Introduction on exposure estimation

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Authorisation
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Products and
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Introduction

- To assess the safety of an PPP the potential exposure needs to be assessed.

- No or few exposure data are available due to costs.

  → Predictive exposure models

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Contents

Introduction exposure scenarios:

- Exposed groups

- Models

- Input parameters (main issues:
  application rate, dermal absorption)

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Introduction

- Exposure scenarios:
    - Operators: persons involved in the mixing/loading and application of a PPP
    - Workers: persons who enter an area or handle crop previously treated with a PPP
    - Bystanders: persons who are located within or directly adjacent to the area where PPP application is taking place or has recently been completed.

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Exposure models

- Operator:
  - EUROPOEM
  - German model
  - UK POEM
  - NL model
  - NL Greenhouse
  - NA PHED
  - ....

- Worker/bystander:
  - EUROPOEM II
  - ...

- Resident:
  - ??

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EFSA Project to assess current approaches and knowledge with a view to develop a Guidance Document for pesticide exposure assessment for workers, operators, bystanders and residents.
http://www.efsa.europa.eu/en/scdocs/doc/26e.pdf

No	Model/Database	Year	Territory where originated	Originators (data source indicated)	Scenarios
1	Pesticide Exposures Handlers Database (PHED)	1992	North America	N. American Industry (data source), US EPA & Health Canada	ML, A, MLA, Flaggers, agricultural/horticultural pesticides, ground based & aerial application
2	German Model	1992	Germany	German industry (data source), and German regulatory authority	ML, A, agricultural/horticultural pesticides ground based application
3	Predictive Operator Exposure Model (POEM)	1986	United Kingdom	UK industry, and UK regulatory authorities (data source)	ML, A, agricultural/horticultural pesticides ground based application
4	The Dutch model	1992	The Netherlands	Dutch authorities, (data open literature)	ML, A, agricultural/horticultural pesticides ground based application
4b	Dutch greenhouse model	1992	The Netherlands	Dutch authorities, (data open literature)	ML, A in greenhouses – this is a subset of 4 that is available as a separate entity

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Which model to select?

- Depends on type of application:
  - Indoors vs outdoors
  - Manual vs mechanical
  - Upwards vs downwards

- No EU consensus (yet) on which model to use for which situation.

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Input data in the models

- Body weight defaults: 70 kg (NL), 60 kg (UK)

- Treated area size and duration, vary with crop, equipment and country:
  - mechanical downward: 10 ha. (NL), 20 ha (D), 50 ha (UK), spraying time 6 h (UK&NL).
  - mechanical upward: 6 ha (NL), 8 ha (D), 15 ha (UK), spraying time 6 h (UK&NL).
  - Hand-held applications: 1 ha (D, NL & UK), spraying time 6 h (UK), 3.5 h (NL).

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Input data in the models

- Application rate

In EU:

instructions of use and intended use table

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SUMMARY OF GOOD AGRICULTURAL PRACTICE FOR PESTICIDE USES
(Application on agricultural and horticultural crops)

Responsible body for reporting (name, address):
Submission date:

Pesticide(s) (common name)............................ :
CCPR No(s).. :
Trade name(s).. :
Main uses (e.g. insecticide, fungicide) .... :

1	2	3	4	5	6				7			8	9
Crop and/or	F or	Pest or group	Formulation rate		Application				Application rate per treatment			PHI	Remarks
situation with code number(a)	G (b)	of pest controlled (c)	Type (d-f)	Conc. of a.i. (i)	method, kind (f-h)	growth stage (j)	number (range)	spray interval (days)	g as/hl	water (l/ha)	g as/ha	(days) (k)	(l)

a) code number according to Commission Regulation (EU) No 600/2010*

b) outdoor or field use (F), or glasshouse application (G)

c) e.g. biting and sucking insects, soil born insects, foliar fungi

d) e.g. wettable powder (WP), emulsifiable concentration (EC), granulate (GR)

e) use CIPAC/FAO Codes where appropriate

f) all abbreviations must be explained

g) method e.g. high volume spraying, low volume spraying, spreading, dusting, drench

h) kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants

i) g/kg or g/l

j) growth stage at last treatment

k) PHI = Pre-harvest interval

l) remarks may include: Extent of use / economic importance / restrictions (e.g. feeding, grazing) / minimal intervals between applications

* Commission Regulation (EU) No 600/2010 of 8 July 2010 amending Annex I to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards additions and modification of the examples of related varieties or other products to which the same MRL applies. Official Journal of the European Union L 174/18 9.7.2010.

