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Annex 3: Report of the Local Lymph Node Assay Sub-Group on the Curation and Evaluation of the Local Lymph Node Assay Reference Data and the Derivation of Associated Substance Classifications According to the UN GHS

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1 Introduction

The performance assessment of Defined Approaches (DAs) needs a reliable and trustworthy reference point. The need to build trust with the regulatory community is of particular importance for the work of the OECD Expert Group on Defined Approaches for Skin Sensitisation (EG DASS), pioneering the implementation of AOP-based DAs at the OECD Test Guideline (TG) level.

This document provides documentation of the EG DASS[1] work with respect to curating and evaluating the available murine Local Lymph Node Assay (LLNA)[2] reference data. Figure 1 provides a brief overview of the chronology of this activity.

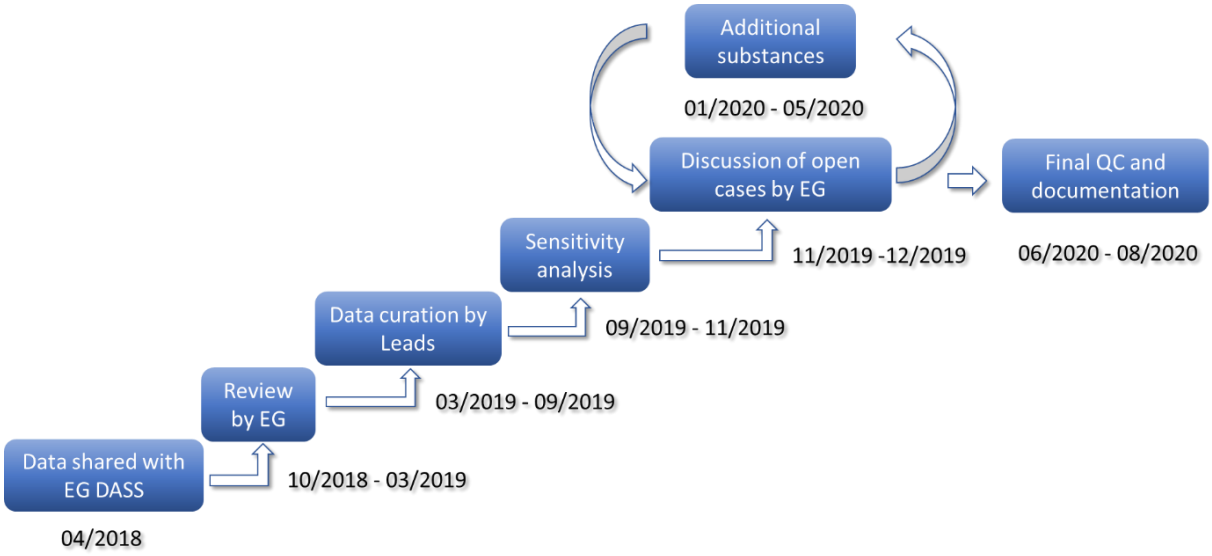

Figure 1: Chronology of the work of the EG DASS on the LLNA reference data

The subsequent sections of this document report on:

- the criteria used for including/excluding LLNA studies (section 2),
- the criteria for interpreting individual LLNA results (section 3),
- the different approaches and criteria applied for concluding on the overall GHS reference classification for substances with multiple LLNA results (section 4),
- an analysis of the reproducibility of the GHS reference classifications (section 5), and
- the resulting LLNA-based reference classifications (section 6).

In addition, Appendix 1 reports the curated LLNA data in detail.

Disclaimer: The views expressed in this report do not necessarily represent an official view of the agencies to which its authors are affiliated, the OECD, or of the EG DASS as a whole.

[1] Major contributions to this report were received from (in alphabetical order): Silvia Casati (European Commission, Directorate General Joint Research Centre, JRC), Matthias Herzler (German Federal Institute for Risk Assessment, BfR), Nicole Kleinstreuer (United States NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NICEATM), Judy Strickland (Integrated Laboratory Systems, ILS supporting NICEATM), and Pierre Therriault (Health Canada, HC).

