SCIENTIFIC OPINION

Guidance on Dermal Absorption[1]

EFSA Panel on Plant Protection Products and their Residues (PPR)[2,3]

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ABSTRACT

This guidance on the assessment of dermal absorption has been developed to assist notifiers, users of test facilities and Member State authorities on critical aspects related to the setting of dermal absorption values to be used in risk assessments of chemical plant protection products. It is based on the opinion on the science behind the revision of the guidance document on dermal absorption (EFSA, 2011) to which the guidance refers to in many instances. Basic details of experimental design, available elsewhere, have not been addressed but recommendations specific to performing and interpreting dermal absorption studies with plant protection products are given. Issues discussed include a brief description of the skin and its properties affecting dermal absorption. To facilitate use of the guidance, flow charts are included. Guidance is also provided, for example, when there are no data on dermal absorption for the product under evaluation. Elements for a tiered approach are presented including use of default values, data on closely related products, *in vitro* studies with human skin, data from experimental animals (rats) *in vitro* and *in vivo* and the so called "Triple pack" approach. Various elements of study design and reporting, that reduce experimental variation and aid consistent interpretation, are presented. A proposal for reporting data for Draft Assessment Reports and Registration Reports is also provided. The issue of nanoparticles in plant protection products is not addressed. Data from volunteer studies have not been discussed since their use is not allowed in EU for risk assessment of plant protection products.

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BACKGROUND AS PROVIDED BY EFSA

The preparation and revision of the EU Guidance Documents to assist the implementation of Council Directive 91/414/EEC was originally the responsibility of the European Commission; this remit has been transferred to EFSA regarding risk assessment Guidance Documents. In 2006, EFSA has consulted Member States on their priorities for development and revision of such Guidance Documents. In response some Member States expressed a wish for an update/revision of the Guidance Document on Dermal Absorption (SANCO/222/2000 rev.7, 19 March 2004).

In the practical use of this Guidance Document during the peer review under Directive 91/414/EEC several issues are recurring since they are not or only insufficiently covered by the current Guidance Document. Moreover re-evaluations (OECD, 2011; Environmental Health Criteria 235; Dermal Absorption, 2006), have been carried out in which refined or alternative approaches to the assessment of dermal absorption were presented. The report from the 2009 public consultation carried out by EFSA on the current Guidance Document suggests clearly that there is a need for substantial changes[4]. In an EFSA outsourced project published in 2010 these comments were analysed, databases on dermal absorption were also analyzed and relevant literature was reviewed. In the report thereof further needs for updates and recommendations for a revised Guidance Document have been presented[5].

After delivery of the report the PPR Panel started working on an *Opinion on the Science behind the Revision of the Guidance Document on Dermal Absorption*, which is in an advanced stage. The current evaluations and recommendations given in it show clearly that such a revision is highly desirable.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The Scientific Panel on Plant Protection Products and their Residues is asked to prepare a revision of the Guidance Document on Dermal Absorption (SANCO/222/2000 rev.7, 19 March 2004). As this Guidance Document has been initially prepared by Commission and includes Management options, Commission and Member States will be consulted as provided by Article 22 of Regulation (EC) No 178/2002 to promote the effective coherence between risk assessment, risk management and risk communication functions.
The revision will be based on:

- the comments received in 2009 within an EFSA stakeholder public consultation on the current guidance document SANCO/222/2000 rev.7,
- the evaluations provided in the final report from an EFSA outsourced project “Proposal for a Revision of the Guidance Document on Dermal Absorption” and
- the results and recommendations already given in a draft “Scientific Opinion on the Science behind the Revision of the Guidance Document on Dermal Absorption” which is already at an advanced stage.
- on a possible additional public consultation on this final draft opinion.
- recommendations of Commission and Member States regarding issues related to Risk Management.

[4] http://www.efsa.europa.eu/en/scdocs/scdoc/282r.htm
[5] http://www.efsa.europa.eu/en/scdocs/scdoc/52e.htm

1. INTRODUCTION

This Guidance is designed to assist notifiers, test facilities and Member States' Authorities on critical aspects related to the setting of dermal absorption values to be used in risk assessments of chemical plant protection products (PPPs) reviewed for authorisation under Directive 91/414/EEC[6] and Regulation (EC) No 1107/2009[7].

The document is aimed at providing guidance based on the available science in order to improve consistency of data derivation, presentation and interpretation. Where science is equivocal or lacking, existing practises and/or recommendations in other regulations/guidance documents are proposed to be followed since overall, taking into account the uncertainties involved, it is the Panel's opinion that the dermal absorption estimates will be sufficiently protective in these cases (see the scientific opinion on the science behind the revision of the guidance document on dermal absorption).

The document does not address every possible scenario and it is expected that case-by-case judgement will be needed in some instances. Where case-by-case case assessments are necessary, they should be designed to provide the same level of scientific rigour as the standard assessment and the evidence and reasoning involved should be fully documented.

Internationally agreed guidelines exist for the performance of dermal absorption studies in vivo and in vitro (EC, 2008; OECD, 2004a, b). These test guidelines are designed to cover all types of chemicals and dermal exposure scenarios, not just pesticide formulations. Notably they give only minimal guidance on the interpretation of results. The document does not address basic details of experimental design, which are addressed in the EC methods B.44 and B.45 (EC, 2008) and in OECD test guidelines 427 and 428 (OECD, 2004a, b). It does, however, provide recommendations for performing and interpreting dermal absorption studies with plant protection products in order to reduce the variability among studies and to improve data interpretation. The potential applicability of this guidance to exposures to other chemical classes (e.g. biocides or industrial chemicals) will need to be determined by bodies responsible for such evaluations.

This guidance also covers scenarios where there are no data on dermal absorption for the product under evaluation and where different types of data are available for either the product under evaluation or related products or the active substance itself. Flow charts were considered an important part of the guidance and are therefore included.

The issue of nanoformulations in plant protection products is not addressed. Currently, there is insufficient information on the penetration of nanoparticles through the skin. It is considered that at present, evaluation of all aspects of nanoparticle based plant protection products should be performed on a case-by-case basis (WHO, 2006).

In the PPR Panel opinion on the science behind the revision of the guidance document on dermal absorption. more detailed explanations and rationales for the decision tools presented in the guidance are provided. Every effort has been made to accurately cross-reference the relevant sections of the opinion.

[6] EC (1991). Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. Official Journal L 230, 1-290. 19 August 1991.

[7] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EC and 91/414/EEC. Official Journal L 309, 1-50. 24 November 2009.

2. THE SKIN AND PROPERTIES AFFECTING DERMAL ABSORPTION

Below is a summary of relevant information that is presented in the PPR Panel opinion and in more detailed reference texts (e.g. WHO, 2006; Marzulli and Maibach, 1996; Zhai et al., 2008).

- The main barrier to absorption of chemicals is the outermost layer of the epidermis, the *stratum corneum*, which is typically made of 15 – 20 layers of non-viable cells.

- The *stratum corneum* varies in thickness with anatomical site and species (10 – 600 μm). Hair follicles and sweat and sebaceous gland density can influence dermal absorption.

- Human skin is considered to be less permeable than that of laboratory animals (Monteiro-Riviere, 2008; WHO, 2006; Holmgaard and Nielsen, 2009).

- Different anatomical sites in humans display a hierarchy of absorption: scrotum > forehead > torso and arms > palms and soles of feet (see opinion section 2.2.).

- Dermal absorption studies normally use the back (*in vivo* studies) or breast/abdomen or upper leg (*in vitro* studies) that are considered to provide realistic dermal absorption values for use in exposure modelling (see opinion section 2.2.).

- Data on the impact of blood flow/vasodilatation are inconsistent (see opinion section 2.3.) and are considered non-relevant variables.

- Sweating and skin hydration have been reported to increase dermal absorption < 2 fold (see opinion section 2.3.) and are not considered relevant variables, also because they are covered by the intra-species variability factors.

- Significant skin irritation is not expected to occur in normal settings and hence to enhance dermal absorption, except when irritants and/or sensitisers are present in the formulation. However, skin irritation by the active substance and/or by the formulation is already taken into account during testing for dermal absorption. This would not be the case if a formulation has sensitising potential only (see opinion section 2.4.).

- The presence of limited areas of damaged skin is not expected to increase the total absorption (see opinion section 2.4.).

- The higher permeability (up to 2-fold) of the skin of an atopic individual is adequately covered by the safety factors applied to derive the Acceptable Operator Exposure Level (AOEL), see opinion section 2.4.

- Age-dependent differences in skin properties and functions do not require a separate approach for children and adults when determining absorption values (see opinion section 2.5.).