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Input data in the models

Dermal absorption
- Based on physical/chemical properties (MW, log Pow)
- Based on dermal absorption studies
  - *in vitro* (rat and/or human skin)
  - *in vivo* (rat)

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The skin

- Largest organ in the body
- Surface area ± 1.8 m^2
- Total weight about 4 kg

WHO, Environmental Health Criteria 235, Dermal absorption (2006)

http://www.inchem.org/documents/ehc/ehc/ehc235.pdf

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Stratum corneum

- Major route of penetration is intercellular pathway

- Lipophilic route

- Size threshold is around 500 dalton. However, MW of about 800 can still penetrate.

  EU default: 10% dermal absorption in case MW>500 and log Pow < -1 or >4, otherwise 100%.

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Important considerations in dermal absorption

- Test compound
  - Physical state, molecular size, lipid/water partition coefficient, ionization, local skin effects
- Skin
  - Species, anatomical site, temperature, hydration of stratum corneum, damage to stratum corneum, metabolism, diseased skin, desquamation, blood and lymph flow
- Vehicle
  - Solubility, volatility, distribution in stratum corneum, excipients, effect on stratum corneum, pH
- Application dose
  - Concentration, finite and infinite dose, skin area dose, total skin area in contact with vehicle, duration of exposure
- Other factors
  - Reservoir effect and its interpretation in risk assessment

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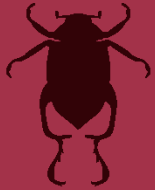
Dermal absorption studies

- For majority of chemicals, laboratory animal skin is considerably more permeable.
- Skin of weanling pigs and monkeys most predictive model, however usually rat is used

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In vitro dermal absorption studies

