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SCIENTIFIC COMMITTEE ON PLANTS **SCP/GUIDE-DERM/002-Final**
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OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE ON DERMAL ABSORPTION (Doc. SANCO/222/2000-rev4 dated 11 April 2001)

(Opinion adopted by the Scientific Committee on Plants, 24 April 2002)

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A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE ON DERMAL ABSORPTION (Doc. SANCO/222/2000-rev4 dated 11 April 2001)
(Opinion adopted by the Scientific Committee on Plants 24 April 2002)

B. Terms of Reference

The Scientific Committee on Plants (SCP) is requested to provide an opinion on the consolidated document.

C. Opinion of the Committee

The Committee is of the opinion that *in vitro* human skin absorption data alone would be sufficient to determine the dermal absorption percentage to be used for risk assessment. When only rat skin data are available, the most conservative approach would be to assume that human skin absorption would be equal to rat skin absorption. There is no biological reason why absorption through skin *in vivo* should be significantly different from absorption through the same appropriately prepared, viable skin *in vitro*. The use of the equation recommended in the Guidance Document is unnecessary. The Committee strongly supports the recommendation made regarding the use of OECD guidelines as referred in the drafts with the suggested adjustments. In addition the Committee recommends:

- **the use of viable skin[1]**
- **the provision of an adequate number of results (a minimum number of samples and donors per experiment/dose should be set)[2]**
- **the selection of appropriate testing conditions (e.g. temperature, humidity, possible occlusion, etc.) to mimic daily practice situations and work conditions.**

In the case of *in vitro* testing, the Committee is of the opinion that the compound found in the skin should be added to the amount recovered from the fluid and considered as absorbed, with the exception of the amount recovered from the stratum corneum.

In the case of *in vivo* testing, the Committee is of the opinion that the compound found in the skin should be considered as absorbed even in the presence of serial non-detects in excreta, with the exception of the amount recovered from the stratum corneum.

The Committee endorses the use of the 100% and 10% default values but did not find sufficient justification provided in the document for the assumption that dermal absorption never exceeds oral absorption, nor did it identify criteria that

[1] Although there is no generally accepted definition for viable skin, the used skin should have 'metabolic activity'.
[2] The ''Notes of Guidance for Testing of Cosmetics Ingredients for their Safety Evaluation'' adopted by the Scientific Committee on Cosmetics Products and Non-Food Products intended for Consumers during the plenary meeting of 24 Nov 2000 set the following requirement: ''a minimum of a total of six available samples of either human or pig skin from at least three donors per experiment/dose''

could lead to the use of values between 10 and 100% of dermal absorption (paragraph 4.1).

The Committee agrees with the general line of the proposed tiered approach. However Figure 1 and Figure 2 should be modified according to the specific suggestions raised in this opinion.

A. Title

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE ON DERMAL ABSORPTION (Doc. SANCO/222/2000-rev4 dated 11 April 2001)

B. Table of Contents

C. Background

In collaboration with experts from all Member States, the Commission has prepared a draft Guidance Documents on dermal absorption. The document is intended to facilitate the review and decision-making concerning inclusion of active substances in Annex I of Council Directive 91/414/EEC.

Source documents made available to the Committee:

1. Draft Guidance document on dermal absorption Sanco/222/2000-rev4, dated 11 April 2001, submitted by DG health and Consumer Protection, 9 July 2001.

2. Terms of reference to the Scientific Committee on Plants, submitted by DG health and Consumer Protection, 9 July 2001 (SCP/GUIDE-DERM/001).

D. Scientific background on which the opinion is based

The Committee is of the opinion that *in vitro* human skin absorption data alone would be sufficient to determine the dermal absorption percentage to be used for risk assessment. When only rat skin data are available, the most conservative approach would be to assume that human skin absorption would be equal to rat skin absorption. There is no biological reason why absorption through skin *in vivo* should be significantly different from absorption through the same appropriately prepared, viable skin *in vitro*. The use of the equation recommended in the Guidance Document is unnecessary. The Committee strongly supports the

recommendation made regarding the use of OECD guidelines as referred in the drafts with the suggested adjustments. In addition the Committee recommends:

- **the use of viable skin[3]**
- **the provision of an adequate number of results (a minimum number of samples and donors per experiment/dose should be set)[4]**
- **the selection of appropriate testing conditions (e.g. temperature, humidity, possible occlusion, etc.) to mimic daily practice situations and work conditions.**

In the case of *in vitro* testing, the Committee is of the opinion that the compound found in the skin should be added to the amount recovered from the fluid and considered as absorbed, with the exception of the amount recovered from the stratum corneum.