- Properties of the active substance that affect absorption include (see opinion section 2.6.):

    - octanol/water partition coefficient (log Pow)
    - molecular size
    - ionisation

- Other factors affecting absorption (see opinion section 2.6.):

    - solvents
    - surfactants
    - dilution

- partitioning between solvent and *stratum corneum*

Review of available data on pesticide formulations indicates that (see opinion section 4.):

- octanol/water partition coefficient of the active substance (log Pow) and molecular weight (MW) were not found to be good predictors of absorption of pesticide formulations.

- exceptions from the above are cases where log Pow < -1 or > 4 and MW > 500 for which a default value of 10% can be applied (see opinion section 4.1.2.).

- the rate of absorption is generally inversely related to the concentration of the active substance. Exceptions may include irritant and volatile compounds, and the presence of co-formulants that strongly affect absorption.

- dermal absorption of > 27% is only seen with formulations having active substance contents of < 4% (see opinion section 4.1.1.).

- for diluted products and in use dilutions, dermal absorption studies do not support a default value below 75% (see opinion section 4.1.1.).

Based on these observations and considering the fact that pesticide formulations contain solvents and surfactants, ideally, dermal absorption data on plant protection products should be generated on the formulated product and on concentrations representative of the spray dilutions as applied to the crop, including the greatest spray dilution (lowest concentration).

3. ELEMENTS FOR A TIERED APPROACH

Keeping in mind that Directive 91/414/EEC and Regulation (EC) No 1107/2009 foresee the use of default values as a first tier approach in the absence of data, the assessment of dermal absorption of plant protection products can be performed in a structured manner using the criteria outlined in section 4. This will ensure the best use of resources (for notifiers, contract laboratories and regulators) and provide the highest level of confidence in the outcome. Before conducting any studies involving experimental animals, exposure assessments should be performed using default values or existing relevant information (see section 6., flow charts 1 and 2).

Below, is a list of studies and approaches that can be used in the suggested tiered approach (flow charts 1 and 2) taking into account that scientifically sound human volunteer *in vivo* data, even if ethically performed, cannot be used in the EU[8].

The following list reflects different levels of refinement:

- Default values or data on closely related products can be used in an initial exposure assessment (see sections 6.1. and 6.2.).

- *In vitro* studies using human skin.

- Data on rats (or other experimental animals); it is widely accepted that results from animal models will over-predict human dermal absorption. Therefore, if animal data from more than

[8] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EC and 91/414/EEC. Official Journal L 309, 1-50. 24 November 2009.

one well-designed and well-performed study are available (either *in vitro* or *in vivo*) it is justified to use the lower dermal absorption value.

- "Triple pack" approach: *in vivo* data in rats (or other experimental animals) are corrected for the ratio of absorption between rats and humans *in vitro*. It should be noted that this will not necessarily provide a value lower than the human *in vitro* data alone (see section 5.9., flow chart 2 and opinion section 5.4.). Rat data generally overpredict dermal absorption and therefore it is justified to take the lower value from human *in vitro* data in case this occurs.

4. ELEMENTS OF A STUDY DESIGN AND REPORTING THAT REDUCE EXPERIMENTAL VARIATION AND AID CONSISTENT INTERPRETATION

In order to improve consistency of interpretation of study data it is important that the study protocols are as closely matched as possible. The EC B.44 and B.45 are designed to cover all types of chemicals and therefore provide a high level of flexibility. This flexibility can lead to a wide variation in study designs for dermal absorption studies on plant protection products and hence variability in how the studies are interpreted. It is therefore proposed that any dermal absorption studies on plant protection products are performed according to EC B.44 and B.45 but with additional considerations:

1. Tests should use the formulated product being considered for authorisation.
   - *(If not, it can be possible to extrapolate between similar formulations – see section 6.2.*)
2. In addition to the concentrated product, the greatest dilution (lowest concentration) of the product recommended for use should be tested. If a wide range of dilutions are proposed then more than one dilution should be tested so that the greatest and smallest recommended dilution rates are covered.
   - *(If the greatest dilution recommended on the label has not been tested, a pro-rata correction can be made from the highest dilution tested; see section 5.5. for further details.)*
3. *In vitro* studies with human skin should preferably use split thickness (200-400/500µm) (dermatomed) skin and be from the abdomen, back, breast or upper leg. This is to improve consistency and comparability particularly as split-thickness membranes tend to have significantly lower levels of residual material than full-thickness preparations (Wilkinson et al., 2006; WHO, 2006; OECD, 2004c, see opinion section 3.1.). The use of epidermal membranes may in some cases overestimate human *in vivo* skin absorption because of insufficient barrier function (see PPR Panel opinion section 3.1.). The use of cultured and reconstructed human skin models (e.g. constructed from keratinocytes) is not recommended for the determination of dermal penetration as these models have not been validated and there are reports that their barrier function is not comparable with that of skin of 'natural origin' (SCCS, 2010).
   - *(If full-thickness skin is used, the main difference is in the amount of material in the receptor fluid and the flux with the sum of receptor fluid plus skin sample being similar for both split-skin and full-thickness samples (Wilkinson et al., 2006; Vallet et al., 2007). Therefore, by including all material remaining in the skin sample, a dermal absorption value can be obtained. However, any calculated fluxes should not be used).*
4. *In vitro* studies with rat skin should preferably use split-thickness (200 – 400/500µm) skin from the abdomen or back.
   - *(If not, see point 3 above.)*

Integrity of skin used *in vitro* should be determined prior to application of the test substance and should be documented. Various methods can be used (e.g. trans-epidermal resistance, trans-epidermal water loss or reference substance penetration) (see OECD 2004c, paragraphs 42 - 46). Any membrane with unacceptable integrity should be replaced prior to application. Post-dosing evaluation of integrity and subsequent exclusion of results obtained with skin having insufficient integrity is not recommended.

5. Solid material should be moistened with a minimal volume of vehicle (e.g. water or physiological saline) to make a paste. This is to mimic sweat on the skin or occlusive conditions under clothing. Since dermal exposure to granular products is usually in the form of dust, the granules should be ground and moistened before application to the skin. Organic solvents should not normally be used (see PPR Panel opinion section 3.2.).

    - *(If solids are not moistened then the validity of the study is questionable. If solids are not moistened but occlusive conditions are used then the study can be considered a reasonable match to actual exposures, except for granules.)*

6. If tape stripping is performed, strips should be analysed separately to permit a profile of the residual material to be determined (for further details see section 5.1. and opinion section 3.6.). Glued (e.g. cyanoacrylate superglue) tape strips should not be used.

    - *(If tape strips are not reported individually then it is not possible to determine whether or not the residue is at the surface or in the lower layers. In such cases the tape strips should be considered as being part of the material in the skin sample/application site; if glue is used, the complete stratum corneum is removed by 1-2 strips, hence the complete amount in the stratum corneum should be considered as potentially absorbed.)*

7. Since there is no guidance on sample numbers in EC B.45 (*in vitro* dermal absorption), as a minimum requirement, results from at least 4 wells should be analysed in *in vitro* studies in line with the recommendations given in EC B.44 (*in vivo* dermal absorption). For statistical reasons a larger number of wells is preferred. The Scientific Committee on Consumer Safety (SCCS, 2010) recommends 8 evaluable samples originating from 4 donors. The PPR Panel proposes to follow this approach for PPPs as well, particularly since animal welfare is not an issue for human skin samples.

    - *(If results from a minimum of 4 wells are not available, it is possible to use the mean value of 3 wells if the results are closely matched, or if there is significant variation (e.g. highest 3-fold above lowest) take the highest value rather than the mean.)*

8. Solubility of the test compound in the receptor fluid must be demonstrated as not being a rate limiting factor and should be at least 10 times higher than the amount of test compound in the receptor fluid at the end of an *in vitro* study (see opinion section 3.3.). Note that although confirming solubility in the receptor fluid is a requirement in EC B.45, it is often not reported.

    - *(If not, the validity of the study is questionable.)*

9. Exposure should mimic a working day (e.g. 6-10 hours) with sampling for up to 24 hours *in vitro* and a minimum of 96 hours *in vivo* (see opinion section 3.5.).