- Full-thickness skin: stratum corneum, viable epidermis and dermis

- Dermatomed skin (split-thickness skin): stratum corneum, viable epidermis

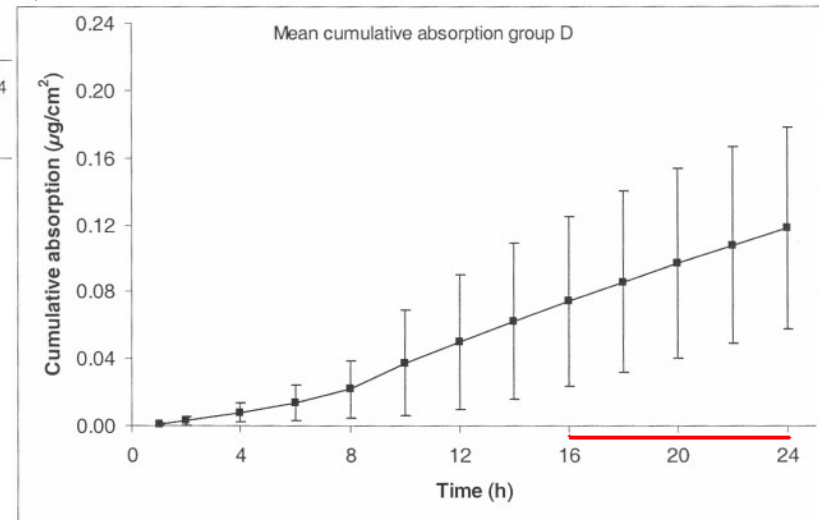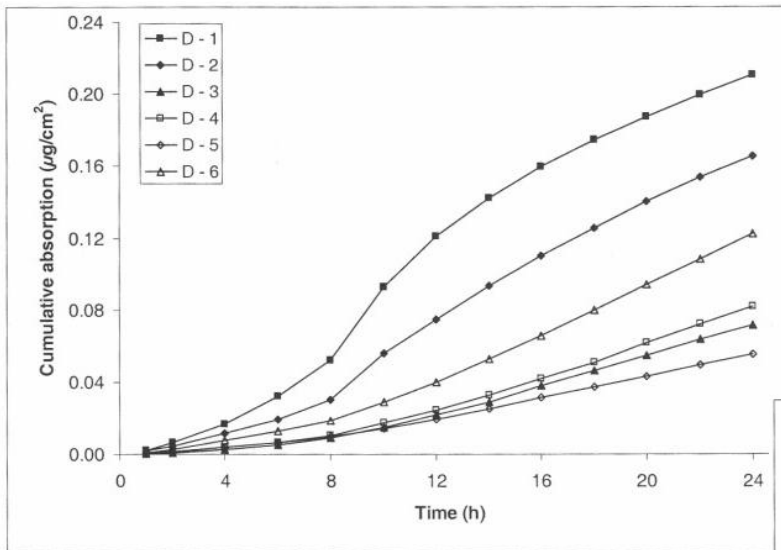- Epidermal membranes: stratum corneum, viable epidermis
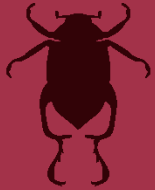
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In vitro dermal absorption studies
Example (human skin, dilution)
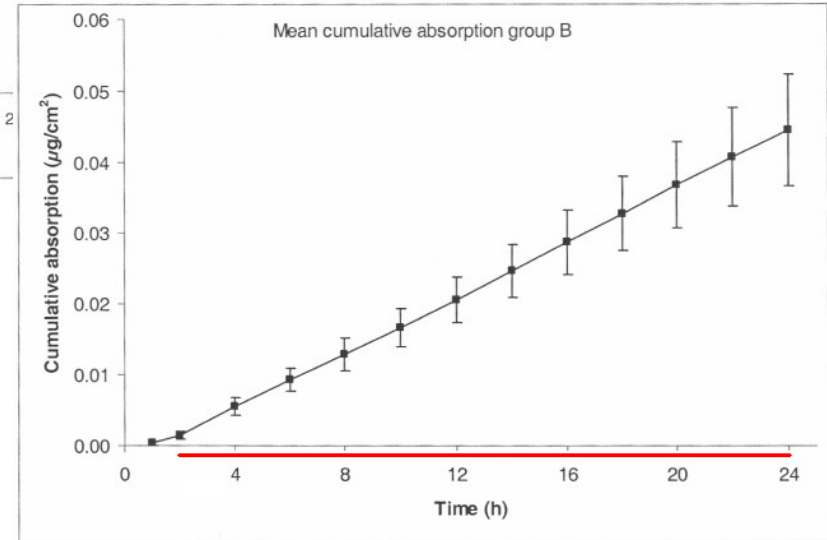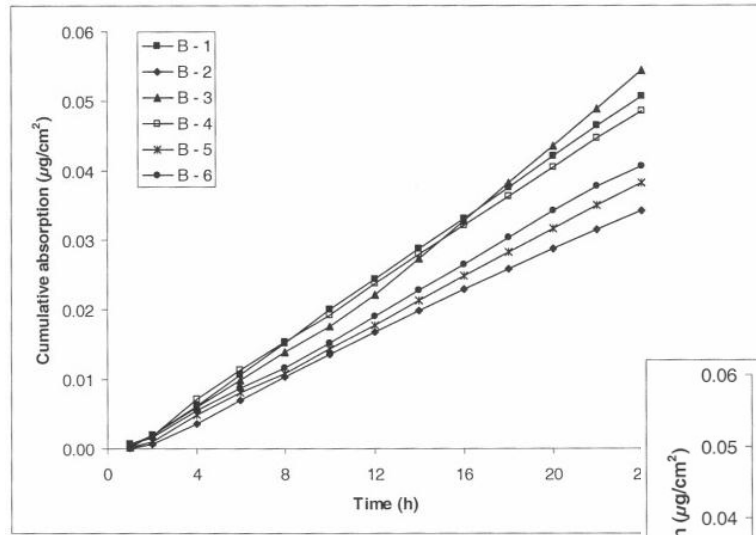
In vitro dermal absorption studies
Example (rat skin, dilution)