[2] As per OECD Test Guideline (TG) 429

2 Criteria for including individual LLNA results in the evaluation

These criteria represent essential test method components from the LLNA Performance Standards for the validation of modifications to the traditional LLNA:

- The test substance must be applied topically to both ears of the mice.
- Lymphocyte proliferation must be measured during the induction phase of skin sensitisation and in the lymph nodes draining the site of test substance application.
- A vehicle control must be included in each study.
- Either individual or pooled animal data may be collected.

Additional inclusion criteria include:

- Concentrations tested and corresponding SI values are available. Rationale: Complete dose-response information provides the evidence for the calculated EC3 or the classification as *NC*[3].
- Administration of ^{3}H-methyl thymidine or other radiolabelled marker must be *in vivo* rather than *ex vivo*. Rationale: This is consistent with the procedure described in OECD TG 429, which uses *in vivo* radioactive labelling.
- Sodium dodecyl sulfate (SDS) was not applied as pre-treatment. Rationale: Pre-treatment with SDS has been used in some studies to enhance responses, mainly to detect weak sensitisers, but such pre-treatment with enhancers is inconsistent with the procedure described in OECD TG 429.
- The EG DASS agreed that studies performed with substances of variable and/or ill-defined composition, e.g. natural extracts, should not be included. LLNA studies for benzalkonium chloride (CAS 8001-54-5), dextran (CAS 3371-50-4), glyceryl monothioglycolate (CAS 30618-84-9), isocyclocitral (CAS 1335-66-6), isocyclogeraniol (68527-77-5), jasmine absolute grandiflorum (CAS 8022-96-6; 8024-43-9; 90045-94-6; 84776-64-7), jasmine absolute (sambac, CAS 91770-14-8), lyral (CAS 31906-04-4), oakmoss (CAS 90028-68-5), tea leaf absolute (84650-60-2), treemoss (CAS 90028-67-4), Tween 80 (CAS 9005-65-6), xylene (CAS 1330-20-7), and ylang ylang (CAS 8006-81-3; 68606-83-7; 83863-30-3) were therefore removed from the database.

The authors of this report wish to highlight that, while these exclusion criteria were developed for the purpose and needs of the present project, this is not to say that studies excluded here might not have played an important role for regulatory decision-making in the past. It is also not intended to invalidate any regulatory conclusions that may have been based upon them.

[3] Note that GHS classification results in italics (strong/extreme - *1A, sensitiser (without sub-categorisation) - 1, moderate/weak - 1B, not classified - NC*) represent actual classification outcomes for LLNA results or for a given (set of) substance(s).

3 Interpreting individual LLNA results with an EC3 outside the measured dose range

3.1 Approach taken by the LLNA sub-group (LSG)

3.1.1 Criteria used for the evaluation of LLNA results with extrapolated EC3 values

The criteria developed for the evaluation of studies in the reference database with reported extrapolated EC3 values were partly based on Ryan et al. (2007). The goal of this paper was to explore whether a study with positive test outcome, for which an EC3 could not be established, might be "rescued" by downward extrapolation (i.e. to concentrations below the lowest concentration tested), and to establish a methodology for that purpose.

The LSG applied the following three criteria to studies with reported extrapolated EC3 values:

- **Criterion 1:** Is the extrapolated EC3 less than 10-fold smaller than the closest tested concentration? This is a measure of how close to measured data the extrapolated EC3 is. A 10-fold decrease in EC3 value represents a 10-fold increase in sensitising potential. An extrapolation beyond an order of magnitude suggests too great a distance from the experimentally tested concentration range.

Example 1: EC3 is 3.3%. Lowest concentration is 5%. 5/3.3 = 1.5. Criterion 1 passed.

Example 2: EC3 is 0.7%. Lowest tested concentration is 25%. 25/0.7 = 35.7. Criterion 1 failed.

- **Criterion 2:** Is the lowest measured SI value less than 5? Ryan et al. (2007) noted that the lowest measured SI should be close to 3, although an exact value was not specified, thus a value of 5 was chosen for the purpose of this project. An SI value above 5 indicates that the animals are reacting strongly, thus the lowest dose tested was not near a threshold value.

Example 1: EC3 is 4.1%. At the lowest tested concentration (10%), the SI is 7.1. Criterion 2 failed.