    - *(If the exposure period is shorter, this can be compared with the lag-phase. If the product is removed before the lag-phase is reached the relevance of the study is in doubt. If the product is removed after the lag-phase is completed, it is possible to make a pro-rata correction for the shorter duration, based on the linear phase. If sampling does not continue for an adequate period, include all material in the skin sample/at the application site or, if possible, extrapolate to an adequate time point.)*

10. After the end of experimental exposure, the skin is washed and the characteristics of the skin rinsing should be indicated in the report. The cleansing agent should be representative of normal hygiene practices (e.g. an aqueous soap solution).
    - *(If washing is not performed, an overestimate of the absorption is likely to occur.)*
11. When performing studies designed to permit correction of rat *in vivo* data with rat and human *in vitro* data, the *in vitro* and *in vivo* data should be as closely matched as possible in terms of rat strain used, exposure time, tested material, skin sample preparation, vehicle and dilution rates (see section 5.9. for details)
    - *(If the rat and human in vitro studies and rat in vivo studies are not comparable, the human in vitro value can still be used.)*
12. Data should be presented for individual animals/wells and as group means +/- standard deviations.
13. Maximum flux should be based on the calculation of the slope of the linear portion of the absorption:time curve and should not include the lag-phase or plateau.
14. If overall recovery is consistently low (mean < 95% for radiolabelled studies) and consistently so for all animals or wells, this does not necessarily mean that the study cannot be accepted but an explanation must be provided as to why the missing material should not be considered as absorbed. A recovery of 100 ± 10% is cited in the OECD guidelines but as dermal absorption values for many pesticides are < 5% it is considered that expecting a recovery of 95% is not unrealistic if such low dermal absorption values are to be supported.
    - *(If recovery (mass balance) is low (< 95%), see section 5.2. for details.)*
15. If there is significant variation within groups or replicates (e.g. standard deviations equal to or larger than 25% of the mean) a case supporting the overall validity of the study must be presented.
    - *(If there is significant variation between replicates, see section 5.4. for details.)*
16. If non-radiolabelled material is used, the analytical methods used to determine the amount of absorbed material must be able to account for metabolism and hydrolysis, or data must be presented to permit back calculation from the analysed components to the amount of active substance absorbed (see section 6.3. for details).
    - *(For non-radiolabelled studies, if the relationship between the recovered material and the amount absorbed cannot be demonstrated, a conservative default could be to assume that any deficit in the mass balance is absorbed material.)*

5. INTERPRETATION OF STUDIES

5.1. Tape stripping

(See PPR Panel opinion sections 3.4., 3.5. and 3.6.)

Tape stripping is a procedure performed at the end of a dermal absorption study that involves the sequential application of adhesive tape to the area of skin that was exposed to a chemical. If the tape strips are analysed separately, a profile of the chemical within the *stratum corneum* can be determined.

There is a general practise within EFSA PRAPeR[9] meetings that the first 2 tape strips will represent material that will not become bioavailable due to desquamation. The Panel proposes to follow this approach. Thus, the first 2 tape strips can be excluded when calculating dermal absorption provided that the application site was swabbed to remove the test material before termination of the study. This applies to both *in vitro* and *in vivo* studies (see opinion section 3.6.).

Only if absorption is essentially complete at the end of the study (> 75% of total absorption occurring within half of the study duration) can all tape stripped material be excluded. This applies to both *in vitro* and *in vivo* studies (see sections 5.5. and 5.7. and see opinion sections 3.4. and 3.5. providing the background for this statement).

For *in vivo* studies where there is evidence that absorption is nearing completion, where less than 75% is absorbed, material from all tape strips can be excluded from the absorbed material if the evidence indicates that it is not bioavailable. However, this should be assessed on a case-by-case basis.

5.2. Recovery

When recovery is low (mean < 95%) there is a need to consider whether the missing material should be considered as absorbed.

1. If all wells have a low recovery, as a worst case assumption the missing material could either be considered as absorbed, or alternatively, a "normalisation" approach could be applied in which dermal absorption is expressed as a percentage of the total amount recovered. Whereas in principle, normalisation is the preferred option since conservatism is built in when using rat/human *in vitro* studies and/or *in vivo* rat studies for the human *in vivo* estimate, critical evaluation of the available data should be performed to determine if significant amounts of the missing material could have been absorbed (e.g. for *in vivo* studies exhaled as CO_2).

2. If there are some wells or animals with adequate recoveries then the results for low and high recovery animals/wells can be compared to see if the losses are from absorbed or non-absorbed material.

Losses that are considered to be from non-absorbed material will have no impact on the results.

If losses appear to be from absorbed material, the values should be corrected for the losses or only values from high recovery samples used to derive the absorption.

Low recovery is less of an issue when there is a high level of absorption as the impact will be proportionally lower. For volatile or potentially volatile compounds, measures should be taken to prevent loss (e.g. charcoal filter occlusion to minimise potential volatilisation, see also section 5.8.).

5.3. Rounding of values

(See PPR Panel opinion section 5.3.)

Dermal absorption studies tend to have a relatively high level of variability associated with the results. So as not to imply spurious accuracy, dermal absorption values:

- of or above 10% should be rounded to two significant figures.
- between 1% and 9% should be rounded to one significant figure.

[9] Peer Review of Pesticide Risk Assessment (carried out under the responsibility of EFSA's Pesticide Unit in the EU)

- below 1% should be rounded to one significant figure (if the data are reasonably consistent, report as a value below 1%, i.e. do not round up to 1%).

For example:

0.15% = 0.2%

1.43% = 1%

2.65% = 3%

10.4%= 10%

15.6%= 16%

For "triple pack" calculations, the rounding should be applied to the product of the calculated correction i.e.

In vivo rat = 2.6%

Correction factor= 1.4

In vivo human= 2.6/1.4= 1.86= 2% (rounded)

5.4. Variability within the results and outliers

If there is significant variation between replicates (i.e. the standard deviation is equal to or larger than 25% of the mean of the absorption as defined in section 5.6. and 5.8.) consideration should be given to using a value other than the mean or rejecting the study entirely. The preferred approach would be the addition of a standard deviation to the mean value. This would give a value that covers the upper 84th percentile value of the results. Such an approach would be reasonably conservative and could reduce the need to repeat studies (particularly *in vivo* studies).

Reasons for excluding outliers should be clearly stated in the study report and summary text. In addition, the full results from the samples considered to be outliers must be presented. It should be noted that results treated as outliers should include spuriously low values as well as high ones.

On a case-by-case basis, expert judgement might ultimately be applied to increase values compensating for deficiencies in the quality of the study. Justification for choosing a certain increased value should be provided and fully documented in such cases.

5.5. Dilution rates (tested concentrations)

(See flow chart 3)

The concentration(s) tested should cover the extremes of those recommended on the product label. If the lowest concentration tested is greater than the lowest concentration recommended on the label, consideration should be given to increasing the dermal absorption *pro rata* to account for any limitation of absorption due to the amount of material applied to the test site. However, if the dermal absorption from the concentrate and the lowest tested concentration shows no indication of concentration related absorption, then there is no need to increase the value for the lower (untested) concentration recommended on the label.

Pro rata correction assuming a linear response is considered to be a conservative but appropriate approach in the absence of data. It should be noted that if the *pro rata* correction gives a value above the default value for dilutions (see section 6.), then the default value of 75% should apply.

For example:

Case 1:

Dermal absorption of concentrate = 1%.

Dermal absorption of 1 + 50 dilution = 12%.

Highest label dilution is 1 + 80 for which a value of 12 x 80/50= 19% can be derived.

Correction necessary.

Case 2:

Dermal absorption of concentrate = 5%

Dermal absorption of 1 + 150 dilution = 6%

Highest label dilution is 1 + 200 for which a value of 6% can be used as there is no notable difference between the concentrate and a 1 + 150 dilution.

No correction necessary.

5.6. *In vitro* studies[10]

(Flow chart 4a, see PPR Panel opinion section 3.1.)

Human skin samples provide the best estimate. If non-human skin is used, then the rat would be recommended for consistency reasons.. If a dermal absorption study with rat or human skin samples has been well performed (see section 4 and EC B.45), the dermal absorption should be calculated on the following basis using mean values:

i. when:

- the sampling period is 24 hours

and

- over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration of the total sampling period

then

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding all tape strips)

ii. when:

- the sampling period is less than 24 hours

[10] Use of reconstituted skin is not recommended, see section 3.1.

or

- less than 75% of the absorption occurs within half the duration of the study

then

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2)

If tape stripping has been performed with strips being pooled, then all tape strips should be included in the absorbed material.

5.7. Non-human primates *in vivo*

(Flow chart 4b, see PPR Panel opinion section 3.9.)

The use of non-human primates is not recommended, however, the following guidance is provided for the evaluation of existing studies.