In the case of *in vivo* testing, the Committee is of the opinion that the compound found in the skin should be considered as absorbed even in the presence of serial non-detects in excreta, with the exception of the amount recovered from the stratum corneum.

The Committee endorses the use of the 100% and 10% default values but did not find sufficient justification provided in the document for the assumption that dermal absorption never exceeds oral absorption, nor did it identify criteria that could lead to the use of values between 10 and 100% of dermal absorption (paragraph 4.1).

The Committee agrees with the general line of the proposed tiered approach. However Figure 1 and Figure 2 should be modified according to the specific suggestions raised in this opinion.

Assessment of dermal absorption is important in the risk assessment process requested by the Council Directive 91/414/EEC as it is essential to model operator exposure and to calculate a systemic AOEL in experiments where the substances are administered through skin route.

Thus the Committee recognises the need for a Guidance document on dermal absorption.

Assessment of dermal absorption can be obtained through *in vitro* and *in vivo* studies, both in rats and in humans[5]. Human skin would be the obvious choice but it is not always readily available.

When reviewing the document, the Committee has identified the following issues.

[3] Although there is no generally accepted definition for viable skin, the used skin should have 'metabolic activity'.

[4] The ''Notes of Guidance for Testing of Cosmetics Ingredients for their Safety Evaluation'' adopted by the Scientific Committee on Cosmetics Products and Non-Food Products intended for Consumers during the plenary meeting of 24 Nov 2000 set the following requirement: ''a minimum of a total of six available samples of either human or pig skin from at least three donors per experiment/dose''

[5] Pig skin is used particularly for the cosmetic substances because it shares essential permeation characteristics with human skin.

1. *In vitro* vs *in vivo* testing and species extrapolation

The Committee is aware that *in vitro* studies under otherwise comparable experimental conditions seem to give more consistent data on percentage of absorption than *in vivo* studies. This occurs because *in vivo* experiments are much more complex and their results can be influenced by a larger number of variables than *in vitro* studies.

The Committee is of the opinion that *in vitro* human skin absorption data alone would be sufficient to determine the dermal absorption percentage to be used for risk assessment. However, the Committee is aware that there are ethical and technical issues regarding the use of human skin that need still to be resolved.

The draft document correctly considers that absorption through rat skin is generally higher than through human skin, although there are cases where no significant differences were found (paragraph 2.2). So, when only rat skin data are available, the most conservative approach would be to assume that human skin absorption would be equal to rat skin absorption.

In vivo studies, in addition to the dermal absorption rate, give information on toxicokinetics (C_{max}[6], AUC[7], half-life of plasma/urinary levels, metabolites) that might be relevant when assessed in comparison with the type of effects and their mechanism/mode of action caused by the compound. For instance in the case of a C_{max}-dependent effect, the percentage of absorption (which is reflected by AUC) has to be considered in the light of the peak plasma concentration obtained after oral or dermal exposure. Due to the generally slower dermal absorption, peak plasma concentration are likely to be lower than the peak plasma level obtained after oral administration, even after correction for percentage of absorption. Such information can only be obtained from an *in vivo* study, but if the objective of the study is to obtain dermal absorption data then it is re-emphasised that *in vitro* data alone are sufficient, therefore, the use of the equation recommended in the Guidance Document is unnecessary. There is no biological reason why absorption through skin *in vivo* should be significantly different from absorption through the same appropriately prepared, viable skin *in vitro*. Those discrepancies that are observed are considered to be due to methodological differences in determining dermal absorption, e.g., summation of metabolite analyses in various tissues and body fluids compared to a simple recovery in a receptor fluid.

