# Supplementary 1 - Collection of physical/chemical, biological and experimental descriptors

## Lipophilicity

Information on the experimental octanol/water partition coefficient logKow was retrieved from the EFSA conclusions on the peer review of the pesticide risk assessment of each active substance or, if the EFSA conclusions were not available in the EFSA online library, from the European Commission pesticide database. Data on Aviglycine Hydrochloride were collected from US EPA. Log Kow values measured at pH5.5 were used only for Captan, Fluroxypyr, and Acetochlor; for all other substances log Kow values at pH7 were used as we could not retrieve any reliable information for pH 5.5.

## Water solubility

Data on water solubility were gathered from the EFSA conclusions on the peer review of the pesticide risk assessment of each active substance or from the European Commission pesticide database. Information on water solubility for Aviglycine Hydrochloride was retrieved from the US EPA, for Azafenidin from the original study report, for Chlorothalonil from PubChem, for Fenoxaprop-P-ethyl from FAO, and for Phenmedipham from the producer. The water solubility for Diniconazole was computed with EpisuiteTM (WSKOWWIN).

Values measured at 20[°C](http://www.rapidtables.com/convert/temperature/celsius.htm) were preferred in accordance with OECD Testing Guideline 105 [1], solubility values measured at 25[°C](http://www.rapidtables.com/convert/temperature/celsius.htm) were also accepted. Additionally, solubility values measured at pH7 were preferred. If not available, known values for the pH closest to pH7 were used, provided that the pH does not significantly influence water solubility of the particular active substance or that the typical formulation’s pH is the same to that of the measurement. In cases where active substances consist of two isomers the overall water solubility was calculated from the solubilities of both isomers after accounting for the isomer ratio. Wherever the water solubility is given as S>Xmg/l the lowest known value was used (e.g., S=Xmg/l).

## Formulation type

Formulation types are assigned to the tested preparations as indicated by the study report. The following formulation types are represented in the dataset: aqueous formulation, capsule suspension, corn grain dust, dispersion, emulsion, flowable concentrate for seed treatment, IPA salt, pasta bait, pellet bait, powder, solution, suspension, suspo-emulsion, water dispersible granules, water soluble granules, wax block, and wettable powder. Water soluble granules and water dispersible granules that were diluted in high quantities of water were considered solutions and dispersions respectively, as indicated by the study reports.

Formulation types with low prevalence in the dataset (lower than 4%) and cases for which no data was found were merged to form one category named as “other.” To explore potential differences in the models’ predictive quality attributed to the formulation type, the following five categories were considered:

1. Suspension (37.6% of the sample)
2. Emulsion (23.8% of the sample)
3. Dispersion (15.1% of the sample)
4. Solution (8.7% of the sample)
5. Other (14.8% of the sample)

Assignment of the various formulation types was as shown in the table below, following the approach as in the respective guidance document [2]. A description of formulation is provided in Table B.2 of the document.

Of the 564 values in the dataset, 10 corresponded to preparations of pure substances in simple solvents. These 10 cases relate to 4 different active substances: 3 different concentrations of Oxydemeton-methyl in water, 3 different concentrations of Methamidiphos in ethanol and 2 different concentrations of Cyflumetofen and Tolylfluanid, respectively, in acetonitrile.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Suspension** | **Emulsion** | **Dispersion** | **Solution** | **Other** |
| 37.6% | 23.8% | 15.1% | 8.7% | 14.8% |
| AICSCS + SCECFLFSMix of CS + SCOFSCWGZC | ECEWME | DCODPelletsSCSGWDGWGWPWS | AISCSGSLSPWGXX | AICSECFSno dataPasta BaitPelletPellet BaitPSSESGWax BlockWGWP |

## Physical state

This parameter was defined by the physical state of the applied preparation in each experiment, as indicated by the study reports. For example, when a solid product was moistened with artificial sweat to mimic exposure conditions it was marked as “paste” and not as “solid.” Following categories were thus considered for further analysis of the models’ predictive quality:

1. Liquid (94.5% of the sample)
2. Paste (2.7% of the sample)
3. Solid (2.3% of the sample)

Cases where no data were found were excluded from the analysis (0.5% of the sample).