In vivo dermal absorption studies
Example (rat, concentrate and dilution)

Test group	Nominal concentration	Dose *	Time group	No. of animals	Exposure time (h)	Sacrifice post application
A	150 g/L	1500 µg/cm^2	T1	4	8	24 h
			T2	4	8	96 h
			T3	4	8	168 h
B	0.15 g/L	1.50 µg/cm^2	T1	4	8	24 h
			T2	4	8	96 h
			T3	4	8	168 h

* 100 µL of the dose preparations was applied to 10 cm^2 of clipped skin

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Dose	1500 µg a.s./cm²			1.5 µg a.s./cm²		
Subroup	T1	T2	T3	T1	T2	T3
Sacrifice time	24 h	96 h	168 h	24 h	96 h	168 h
Urine						
0 - 24 h	5.76	5.32	5.50	3.84	5.28	2.26
24 - 48 h		2.02	2.42		1.76	1.24
48 - 72 h		1.06	1.14		0.89	0.72
72 - 96 h		0.58	0.66		0.48	0.52
96 - 120 h			0.57			0.41
120 - 144 h			0.37			0.30
144 - 168 h			0.22			0.29
Total	5.76	8.98	10.89	3.84	8.41	5.75
Faeces						
0 - 24 h	1.60	1.51	1.37	0.95	1.32	0.36
24 - 48 h		0.95	0.95		0.75	0.31
48 - 72 h		0.44	0.43		0.29	0.15
72 - 96 h		0.26	0.23		0.21	0.12
96 - 120 h			0.15			0.07
120 - 144 h			0.19			0.04
144 - 168 h			0.23			0.02
Total	1.60	3.16	3.55	0.95	2.57	1.07
Cage Wash	0.30	0.21	0.23	0.48	0.21	0.24
Tissues*	0.19	0.04	0.13	0.23	0.03	0.04
GI-tract	1.01	0.11	0.11	0.43	0.10	0.05
Carcass	2.56	0.80	0.66	2.69	0.53	0.83
Systemic Absorption	**11.42**	**13.30**	**15.56**	**8.61**	**11.85**	**9.41**
(± SD)	(2.51)	(4.86)	(5.11)	(2.34)	(2.78)	(3.58)
Skin strips	4.15	1.59	1.62	9.61	6.04	7.92
Stripped skin	1.80	1.10	0.35	1.85	0.46	0.19
Total skin	**5.96**	**2.69**	**1.97**	**11.46**	**6.50**	**8.12**
Dislodgeable dose						
Skin wash	63.50	63.88	60.99	72.96	61.54	67.02
O-Ring + Cover	9.62	6.01	6.43	4.55	1.95	2.61
Not absorbed	**73.12**	**69.89**	**67.42**	**77.50**	**63.49**	**69.63**
Total Recovery	**90.50**	**85.89**	**87.03**	**97.57**	**81.84**	**87.15**

Conclusion

Issue to consider for exposure estimations:

- Protection goals (operator, worker, bystander/resident)

- GAP table

- Dermal absorption

- Several default input parameters

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Background information

- EFSA Guidance on the assessment of exposure for operators, workers, residents and bystanders in risk assessment for plant protection products
  http://www.efsa.europa.eu/en/efsajournal/doc/1501.pdf
- EFSA Project to assess current approaches and knowledge with a view to develop a Guidance Document for pesticide exposure assessment for workers, operators, bystanders and residents. http://www.efsa.europa.eu/en/scdocs/doc/26e.pdf
- OECD guidance notes on dermal absorption
  www.oecd.org/dataoecd/63/12/48532204.pdf
- EFSA opinion on guidance document on dermal absorption
  www.efsa.europa.eu/en/efsajournal/pub/2294.htm

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