2. Experimental conditions

The Committee strongly supports the recommendation made regarding the use of OECD guidelines as referred in the drafts with the suggested adjustments of e.g. time of exposure to field conditions. In particular very important points are:

- the use of the vehicle(s) as present in the final formulation (paragraphs 2.4, 4.2, 4.3);
- the concentration of the compound to be tested should be as in the real uses (undiluted preparation for mixer/loaders, diluted for applicators by using typical concentrations that will be applied in the field) (paragraphs 2.4, 4.2, 4.3);
- the proper timing of application to the skin according to the exposure to be evaluated (one-day work) (paragraphs 3.1 and 3.2);
- the measurement of penetration/absorption until the compound and its metabolites no longer detectable, e.g. in receptor fluids or in excreta (paragraphs 3.1 and 3.2);

[6] Peak blood concentration.
[7] Area Under the Curve.

- the use of radiolabelled compounds is strongly recommended in dermal absorption studies;
- the clear definition of the area of the skin to be treated and the consequent measurement of the maximal flux per unit of area and unit of time (paragraph 4.2);
- the use of control compounds with known rates of absorption in *in vitro* tests (paragraph 3.1).

In addition the Committee recommends:
- the use of viable skin[8];
- the provision of an adequate number of results (a minimum number of samples and donors per experiment/dose should be set)[9];
- the selection of appropriate testing conditions (e.g. temperature, humidity, possible occlusion, etc.) to mimic daily practice situations and work conditions.

So-called 'static' and 'flow through' systems can be used to establish the *in vitro* percutaneous absorption of substances. The flow through cell was developed to mimic the blood flow in *in vivo* experiments, as it refreshes the receptor fluid constantly. However, according to experience, static cells may give good results when a small magnetic stirring bar is introduced in the receptor fluid compartment and the fluid is constantly stirred. The amount of penetrant in the receptor fluid should be less than 10% of its saturation level at any time.

3. Inclusion of the amount of compound found in the skin for the calculation of absorption

In the case of *in vitro* testing, the Committee is of the opinion that the compound found in the skin should be added to the amount recovered from the fluid and considered as absorbed, with the exception of the amount recovered from the stratum corneum.

In the case of *in vivo* testing, the Committee is of the opinion that the compound found in the skin should be considered as absorbed even in the presence of serial non-detects in excreta, with the exception of the amount recovered from the stratum corneum.

This is mainly because non-detects depend on the sensitivity of the analytical method. However, there might be exceptions which have to be judged case by case based on adequate justifications.

4. Default assumptions

The Committee recognises that the 100% default value to be used when no information at all is available is very conservative. However it endorses its use for regulatory purposes as the situations with absolutely no information should indeed be exceptionally rare.

The Committee is of the opinion that the arbitrary default 10% absorption value based on certain physical-chemical characteristics of the compound can be acceptable provided

[8] Although there is no generally accepted definition for viable skin, the used skin should have 'metabolic activity'.

[9] The ''Notes of Guidance for Testing of Cosmetics Ingredients for their Safety Evaluation'' adopted by the Scientific Committee on Cosmetics Products and Non-Food Products intended for Consumers during the plenary meeting of 24 Nov 2000 set the following requirement: ''a minimum of a total of six available samples of either human or pig skin from at least three donors per experiment/dose''.

that the toxicological profile does not raise concerns with regard to toxic effects deriving from dermal exposure.

The Committee did not find sufficient justification provided in the document for the assumption that dermal absorption never exceeds oral absorption, nor did it identify criteria that could lead to the use of values between 10 and 100% of dermal absorption paragraph 4.1). Therefore it is suggested that the paragraphs dealing with these issues be deleted.

Regarding the assessment of the dermal acute toxicity studies (LD_{50}), the Committee agrees that the results of these tests cannot be used as such to determine the percentage of absorption. Therefore a modification of the 100% default value cannot be based only on LD_{50} given the limitations of these studies. However, it might be possible that some useful information can be obtained from these studies if taken in the context of the toxicological profile of the compound. Therefore, the overall available toxicological data should always be taken into consideration, at least for a check of data consistency.

5. Tiered approach

The Committee agrees with the general principle of the proposed tiered approach. However some aspects of Fig 1 and Fig 2 should be modified according to the specific suggestions raised in this opinion.

D. REFERENCES

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