Example 2: EC3 is 2.1 %. At the lowest tested concentration (10%), the S1 is 4.2. Criterion 2 passed.

- **Criterion 3:** Is the slope ratio less than 2? This criterion is explained by Ryan et al. (2007) as follows:

  "Specifically, the slope of the curve between the second and third data points above SI = 3 was computed and divided by the slope of the first and second points above SI = 3 to obtain a slope ratio. This ratio was used since values less than one would indicate a slope that is decreasing in the neighborhood of the first three data points above SI = 3. A ratio greater than one would indicate a slope that is increasing in this neighborhood. On a typical sigmoid dose-response curve, slope increases near the bottom of the curve, is constant in the middle of the curve, and decreases near the top of the curve, so calculating this ratio would provide information regarding the location on the dose-response curve of the values used for log-linear extrapolation." (Ryan et al., 2007)

  If a slope ratio of less than 2 is observed, this indicates that the data points used for downward extrapolation do not belong to a part of the dose-response curve with a significant change in slope, which could give rise to significant extrapolation error. This criterion, however, is considered to have the smallest weight of the three.

All three criteria had to be met in order to accept the reported extrapolated EC3 value.

3.1.2 Extrapolation to obtain EC3 values for LLNA results for which EC3 values were not reported

In some cases where the original study report did not report an EC3, or the reported EC3 appeared questionable, and the dose-response relationship suggested that an EC3 might be determinable via extrapolation[4], the method proposed by Ryan et al. (2007) was applied by the LSG:

> *"Extrapolated EC3 (EC3ex) values were calculated on the same data sets using the two SI values greater than 3 with the lowest of the SI values having the lowest % concentration. The point with the higher SI is denoted (a,b) and the point with the lower SI is denoted (c,d). The formula for the extrapolated EC3 value is as follows:*
>
> $$EC3ex = 2^{\left\{log2(c)+\frac{(3-d)}{(b-d)}\times[log2(a)-log2(c)]\right\}}$$
>
> *By log-transformation of the data, extrapolated EC3 values never fall below zero."*

The same approach for downward extrapolation was followed in some cases in which the LSG saw a need to verify reported EC3 values by recalculation.

3.1.3 Determination of the resulting GHS classification for individual positive LLNA results

If, based on the criteria and procedures described in sections 3.1.1 and 3.1.2, a study result was considered positive and an EC3 could be determined with sufficient reliability (i.e., interpolated or extrapolated according to the criteria in 3.1.1), the study was found to be suitable for GHS sub-categorisation (GHS sub-category 1A vs. sub-category 1B).

If a sufficiently reliable EC3 could not be determined for a positive LLNA test result, but the lowest concentration tested with an SI ≥ 3 fell below 2% (the cut-off between the GHS sub-categories 1A and 1B), the resulting classification was *1A*.

In all other cases in which a reliable EC3 could not be determined for a positive LLNA result, the LSG considered the study result unsuitable for sub-categorisation. Nevertheless, it was regarded as sufficiently reliable to be used as a positive test result for binary GHS classification without sub-categorisation (GHS category 1). The result of such a study was then termed *POS*[5].

3.1.4 Handling negative LLNA results

OECD TG 429 requires that the concentration series tested should include the maximum possible test concentration to avoid false negatives, i.e. "the highest concentration that maximises exposure while avoiding systemic toxicity and/or excessive local skin irritation". A synopsis of this statement together with the exemplary concentration series provided in TG 429 ("100%, 50%, 25%, 10%, 5%, 2.5%, 1%, 0.5%, etc.") and the requirement that "an adequate scientific rationale should accompany the selection of the concentration series used", leads to the conclusion that TG 429 expects 100% to be the maximum test concentration, unless a scientific rationale explains why a lower maximum test concentration was selected. Such a rationale could be based on e.g. observed toxicity (including excessive irritation), technical limitations (e.g. limited solubility) or, possibly, other scientifically valid reasons[6]. Unfortunately, however, it is often absent from study reports found in the published

[4] This was not the case e.g. for dose-response curves where lower SI values were observed at higher doses compared to those observed at lower ones.

