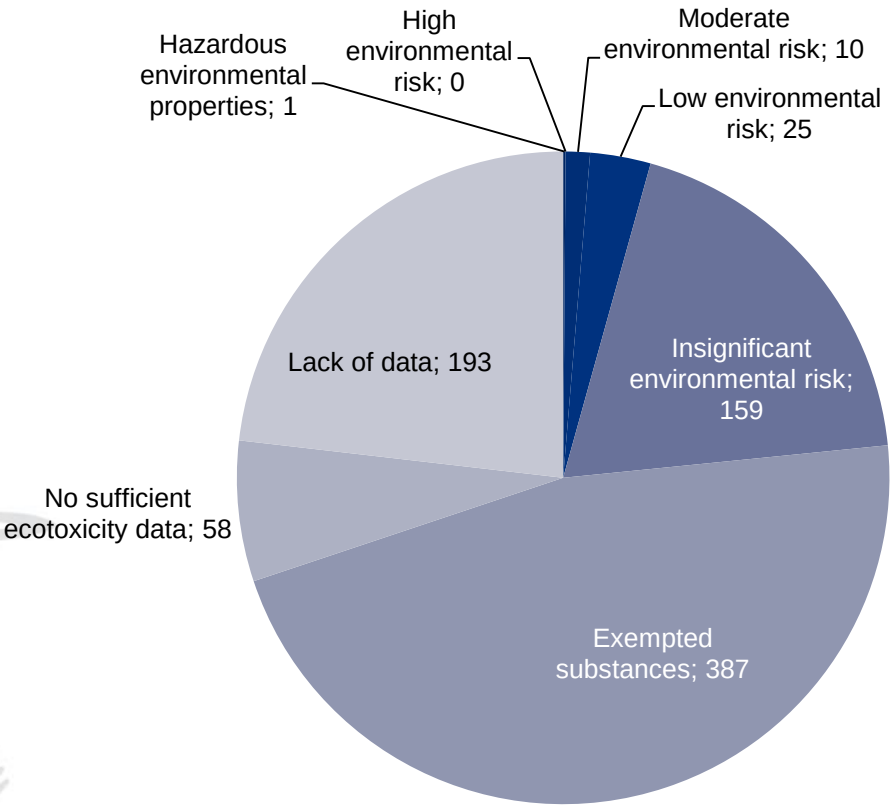
There are 581 substances with data allowing for risk classification (including substances exempted from environmental risk assessments according to EU ERA Guidance since they pose no risk to the environment)

High (0) and Moderate (10) risk substances represent 2% (10/581=0.017)

Low risk substances represent 4% (25/581=0.0430)

Substances with insignificant environmental risk represent 94%
(159+387 / 581 = 0.9398)

1 substance has PBT/vPvB properties



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Bio-accumulation

There are 358 substances with data allowing for classification of bioaccumulation:

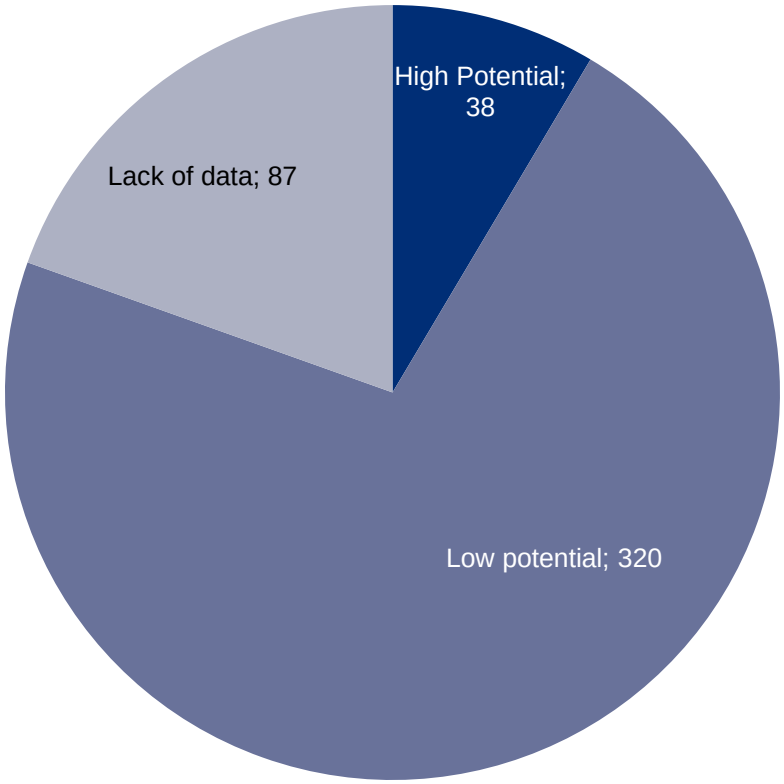
High potential: 38/358=0.106

10%

Low potential: 320/358=0.893

90%

1 substance has PBT/vPvB properties



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Degradation

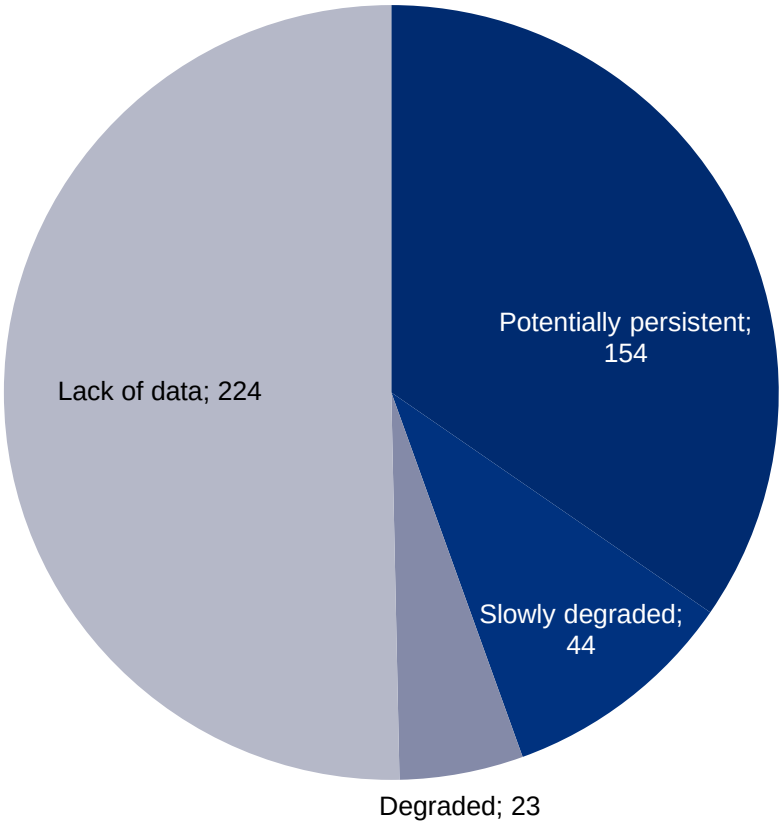
There are 221 substances with data allowing for classification of degradation:

Potentially persistent:
154/221=0.697 70%

Slowly degraded:
44/221=0.199 20%

Degraded:
23/221=0.104 10%

1 substance has PBT/vPvB properties



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