In order to use *in vivo* data on non-human primates the following points need to be addressed:

- A minimum group size of 4 should be used (this is in line with EC B.44). If smaller numbers are used then the highest result, rather than the mean, should be chosen.
- The application site should be one that gives a realistic level of dermal penetration (e.g. forearm, torso, forehead). Correction for mass balance needs to be done if non-human primates were not sacrificed at the end of the study and non-radiolabelled material was used.
- The analyses need to cover possible metabolites or use a marker compound(s) that can be back extrapolated to absorbed material based on the amount in urine, faeces and exhaled air.
- It is not usually possible to determine the residue in the dermis at the application site or distributed within the body.
- Compare the excreted material following oral or intravenous and dermal dosing. The dermal study should include a long enough sampling duration to confirm that excretion is essentially complete. For example, if 25% of an intravenous dose is detected in excreta using a particular analytical technique and 5% of a dermal dose is detected in excreta then the dermal absorption can be considered to be 20% (5% x 100/25).
- Exclude an extensive first pass metabolism, incomplete absorption or extensive biliary excretion. A first tier approach would be to assume 100% oral absorption, and determine the ratio of the amount detected in urine in the dermal study with the amount in urine from the oral study.
- Take blood samples and determine the ratio of the area under the curve (AUC) from intravenous or oral dosing with that from an equivalent dermal dose. The default assumption is 100% absorption from the oral route: e.g. (AUC dermal/AUC oral) x 100 = % dermal absorption.

It is the responsibility of the notifier to present a justification for the analytical method used and how the recovered material relates to the amount actually absorbed. Alternatively, as a conservative approach, all material not recovered in the skin washes plus the first two tape strips (if performed) can be considered as absorbed.

5.8. **Rat**[11] ***in vivo***

(Flow chart 4b, see PPR Panel opinion section 3.4.)

If a dermal absorption study in rats has been well performed (see OECD 427), the dermal absorption should be calculated on the following basis using data from the terminal sampling time:

i. When:

- the sampling period is 24 hours or longer

and

- over 75% of the total absorption (material in excreta, exhaled gasses and in the carcass at the end of the study) occurred within half of the duration of the total sampling period

then

Absorption = excreta + CO_2 / volatiles (in exhaled air) + carcass + skin (excluding tape strips)

ii. When:

- the sampling period is less than 24 hours

or

- significantly less than 75% of the absorption occurs within half the duration of the study

then

Absorption = excreta + CO_2 / volatiles (in exhaled air) + carcass + skin (excluding tape strips 1 and 2)

If tape stripping has been performed with strips being pooled then all tape strips should be included in the absorbed material

iii. In cases where the evidence indicates that absorption was essentially complete at the end of the study (e.g. marked decline in the amount over the last three sampling times) but the criteria in section i. above were not met, a case-by-case consideration of the potential bioavailability of the application site residue can be made. This should take account of factors such as whether the remaining material is in the outer layers of the *stratum corneum* and the duration of the study. For example, if the study was run for only 96 hours and the majority of the residual material is in tape strips from the lower layers of the *stratum corneum*, then the material is probably bioavailable. If the study was run for 168 hours and the majority of the material is in the tape strips from the upper layers of the *stratum corneum*, it is reasonable to exclude these tape strips.

iv. Poor recovery in *in vivo* studies can be due to a variety of reasons that can be investigated further using data normally available.

- If the exhaled volatiles have not been measured and the radiolabel is on a part of the molecule that could be cleaved and give rise to CO_2 and/or exhaled volatiles, it is

[11] Rat or any other non-primate experimental animal.

reasonable to assume that some or all of the missing material was absorbed and lost via exhalation. Some information on exhaled volatiles/CO_2 is often available from the oral ADME data (assuming the same radiolabel position is used). If no volatiles or CO_2 were detected in the oral ADME study, it is reasonable to conclude that this route will not be the reason for poor recovery following dermal exposure.

- Desquamation might be a cause of poor recovery particularly if the study is of a duration of 7 days or longer. If a significant amount of material is removed by the final swabbing and/or is present in the first tape strip, this could support an argument that the poor recovery is due to desquamation and the missing material was not absorbed. On the contrary, if there is only a small amount of material obtained with the final swabbing or the first tape strip, it is unlikely that desquamation would have been a cause of significant loss.

In all cases of poor recovery (mean < 95%) reasoning why the missing material should not be considered as absorbed, has to be presented (see section 5.2.).

5.9. Integration of *in vivo* and *in vitro* data

(See PPR Panel opinion section 5.4.)

To ensure scientific validity it is essential that the study protocols for the *in vitro* studies are well matched for variables that could influence the results e.g.:

- Skin type (i.e. split-thickness)
- Test material/formulation/vehicle/concentration of the active substance
- Exposure duration and sampling period
- Receptor fluid composition
- Swabbing technique
- Analytical techniques

In the *in vivo* study the same test material/formulation/vehicle/area dose (concentration) and a similar exposure time and swabbing technique should be used as in the *in vitro* studies.

Normally this will be achieved by performing the studies contemporaneously at the same test facility, however, this is not an essential requirement. If the *in vitro* studies are not well matched then the possibility of a comparison of the relative dermal absorptions should be very carefully evaluated.

If the *in vitro* studies are closely matched to each other and to the *in vivo* study, the *in vivo* human dermal absorption can be derived based on the following equation:

In vivo human absorption = [(*in vivo* rat absorption) x *in vitro* human absorption)]/(*in vitro* rat absorption).

The calculation can be based on either % absorption (option 1) or flux (option 2).

<u>Option 1:</u>

- Calculate % absorption.

- The relative absorption can be estimated by taking the ratios of the % absorption.

Then the derived human *in vivo* value will be:

***In vivo* human= *in vivo* rat/(% absorption in rat *in vitro*/% absorption in human *in vitro*)**

Option 2:

- Calculate the maximum flux, normally from a linear portion, of 2 hours or longer, of the absorption-time curve. A shorter time period may be used if absorption is very rapid and essentially complete within 4 hours.

- The relative absorption can be estimated by taking the ratios of the maximum flux.

Then the derived human *in vivo* value will be:

***In vivo* human = *in vivo* rat/(maximum flux in rat *in vitro*/maximum flux in human *in vitro*)**

There are circumstances when the flux might not be appropriate (e.g. the linear phase is significantly longer in the human samples). In these cases the comparison can be performed using the % absorbed but it must have the same basis for both rat and human samples (i.e. in terms of inclusion of tape strip material or residue in the skin sample).

5.10. Choice of dermal absorption values for worker/resident exposure

Until the outcome of the ongoing research is available and conclusions have been drawn, it is proposed that the appropriate dermal absorption value for exposures to dried dispersed residue should be the higher of the values for the concentrate and the in-use dilution.

If an acceptable estimate of worker/resident exposure cannot be obtained using this approach, specific evaluations could be performed on a case-by-case basis. These could take into account factors such as the level of the dislodgeable foliar residue (mass/unit area) and transfer coefficient versus the loading used in the dermal absorption studies with concentrate and dilution(s) to help determine which is the most appropriate dermal absorption value to use. Any lowering of default values commonly applied in exposure models should be justified.

5.11. Use of data from field studies

Dermal absorption estimated in field monitoring studies of workers/operators is rarely accurate because of difficulties in measuring skin deposition and of knowing metabolism in humans. Therefore, data obtained in these studies can only be used to support experimentally determined values.

6. HOW TO PROCEED WHEN THERE ARE NO DATA ON THE FORMULATION UNDER CONSIDERATION

This approach is outlined in flow chart 1. When using it, care should be taken to ensure that the outcome is relevant for the product under consideration.

6.1. Default values

Based on an evaluation of agreed dermal absorption values for a range of concentrated pesticide formulations and their dilutions, the following default values are recommended (see opinion section 4.1.1.for details).

A default dermal absorption value of 25% may be applied for products containing > 5% (50 g/kg for solids or 50 g/L for liquids) active substance.

A default value of 75% should be used for products or in use dilutions containing ≤ 5% active substance.

If log Pow < -1 or > 4 and MW > 500 a default dermal absorption value of 10% may be applied (de Heer et al., 1999).

6.1.1. Consideration of the oral absorption value when setting a default value

(Flow chart 1, see PPR Panel opinion section 5.1.)

If oral absorption is less than 75% this can be used as a surrogate dermal absorption value for diluted products/in-use dilutions. If oral absorption is < 25% it can be used instead of the default value for both the concentrated and the "in use" dilution products. There are usually no oral ADME studies for formulations that include co-formulants which are possibly modifying dermal absorption. For these reasons, estimates based on oral absorption should be applicable in only a limited range of circumstances after careful consideration of doses and vehicle used in the ADME studies, where bile-cannulation was also performed.

6.2. Use of data on similar formulations

(Flow chart 5, see PPR Panel opinion sections 2.6. and 4.4.)

Data on another (reference) formulation can be used if the formulation to be assessed is closely related. This occurs when all the following conditions are met:

- Synergist and safener content is within +/-25% w/v of that in the reference formulation (see opinion section 2.6.).
- Synergist and safener are closely related chemically and in terms of physical-chemical properties (e.g. toluene versus xylene; octanol versus nonanol) and interaction with the active substance (e.g. solubility of the active substance).
- Formulation is of the same or lower skin irritancy based on scores in studies. These must include initial findings (as dermal absorption is often significant within the first 24 hours), not just the classification. If no skin irritation study is available, a comparison based on the irritancy of the components can be performed, but the outcome should be interpreted with care as classification does not take initial irritation scores into account.
- Formulation having the same or no sensitising potential based on classification.