[5] Since this result corresponds to the GHS classification Skin Sens. 1, it could also have been called *1*. However, POS was chosen in order to avoid confusion with EC3 values of exactly 1%.

[6] For instance, positive test results observed with lower test concentrations in other tests for skin sensitisation may suggest using maximum concentrations < 100%.

literature. For chemicals with negative results that were not tested up to 100%, this results in uncertainty, because the rationale followed (if any) is not accessible for review.

When calculating Median-Like Location Parameter (MLLP; cf. 4.1) values for the 2019-09-20 version of the LLNA reference database, the LSG accepted study results as negative (for details, cf. 3.2.4), if for all test concentrations SI values were < 3 and if the test substance was tested up to a highest concentration tested (HCT) of at least 50%. This was based on the assumption that likely only very few of these substances would have shown SI values ≥ 3 at a higher test concentration and that this would at most indicate only a very weak sensitisation potential.

These assumptions were further supported by an analysis of a later version of the curated LLNA database: For 367 of the 541 LLNA results accepted[7] for this report, an EC3 could be determined by inter- or extrapolation (cf. 3.1.1 and 3.1.2). Out of these, only 9 (2.5%) showed EC3 values > 50%. Another way to put this is that 97.5% of the substances with a positive test result in the database are more potent than a substance with an EC3 > 50%, or that in comparison with the whole database the potency of such a substance would be very low.

This number is somewhat uncertain, because high EC3 values would have gone unnoticed in many tests not performed at sufficiently high concentrations. On the other hand, as noted by the LSG, 50% may indeed in some cases have been the highest achievable test concentration, e.g. for substances of low solubility.

It needs to be stressed, however, that this should not be understood as an endorsement of 50% as a generally acceptable maximum test concentration under OECD TG 429.

Negative tests with an HCT < 50% were only included in the MLLP calculation if dose selection was rationalised and documented in the original study (e.g. based on limited solubility, excessive irritation, excessive systemic toxicity) or if other, positive test results were present for the same test substance which were obtained using the same or lower test concentrations[8].

3.2 Modified approach for sensitivity analysis

In his assessment submitted to the EG DASS on 14 November 2019, an expert from the group proposed some modifications to the LSG's approach as outlined below. This modified approach is used for the evaluations presented in sections 4.2 (MSPE method) and 4.3 (WoE score). The modifications were motivated by the expert's perception that in some instances, the rules followed by the LSG to calculate the MLLP may result in partial information loss and/or non-conservative choices with a possible impact on the reliability of the overall classification call.

Comparing the results with those obtained by using other, more conservative approaches would provide for a sensitivity analysis with respect to whether the choices made had a significant impact on the overall reference classifications and, hence, on DA performance statistics (and if so, to what extent). If such differences were only small, this would increase regulatory trust by addressing possible concerns about a lack of sufficient conservatism.

In addition, the LSG did not include a concept for identifying borderline results, i.e. results for which the decision sensitiser vs. not classified or strong vs. moderate/weak sensitiser cannot be made with the same confidence as for more clear-cut cases.

[7] Out of a total of 806 studies evaluated

[8] This reasoning stems from the MLLP approach as applied in the Hoffmann et al. (2018) paper, cf. section 4.1 for details.

The modified approach is explained in detail in the following sub-sections. Some of its choices may seem quite conservative, but it is once again highlighted that the intention behind the approach is to identify whether, for certain substances, reasonable and comparatively small differences in assessment methodology lead to a different overall reference classification. In such cases, further discussion would be necessary to determine which method delivers the most acceptable result.

3.2.1 The "Sensitisation Potency Estimate" (SPE)

As a first step, the concept of the "Sensitisation Potency Estimate" (SPE) is introduced as a general term for reporting individual LLNA results[9]. The SPE can be numerical (EC3 values), but also non-numerical. For positive test results without a reliable EC3 value, the SPE corresponds to the respective GHS sub-category, e.g. *1A,* or is assigned the non-numerical value *POS*, if sub-categorisation is not possible. For clearly negative test results it is *NC* (not classified). Under the modified approach, this general concept then allows for the inclusion of further non-numerical SPE values representing borderline cases, which are explained in more detail in the following sub-sections.

