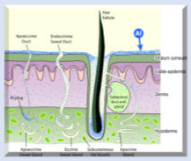
Deriving dermal absorption values for a new ICPPE hand-held operator exposure model for agricultural and non-agricultural scenarios

Ensuring safe use of pesticides globally

Risk assessments for pesticides are vital in ensuring acceptable exposures for operators applying plant protection products. In some countries, handheld application is still prevalent yet there is no global harmonized predictive model for exposures associated with this equipment. A consortium of experts including regulators, academics and industry was assembled to consider available data and develop such a model.

The importance of dermal absorption

Dermal absorption is a key factor in risk assessment as the skin is the primary route of exposure. It is well studied, and influential factors include formulation type and composition, dose per unit area and the physico-chemical properties of the active ingredient. Although regional regulatory guidance can lead to studies being conducted almost on a per formulation basis (EFSA 2017) default values have been derived for use when no specific data are available. No such agreed defaults are available for use globally.

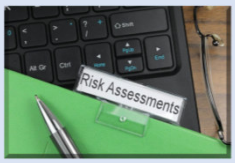


Appropriate default values based on a new analysis

To derive defaults for the new model, a database of over 400 dermal absorption studies was made available by industry associations. The database comprises some of data included in the EFSA analysis to set defaults for European risk assessment along with data from newer studies. Some data from the EFSA database were not included due to the complexity of data ownership. Each of the studies included had previously been used in a regulatory submission. Experts in the Working Group agreed on the parameters of interest and independent statistical analysis was carried out to determine which of these can be used to propose appropriate defaults. These will be invaluable as specific data may be less available in countries where the new model will be of most use.

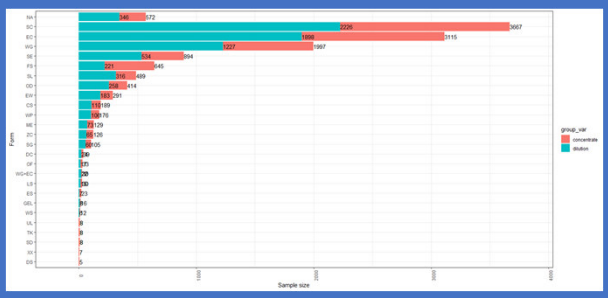
Requirements of the default proposals:

- simple to use for inexperienced risk assessors
- sufficiently protective of human health but not unduly prohibitive
- cover all likely combinations of formulation type and dose
- transparent enough for inclusion in a model which can be part of the FAO Toolkit

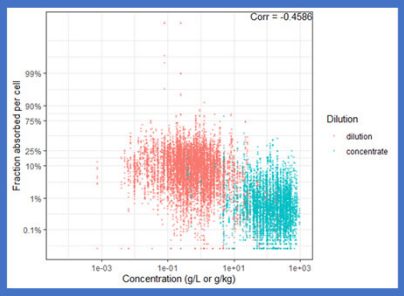


Considerations for preliminary statistical analysis:

- Factors considered as primary
  - Formulation type (solid/liquid, water based/solvent based etc.)
  - Concentrated product (mixing/loading) or diluted spray (application)
  - Concentration/dose per unit area applied to skin
  - Potentially absorbed dose (receptor fluid + whole skin - tape strips 1/2)
  - Exposure time limited to 6 to 10 hours to reflect operator task duration



Sample sizes versus formulation type



- Strongest correlation was between percentage of applied material absorbed and concentration/dose
- Several options considered for combining formulation types into fewer groups for simplicity
- 3 modelling approaches (Bayesian logistic regression)
  1. Posterior predictive
  2. Parameter uncertainties
  3. Posterior predictive + a.s. random effect

Results

Flexible options available for use in the exposure model, depending on the available parameters

All model estimates include variation in active substances (and uncertainty)

Posterior predictive estimates include individual variation

75th percentile

Group	Empirical (upper CI)	Model1 (posterior predictive)	Model2 (parameter uncertainties)	Model3 (pp with a.s. random)	Max. of models
Org.solvent.dilution	21.7	23.9	25.1	22.8	25.1
Water.based.dilution	13.8	11.6	12.6	13.2	13.8
Solid.dilution	14.9	13.5	14.7	12.2	14.9
Other.dilution	25.4	11.2	13.1	9.8	25.4
Org.solvent.concentrate	2.1	2.1	2.2	2.0	2.2
Water.based.concentrate	1.0	1.1	1.1	1.1	1.1
Solid.concentrate	0.9	0.9	1.0	0.8	1.0
Other.concentrate	2.7	1.9	2.5	1.6	2.7

95th percentile

Group	Empirical (upper CI)	Model1 (posterior predictive)	Model2 (parameter uncertainties)	Model3 (pp with a.s. random)	Max of models
Org.solvent.dilution	43.0	55.4	57.8	57.7	57.8
Water.based.dilution	35.0	35.1	37.2	40.0	40.0
Solid.dilution	40.0	39.6	41.4	37.5	41.4
Other.dilution	40.5	34.6	38.1	32.3	40.5
Org.solvent.concentrate	7.8	7.9	8.5	8.8	8.8
Water.based.concentrate	4.8	4.2	4.5	4.7	4.8
Solid.concentrate	4.5	3.6	4.0	3.4	4.5
Other.concentrate	7.6	7.9	9.5	7.2	9.5

For discussion

- Which is the appropriate percentile to ensure a safe use for individual products in a model which employs 75th percentile values for dermal exposures (no acute exposure)?
- What is the simplest categorisation of formulation types which is supported by the statistics and expert judgement?
- Can models be fitted to these categories to allow calculation of dermal absorption defaults based simply on dose
  - This would negate the arbitrary definition of concentrates and dilutions
  - It would create a new paradigm for exposure-based setting of defaults
  - Could be simple for the end user if included in the calculator
    - Formulation group is a required input for exposure calculation
    - Dose can be calculated “behind the scenes” from predicted exposures and default surface area values for body parts

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