- Co-formulant (e.g. solvent, stabiliser, surfactant, detergent, emulsifier, adhesive, antifreezing substance) content is within +/- 25% w/w of that in the reference formulation.

- Co-formulant of similar chemical type (e.g. linear alkyl sulphonate is not replaced by an aromatic sulphonate derivative).

It is considered unlikely that the above criteria will be met when moving from one formulation type to another (e.g. suspension concentrate to emulsifiable concentrate).

6.3. Data on the active substance

(Flow chart 6)

Data generated with the active substance should only be used when the formulation under evaluation is very closely related to the vehicle used in the study with the active substance, in terms of solvent, surfactant content, skin irritancy and active substance content.

6.4. Microencapsulated formulations

(see PPR Panel opinion section 5.6.)

The dermal absorption values used in exposure assessments should, by default, be based on the product within the capsules. If acceptable exposure assessments cannot be achieved with this approach, a case-by-case evaluation based on the properties of the encapsulated product relevant to specific exposure scenarios can be performed:

- If the capsule is shown to remain intact within the formulation over 2 years (standard storage stability test) then any exposure to the concentrate during mixing and loading can be assumed to be to the encapsulated product and the dermal absorption value for the encapsulated concentrate can be used, if available.

- If the capsule is seen to remain intact on dilution and throughout the application process (e.g. through pressurised spray nozzles) then exposures relating to the time of application can be based on the dermal absorption value for the diluted encapsulated product, if available.

- Dermal absorption values of the product within the capsule should be used if the integrity of the capsule has not been demonstrated and in all cases for re-entry workers and residents (see section 5.10.) since they are likely to be exposed to the material within the capsules that needs to be released in order to be effective. Should dermal absorption studies be available for the active substance both in a concentrated solution and in a dilution, the higher of the two figures should be used for assessment of dermal exposure for workers and residents.

6.5. Formulations containing more than 1 active substance

Dermal absorption of active substances from combined formulations can be considered to be independent of the other active substances provided that none of the active substances is a significant irritant and/or sensitiser. Dermal absorption values should be based on the results of studies on the individual active substances in formulations similar to the combined formulation (as defined above) or on data using the combined formulation.

6.6. Use of other information

6.6.1. (Q)SAR

(See PPR Panel opinion sections 4.3. and 5.5.)

The use of existing (Q)SAR approaches for predicting dermal absorption of active substances from pesticide products cannot be recommended. If (Q)SAR approaches are used, the "applicability domain" must be clearly defined and shown to be appropriate.

6.6.2. Information on related active substances

(See PPR Panel opinion section 5.5.)

The use of data on related active substances needs to be considered on a case-by-case basis, taking account of the properties of the active substances and formulations and the uncertainties in the datasets. If such an approach is applied, sufficient reasoning must be provided.

Molecules of very similar structure (e.g. ethyl substituent replacing methyl) and physical chemical properties would be expected to have similar dermal absorption characteristics in the same co-formulants.

Similarly it might be possible to interpolate data from a number of similar active substances for drawing conclusions on a new active substance that is within the series For instance, if the dermal absorption of a group of 5 closely related active substances in similarly formulated products is between 15 and 20%, it is reasonable to conclude that a sixth compound in the series would have a dermal absorption of around 15 – 20% if it has a similar formulation. However, it would not be appropriate to extrapolate data from a series of 3 closely related compounds with dermal absorption values of 2 – 12% based on significantly different formulations.

6.6.3. Comparison of oral and dermal toxicity data

It is not recommended to derive the dermal absorption of a compound by comparing the toxicity produced at different dose levels via the oral and dermal routes.

For the limitations, conditions and circumstances when this approach might be applied, see the PPR Panel opinion section 5.2.

7. DATA PRESENTATION IN DRAFT ASSESSMENT REPORTS AND REGISTRATION REPORTS

In order to aid the independent evaluation of dermal absorption data, without needing to go back to the full study report, it is recommended that, as a minimum, the information given in Table 1 is presented.

Table 1: Template with minimum information on dermal absorption studies to be presented in Draft Assessment Reports and Registration Reports

In vitro and in vivo studies
Material/product tested (name/code number)
Type of formulation
Concentration of active substance in the formulation
Vehicle used (if any)
Animal species/strain
Dilution rates
Application rates in micrograms active substance per cm^2
Exposure time
Sampling duration (time of last sample)
Skin sample source/application site
Group size/number of wells
Total recovery (%, mean +/- SD)
Amount absorbed (%, mean +/- SD)
Which samples contribute to the amount absorbed
Type of tape strip used
In vivo studies
Amount in excreta (%, mean +/- SD)
Amount in carcass (%, mean +/- SD)
Amount in exhaled volatiles/CO_2 (%, mean +/- SD)
75% excreted in first half of study?
Amount in stripped application site (%, mean +/- SD)
Amount in tape strips 3 to ∞ (%, mean +/- SD)
Amount in tape strips 1 + 2 (%, mean +/- SD)
Amount in application site washes (%, mean +/- SD)
Swabbing
In vitro studies
Receptor fluid composition
Adequate solubility in receptor fluid confirmed?
75% absorbed in first half of study?
Amount in receptor fluid and chamber wash (%, mean +/- SD)
Amount in stripped skin sample (%, mean +/- SD)
Amount in tape strips 3 to ∞ (%, mean +/- SD)
Amount in tape strips 1 + 2 (%, mean +/- SD)
Amount in skin sample washes (%, mean +/- SD)
Swabbing
Skin preparation used (e.g. split/full thickness skin)

Modifications to this template will be required to match study designs e.g. if tape stripping is not performed or if all the strips are pooled.

8. FLOW CHARTS

Flow chart 1: Procedures to follow when there are no dermal absorption data on the actual formulation under evaluation

Flow chart 2: General procedure for decision of dermal absorption of plant protection products

Flow chart 3: Procedures to follow when using dermal absorption data generated at dilutions different to those representing "in use" conditions

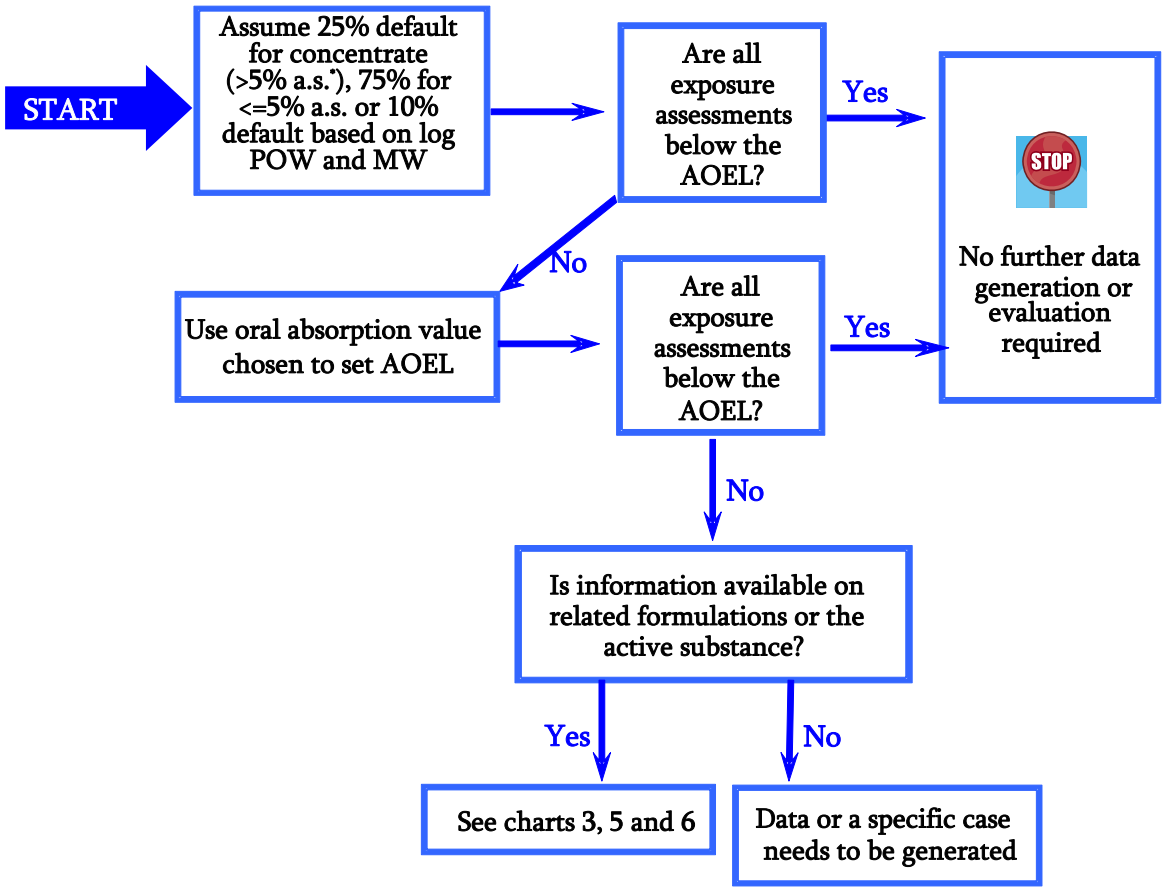
Flow chart 4a: Consideration of *stratum corneum* and application site residues *in vitro*