3.2.2 Approach for borderline positive results

OECD TG 429 specifies an SI of 3 as the critical value for a positive test result, i.e. the first decimal is not specified. In common practice, however, the value of 3.0 is used. Consequently, the LSG did not consider maximum SI values of e.g. 2.9 as indicating a potentially positive result. In this approach, while being the one commonly applied, the inherent uncertainty in the EC3 value may be significant, but is not accounted for. This uncertainty, *inter alia*, arises from the fact that EC3 values are subject to both sampling and model error, because they are obtained via inter-/extrapolation based on mean SIs for normally only four animals/dose group.

To at least partly address this uncertainty, the modified approach treats all maximum SI values between 2.5 and 2.9 (i.e. SI values equalling 3, if rounded off) as if they had been 3. To distinguish these results from "real positives" (i.e. those considered positive under the standard approach taken by the LSG), they are identified as "potential positives" under the modified approach. This can be justified by the understanding that for maximum SI values so closely below the cut-off, there is a considerable chance that, upon repetition of the experiment, an SI slightly above the cut-off might have been obtained[10]. Another way to put this is that the SI zone of 2.5 – 2.9 is considered an uncertainty or borderline zone.

Given the inherent variability of the SI values, the modified approach also does not ask for the presence of a clear dose-related trend in the data. Each experiment with a maximum SI of 2.5 – 2.9 is considered a "potential positive". The lowest concentration with an SI in that range is termed the "Lowest Potentially Positive Concentration" (LPPCT) and is used as the SPE for that LLNA result.

3.2.3 Approach for borderline 1A/1B results

With the critical EC3 value for sub-categorisation as 1A or 1B, the situation is the same as with the SI cut-off: the UN GHS specifies a value of 2%, not 2.0%. Arguably, the critical cut-off should therefore be 2.4 (the highest number that would be rounded off to 2), not 2.0%. While it is common practice to use the latter value, for the modified approach – in analogy to handling the SI cut-off above - the more conservative value of 2.4% was used in order to account (to some degree) for the inherent uncertainty in the EC3 values used to determine the correct GHS sub-category.

[9] The term SPE was chosen in analogy to the "Acute Toxicity Estimate" (ATE) values used under the UN GHS.

[10] Arguably, this also works the other way around: with SI values slightly above 3, a repetition of the experiment might have yielded a result slightly below the cut-off. This, however, was not considered in the modified approach, which was introduced as a means of probing the LSG results for sufficient conservatism, to build trust with the regulatory community.

Note that in these cases (2.0% < EC3 ≤ 2.4%) the SPE would still be the EC3 value, e.g. 2.4%. However, the resulting GHS sub-category would be 1B under the standard approach taken by the LSG, while the modified approach would assign GHS sub-category 1A.

3.2.4 Approach for negative test results

In line with the considerations in the previous sub-section, study results with maximum SI values < 2.5 at all tested concentrations were considered "potential negatives" in the modified approach, with final confirmation based on considerations around the highest tested concentrations, as described below.

Obviously, negative values cannot receive a numerical SPE value. Therefore, in the present report, the following rules are applied:

- The decision of the LSG to accept potential negatives with HCT ≥ 50% as such (cf. 3.1.4) is supported also under the modified approach and the non-numerical SPE *NC* (not classified) is assigned in these cases.
- On the other hand, potential negatives with 2.4% < HCT < 50% cannot be accepted as *NC* without further knowledge about their irritancy and solubility (or any other scientific rationale that might have precluded the study authors from using higher test concentrations). Out of the 367 test results with an available EC3, 39 (10.6%) had an EC3 value > 25%, and for 108 (29.4%) it was > 10%. It would not be appropriate to say that positives found at higher concentrations would represent rare events or that such substances would necessarily have a weak potency (as argued for negatives with a HCT of 50%, cf. 3.1.4). It follows that such test results are only acceptable if (as per the requirements of OECD TG 429) a rationale is presented why using a higher HCT was not reasonable or possible. Nevertheless, these test results can be used to demonstrate that for the test substance, a strong sensitisation potential can be considered unlikely, and therefore the ambiguous SPE *NC/1B* (translating into "not classified or weak/moderate sensitiser, but likely not a strong/extreme sensitiser") is assigned to maintain this information.
- Potential negative test results with very low HCTs smaller than the 1A/1B sub-categorisation threshold (unless determined by a valid scientific rationale, cf. above) cannot demonstrate that the substance should not be classified for skin sensitisation. They cannot even exclude the possibility that the substance should be considered a strong sensitiser. For this reason, all potential negatives with an HCT ≤ 2.4%[11] receive the ambiguous SPE NC/1 ("could – or could not – be a sensitiser"). In fact, this is another way of stating that such test results do not provide any relevant information for classification. For this reason, they are excluded from further evaluation. Notably, only two test results in the database were affected by this criterion.

