FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

BfR Proposal for a Harmonised Procedure for Estimating the Dermal Absorption

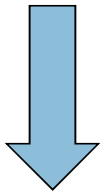
Lars Niemann

Why is an accurate estimate of dermal absorption so critical?

Exposure of operators, bystanders, workers to pesticides occurs mainly by inhalation and by the dermal route

Dermal absorption rate must be known to calculate expected internal exposure

Exposure vs. AOEL



Is registration of a product possible?
Are risk mitigation measures needed?

And why is it so difficult to predict?

Dermal absorption

depends on many factors, and can be:

- **Assumed** (default values, no experimental data needed)

- **Estimated** (various approaches to give an idea of the magnitude of absorption, some data necessary)

- **Measured** (studies *in vivo* and/or *in vitro that* provide precise values but often result in contradictory interpretations and conclusions)

How can we achieve better (international) harmonisation?

OECD: Guidance Notes on Dermal Absorption, 2011 [ENV/JM/WRPR(2011)30; OECD Homepage]

EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption, 2012 [EFSA Journal 2012, 10(4), 2665-2695]

What are the merits of the two guidance documents?

- Practical advice for interpretation and use of experimental data (e.g.: *What should be considered as absorbed/absorbable and what not?)*
- Clear discription of the possibilities to estimate dermal absorption in the absence of product-specific data

including
- **New default values**
- Criteria for assessing “similarity“ of a product to another

How can we make the best use of them?

The regulatory approach should be …

- … science-based (as far as possible)
- … transparent
- … consistent
- … simple

How can we make the best use of them (BfR proposal)?

Two general situations to be distinguished:

A. **Product-specific** experimental data is available

If valid product-specific dermal absorption studies were submitted (although not required), use them!

B. Such data is not available or cannot be used : **look for an alternative!**

What is the preferred study?

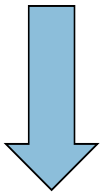
In vitro human skin (OECD 428) as "point of departure"

- Accepted as "stand alone" information (dermatomed skin / isolated epidermis – both acceptable)
- In the first step, results will be used for risk assessment without taking rat data (*in vivo/in vitro*) into account – perhaps sufficient yet!
- If there is a **risk** (exposure > AOEL) and a **triple pack** is available, it may be used for refinement *(but this will not always help)*

And what if human *in vitro* is absent?

Is Rat *in vivo* avaiblable? If yes, results will be used.

If not, rat *in vitro* will be considered.



Conservative estimates will be obtained.

How to interpret all these studies?

In principle, follow the EFSA guidance!

In particular,

- with regard to the amount in *Stratum corneum*,
- with regard to total recovery as a quality criteria.
- with regard to inclusion of flux rate information,
- with regard to criteria for recognition of a triple pack. (When is a triple pack a triple pack?)

Look carefully at the number of donors and samples in the *in vitro* studies!

Always round the figures according to EFSA Guidance!

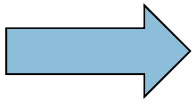
What about the *Stratum corneum*? Implications?

In vitro	***In vivo***
May be excluded if 75 % of total radioactivity in receptor fluid was found there after one half of study duration (usually 12 hrs);	May be excluded if 75 % absorption was complete after one half of study duration (time may differ), based on radioactivity in excreta, carcass, and skin

What about concentrations that were not tested?

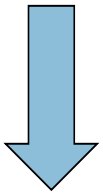
Case 1: Product concentration in between two tested concentrations

1:25 dilution – 3 % dermal absorption
1:500 dilution – 9 % dermal absorption
1:125 dilution – no data, but to be assessed



Take the higher value!

Case 2: Product concentration lower or higher by more than 2 times as compared to any tested concentration



Reservations about „pro rata“, use the defaults!

What to do in the absence of product-specific study data?

1. **Usual approach of authorities:**

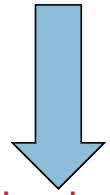
   Apply the default values (10 % in spite of certain reservations, 25 / 75 %) !

2. **If suggested and sufficiently justified by applicant and found reasonable und suitable by authorities:**

   Read-across

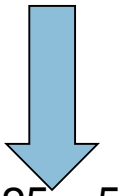
How to perform a “read-across“?

1. “**One-to-one approach“** (EFSA Guidance): Check the similarity of a formulation strictly according to criteria!



Use the experimental values obtained with this formulation (if in fact similar)!

2. **“Many-to-one approach“** (OECD Guidance): Look for suitable data (provided be applicant) to support expert judgement



Rough estimates (10 – 25 – 50%) may result

What data shouldn‘t be used and why?

- Comparison of results from toxicological studies with the active substance
- Oral absorption rate of the active substance
- Studies in human volunteers or monkeys
- QSARs (*for the time being*)

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Thank you for your attention

Lars Niemann

Federal Institute for Risk Assessment

Thielallee 88-92 • D-14195 Berlin

Tel. +49 30 - 184 12 - 0 •

lars.niemann@bfr.bund.de • www.bfr.bund.de