Flow chart 4b: Consideration of *stratum corneum* and application site residues *in vivo*

Flow chart 5: Procedures to follow when reading across dermal absorption data between formulation types

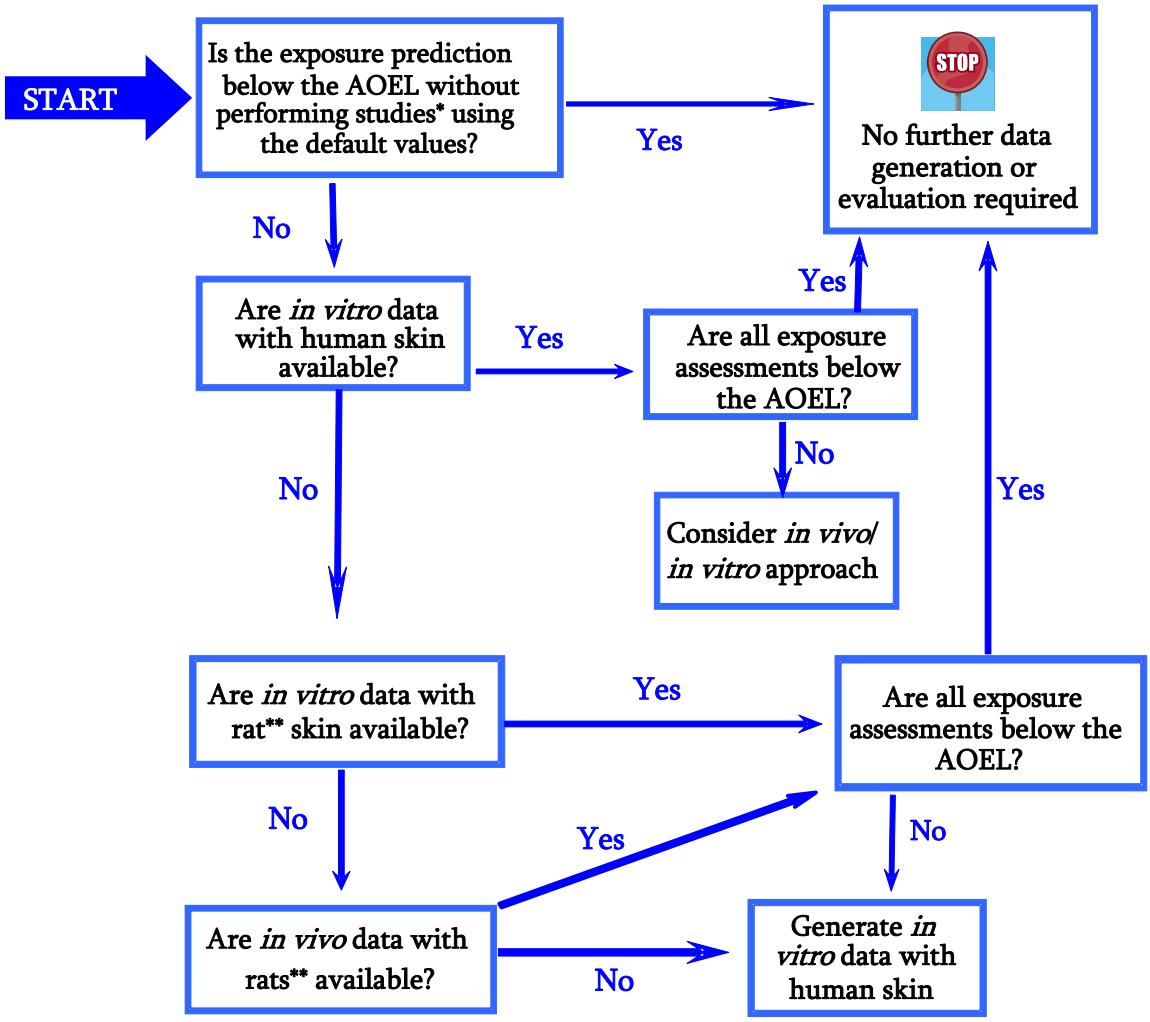
Flow chart 6: Procedures to follow when extrapolating dermal absorption data on an active substance to a formulated product

FLOW CHART 1: Procedures to follow when there are no dermal absorption data on the actual formulation under evaluation



* a.s. Active Substance

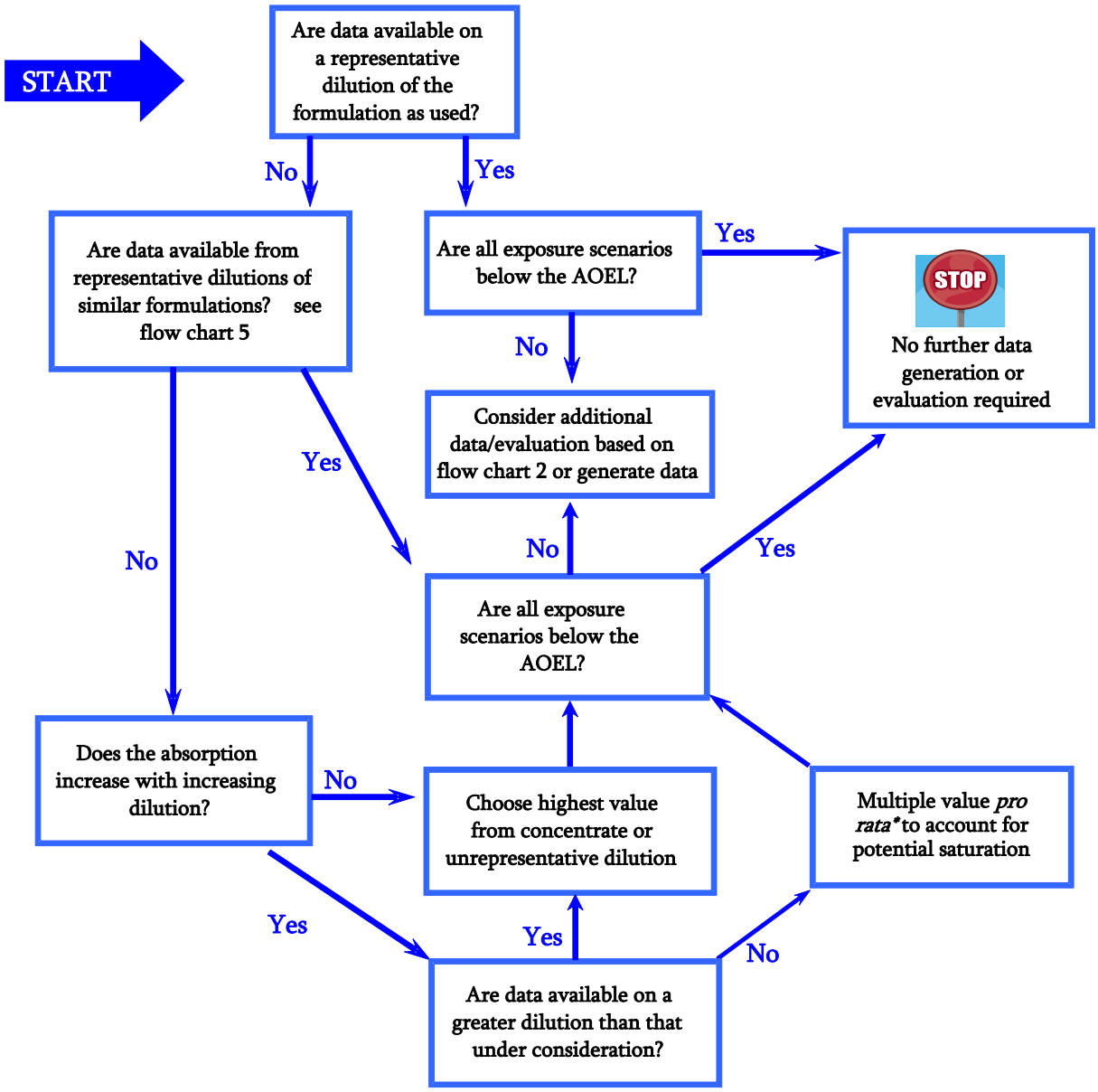
FLOW CHART 2: General procedure for decision of dermal absorption of plant protection products