3.2.5 Summary: Assignment of SPEs by the modified approach

SPEs are assigned by the modified approach as follows:

- If a reliable EC3 is available, this is taken as the SPE;
- If SI values ≥ 3.0 are observed, but an EC3 cannot be determined, the SPE is either *POS* or *1A* (cf. section 3.1.3).
- If the maximum SI value observed in the study is < 3.0, SPEs are assigned as explained in the previous sub-sections and summarised in Figure 2.

[11] Note that here the upper limit of "figures which can be rounded off to 2%" is used.

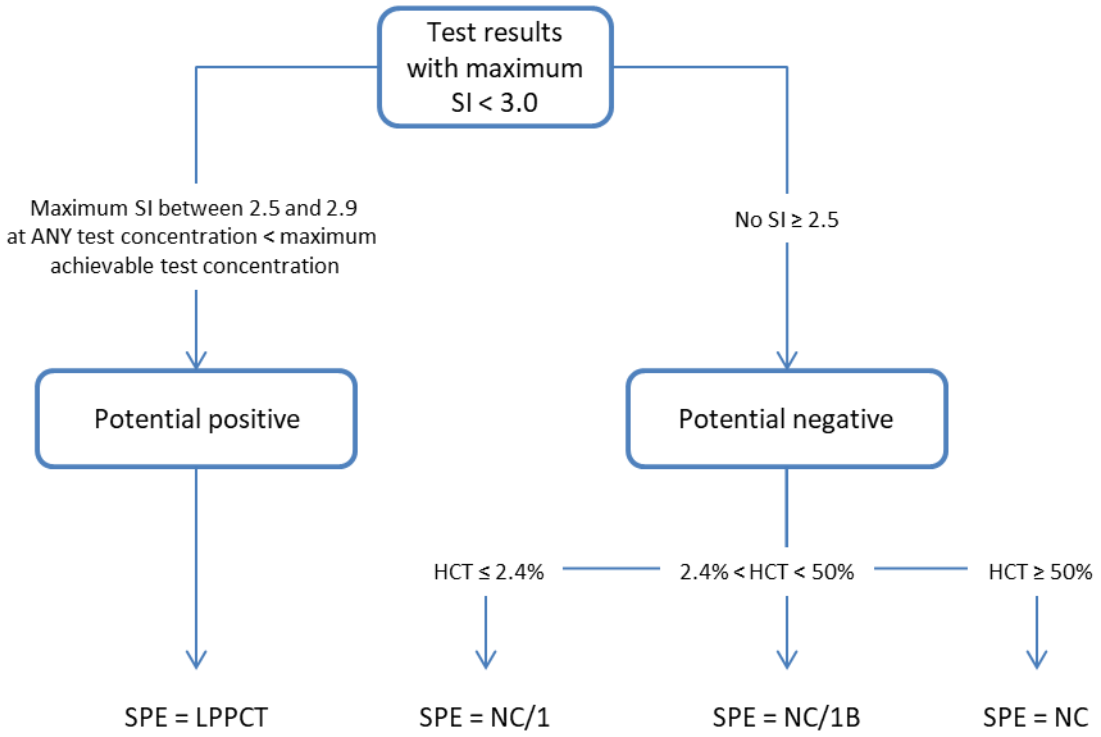

Figure 2: Schematic representation of the modified approach to assigning Sensitisation Potency Estimate (SPE) values to individual LLNA test results with a maximum observed SI < 3 (see text for a more detailed explanation). HCT = Highest Concentration tested; LPPCT = Lowest Potentially Positive Concentration Tested.