## Irritancy/Corrosiveness potential of the active substance

Data on the skin irritancy/corrosiveness of the active substances were either collected from the EFSA conclusions on the peer review of the pesticide risk assessment or from the European Commission pesticide database or the ECHA database. The irritation/corrosion potential of every active substance classified as irritant/corrosive was adjusted according to the ECHA Guidance on the Application of the CLP Criteria after accounting for the substance’s concentration in the tested preparation [3]. Preparations with less than 3% concentration of irritant substances were categorized as non-irritants. Preparations, where the active substances are not classified as irritants but are identified by EFSA as “slight irritants”, were treated accordingly. Preparations with less than 1% concentration of corrosive substances (CLP classified) were categorized as irritants, while preparations with less than 0.1% concentration of corrosive substances were categorized as non-irritants. Irritant properties of co-formulants could not be taken into account, although this is foreseen by the CLP criteria for mixtures, as the required data on product composition was not available. These adjustments gave rise to the following four categories:

1. Non-irritants (90.4% of the sample).
2. Slight irritants as indicated by the EFSA peer-reviewed conclusions (4% of the sample).
3. Irritants (CLP category 2) (4.6% of the sample).
4. Corrosives (CLP category 1C) (0.4% of the sample).

These categories were considered in order to explore potential differences in the models’ predictive quality attributed to the skin irritancy/corrosiveness potential of the active substance. Cases, for which no data were found, were excluded from the analysis (0.6% of the sample).

## Skin type

Information on the skin sample is provided in the database by the original study reports. Cases, where the entries are marked as “scissors” or “full thickness”, were changed to “dermatomed,” after confirming from the original study reports that the skin thickness was lower than 1mm. The resulting “dermatomed” category comprises cases with skin thickness varying from 200 μm to 800 μm. Quantitative information on the thickness of individual skin samples was not collected in the database.

# Supplementary 2 – Buist model equations [4]

The flux of a substance across the skin is described by the modified Fick’s law:

.

1

Correction factor for steady state distribution. It represents the proportion of substance present in the donor fluid after distribution in the stratum corneum and is defined as:

2

Equation (1) is solved for t, after substituting the concentration with and correcting it by f (due to distribution into the stratum corneum), and after taking the lag time ( into account:

.

3

The total mass present is equal to the sum of the mass present in the donor at time t, , and the receptor at time t, :

4

The amount still present in the stratum corneum immediately after exposure, , is given by:

.

5

The theoretical absorption in % is given by the following relationship:

.

6

The stratum corneum/water partition coefficient can be estimated by the following QSAR [5]:

.

7

The lag time can be estimated by the formula suggested by Shah [6]:

.

8

# Supplementary 3 – Detailed results of non-parametric testing

Non-Parametric tests (Kruskal Wallis and Jonckheere-Terpstra) between categorical variables for the assessment of factors influencing the models’ predictivity. Eta squared gives the amount [%] of the variability in the prediction factor that was accounted for by each parameter and is calculated by Chi sq./(n-1). R1 and R2 are the mean ranks for each pair.

## Potts Guy & TNO



## Mitragotri & TNO



## Cleek Bunge & TNO



## COSMOS & TNO



## Potts Guy & Buist



## Mitragotri & Buist



## Cleek Bunge & Buist



## COSMOS & Buist



## IH Skin Perm



# Supplementary 4 – Sensitivity of Buist and TNO equations to kp

 for Buist

 for TNO

Partial derivation with respect to kp yields:

Comparison of the two equations yields:

The term is always negative since all parameters can only take positive values. Therefore is always <1. can only take values between 0 and 1, so that is also always <1. It follows that and thus:

# Referencestosupplementary data

[1] OECD, Test No. 105: Water Solubility, OECD Guidelines for the Testing of Chemicals, Section 1, OECD Publishing, Paris, 1995.

[2] European Food Safety Authority (EFSA), H. Buist, P. Craig, I. Dewhurst, S. Hougaard Bennekou, C. Kneuer, K. Machera, C. Pieper, D. Court Marques, G. Guillot, F. Ruffo, and A. Chiusolo, Guidance on dermal absorption, EFSA Journal 15(6):4873 (2017), doi: 10.2903/j.efsa.2017.4873

[3] European Parliament and European Council, Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, Official Journal of the European Union, 2008.

[4] H.E. Buist, J.A. van Burgsteden, A.P. Freidig, W.J. Maas, and J.J. van de Sandt, New in vitro dermal absorption database and the prediction of dermal absorption under finite conditions for risk assessment purposes, Regul. Toxicol. Pharmacol. 57 (2010), pp. 200–209, doi: 10.1016/j.yrtph.2010.02.008

[5] X. Hui, Partitioning of chemicals from water into powdered human stratum corneum (callus) - A model study, Vitro Toxicol. 8 (1995), pp. 159–167.

[6] J. Shah, I. Kaka, S. Tenjarla, S. W.J. Lau, and D. S.-L. Chow, Analysis of percutaneous permeation data: II. Evaluation of the lag time method, Int. J. Pharm. 109 (1994), pp. 283–290.