*studies should be on a representative formulation

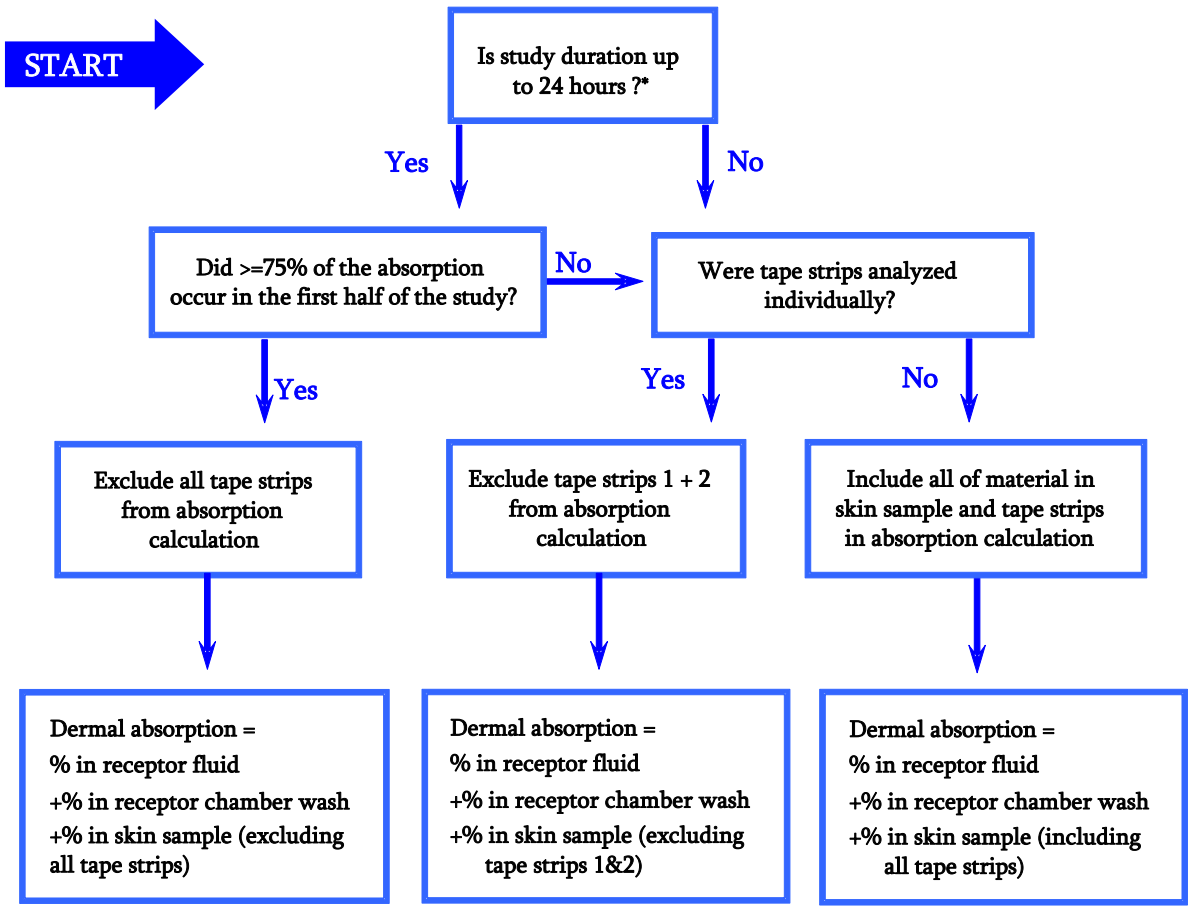
**or other species

FLOW CHART 3: Procedures to follow when using dermal absorption data generated at dilutions different to those representing "in use" conditions



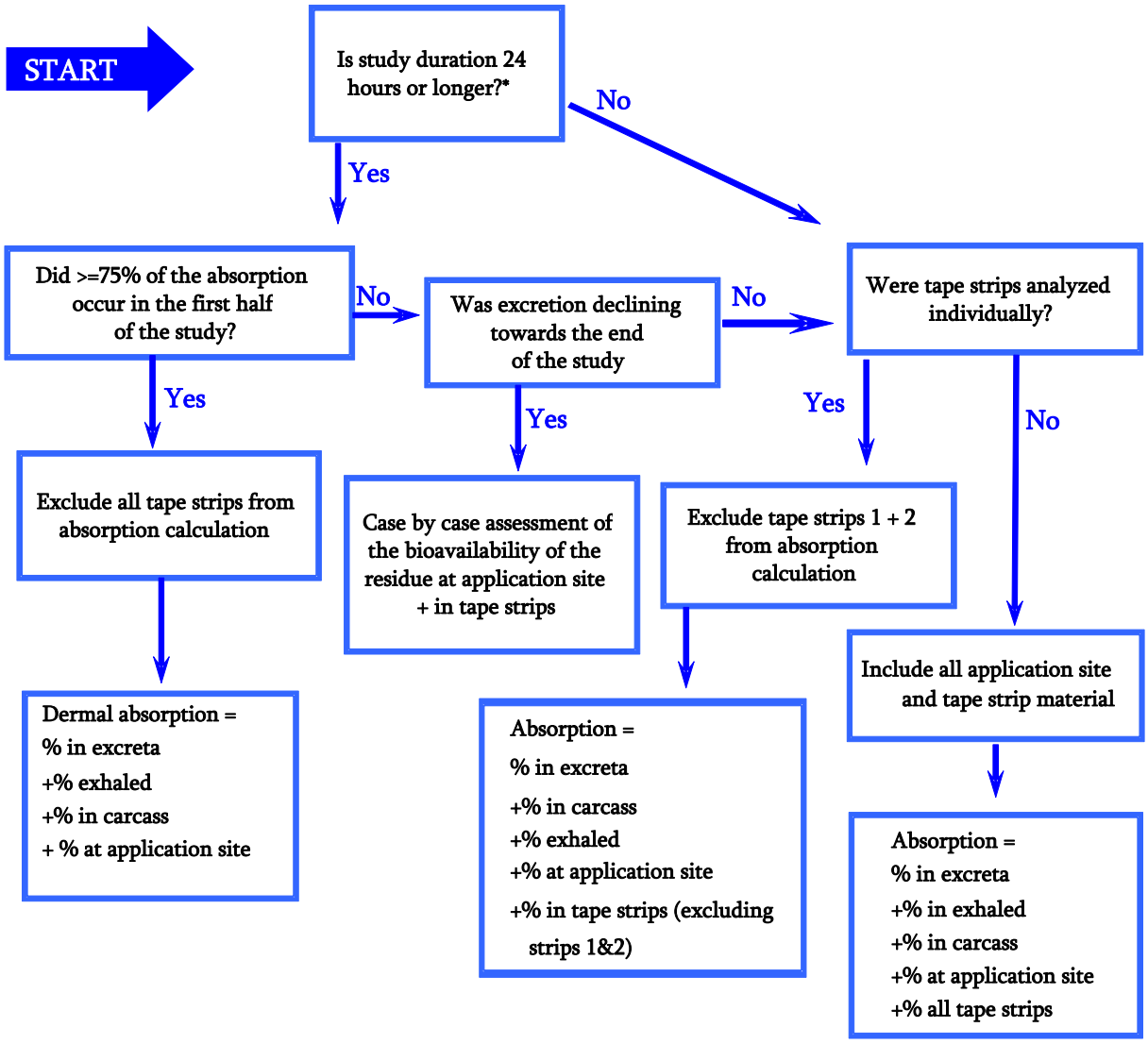
*e.g. if data are for 1+300 dilution but required dilution is 1+1200, multiply by 4

FLOW CHART 4a: Consideration of *stratum corneum* and application site residues *in vitro*



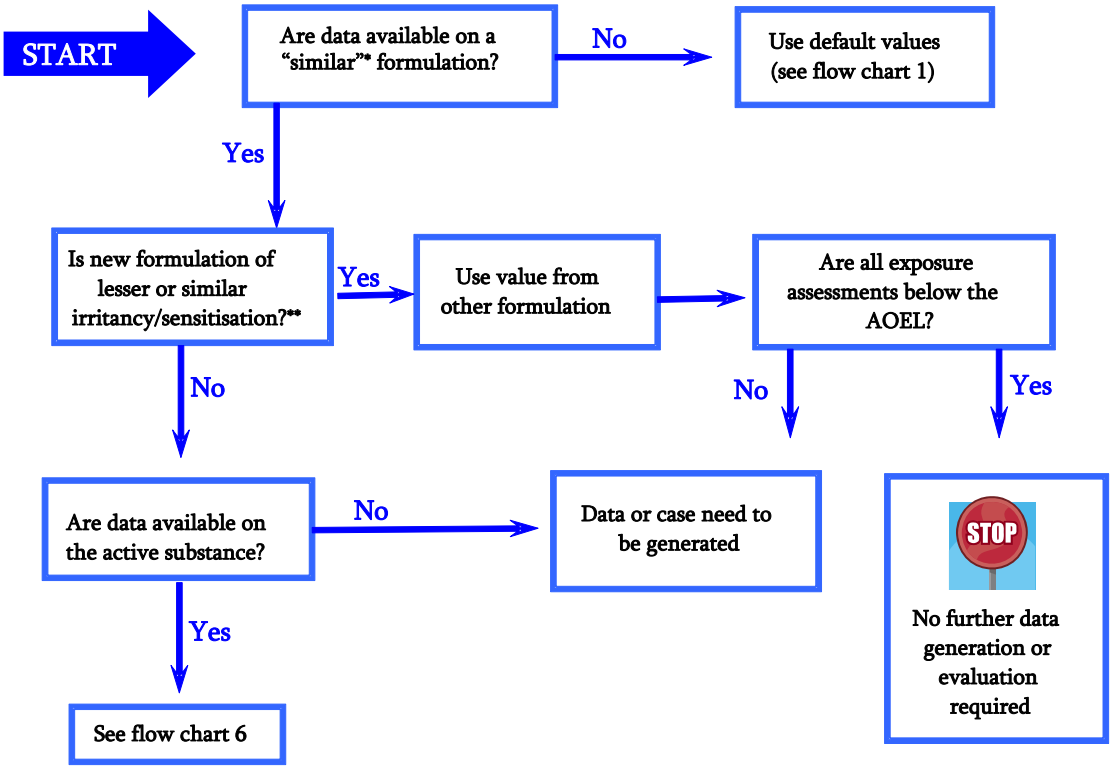
* Duration refers to the study and not to exposure of skin

FLOW CHART 4b: Consideration of *stratum corneum* and application site residues *in vivo*



*Duration refers to the study and not to exposure of skin

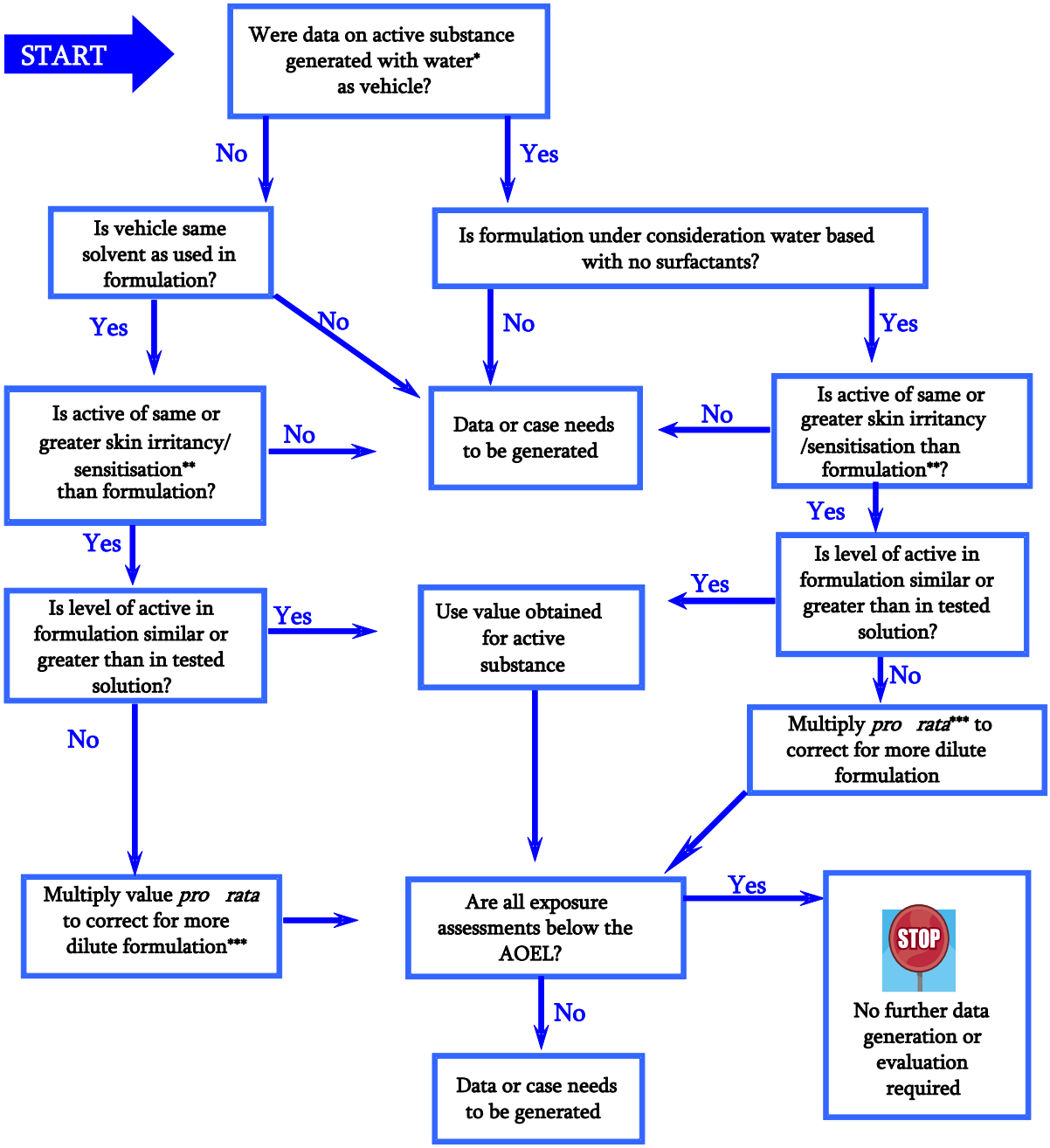
FLOW CHART 5: Procedures to follow when reading across dermal absorption data between formulation types



*See Section 6.2 for details of when formulations can be considered similar

**Based on scores, not just classification for irritation. Consider classification for sensitisation

FLOW CHART 6: Procedures to follow when extrapolating dermal absorption data on an active substance to a formulated product



*or simple aqueous vehicle e.g. 1% carboxymethylcellulose

** based on scores not just classification for irritation. Consider also classification for sensitisation

***e.g. if data are for 1+300 dilution but required dilution is 1+1200, multiply by 4

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GLOSSARY

ADME study: Absorption, distribution, metabolism, excretion study.

Area under the curve (AUC): Area under the plasma drug concentration versus time curve; a measure of drug exposure.

Dermal absorption: The movement of a chemical from the outer surface of the skin into the circulatory system leading to systemic exposure. Also called percutaneous absorption.

Dermal penetration: The movement of a chemical from the outer surface of the skin into the epidermis, but not necessarily into the circulatory system.

Flux: The amount of material crossing a defined area in a set time. A chemical with a high dermal flux will be absorbed more readily than a chemical with a lower flux.

Full-thickness skin: Full-thickness skin preparations consist of a 500–1000 μm thick skin sample, incorporating the *stratum corneum*, viable epidermis, and dermis.

Lag-phase: The time taken for the absorption of a chemical across the skin to reach a linear flux. Can be determined by extrapolating the line of linear flux back to the intercept at the X-axis of an absorption:time plot.

Log Pow: The logarithm of the partition coefficient of a substance between octanol and water (i.e. the relative maximum amount of a chemical that will dissolve in octanol and in water). A compound with a solubility of 100 g/L in octanol and 1g/L in water would have a log Pow of 2.0.

Split-thickness skin: Split-thickness (dermatomed) skin consists of 200–400/500 μm thick sample, in which the lower dermis has been removed. A surgical instrument for cutting skin grafts, called dermatome, is used to obtain samples of uniform shape and thickness.

Stratum corneum: The outermost layer of the epidermis. Consists of several layers of non-viable cells (typically 15 – 20), the outermost cells are lost by sloughing off. Varies in thickness with anatomical site. Presents the major barrier to dermal absorption.

Tape stripping: A procedure performed at the end of a dermal absorption study that involves the application of adhesive tape to the area of skin that was exposed to a chemical. An even (often predetermined) pressure is applied to the tape before it is removed, taking a layer of *stratum corneum* cells with it. The tape strip is then analysed to determine the amount of chemical that was present in the removed *stratum corneum*. The process is repeated to remove sequentially lower layers of the *stratum corneum*.

Transfer coefficient: The rate at which dislodgeable foliar residues can be transferred to a worker during a specified activity (expressed in terms of the area of contaminated foliage or fruit from which residues are transferred per hour).