4 Criteria for concluding on the overall LLNA-based GHS reference classification for substances with multiple LLNA results

For the interpretation of individual studies and for the determination of the overall reference classifications, different methods were applied to provide for a sensitivity analysis with respect to different data interpretation strategies. Moreover, while the LSG had used the MLLP approach, the EG DASS Human Data Sub-Group (HDSG) applied a different, mean-based approach (WoE score method) and it was felt that the two datasets should be analysed with the same methodology. In addition, the different approaches might complement each other in certain situations.

4.1 MLLP method

The approach taken by the LSG uses the MLLP as introduced by NICEATM/Cosmetics Europe in 2018:

> *"This parameter was defined as the median for substances with repeat studies with an EC3 in more than 50% of the repeats. For substances with at least 50% negative repeat studies, i.e. no EC3 value was available, the parameter was defined as the modified median. The first step in deriving the modified median was to review the negative studies in detail: when the maximum concentration tested in a given study was lower than the median EC3 of the positive studies for the same chemical, the respective negative study was excluded, because it was considered a limited validity as tested concentrations were too low. From the remaining negative and all positive studies, the median was used as a location parameter (modified median). In the case of 50% of repeat studies being negative and 50% being positive, the highest EC3 value was defined as the modified median."* (Hoffmann et al., 2018)

In other words:

- If (after applying the inclusion rules described in section 2 of this report), multiple study results are available and the majority of these tests is positive, the median of all studies is taken as the basis for deciding on the overall classification.
- If (after applying...), multiple test results are available and the number of negative test results is equal to or greater than the number of positives, all negative studies with an HCT < the median EC3 of the positive studies are removed. The median of all remaining studies is then taken as the basis for deciding on the overall classification.

4.2 MSPE method

In his review of 2019-11-14 (cf. 3.2), the expert listed a number of choices implied by the MLLP method, which he considered as potentially non-conservative or otherwise critical. Again, he proposed to also apply alternative methodological approaches to test the LSG approach for its sensitivity towards comparatively small changes in methodology.

For that purpose, he introduced the so-called "Median Sensitisation Potency Estimate" (MSPE) approach based on the SPE values derived according to the decision logic described in section 3.2 of the present report (Figure 2). For a given substance, the determination of the overall classification based on the MSPE was then performed as follows.

- *NC/1* test results were completely excluded from the assessment, since they do not add any relevant information (but add noise to the median determination). Moreover, if "potential positive" and "potential negative" test results were present, negative test results were excluded if their HCT was lower than the median SPE of the positive studies (same as in the MLLP approach applied by the LSG).

- Positive test results with a *POS* outcome (i.e. without an available EC3 value) were included in the median calculation.
- All test outcomes, whether numerical (EC3 values) or non-numerical (*POS*, *NC/1B*) are called "Sensitisation Potency Estimates" (SPEs)[12] and the median test result is therefore called the "Median Sensitisation Potency Estimate" (MSPE).
- The MSPE is then calculated by sorting all SPE values from low to high potency in the following order:

  NC → *NC/1B*[13] → Numerical SPE (EC3) values > 2.0% in descending order → *POS* → Numerical SPE values ≤ 2. % in descending order.
- When the median falls between a numerical and a non-numerical result, the numerical result is taken as the MSPE.
- If there are one or more *1A* results and all other outcomes are *POS*, the median EC3 of the *1A* results is taken as the MSPE.
- In all cases in which only positive studies are available and the number of *1A* study results equals that of the *1B* results, the MSPE is *POS*. In the MLLP approach used by the LSG, the average between the highest *1A* EC3 and the lowest *1B* EC3 would have been taken instead, resulting in an overall classification as either *1A* or *1B*, depending on which of the two EC3 values was closer to the cut-off of 2%. Averaging *1A* studies with EC3 values of 0 - 2.4% with *1B* studies, which can have EC3 values of 2.5 - 100%, will, however, in most cases result in an MSPE value indicating classification as *1B*. This approach (taken by the LSG for calculating the MLLP) is therefore non-conservative in a situation where there is equal evidence for overall *1A* or *1B* classification. Stating that sub-categorisation in this case is not possible would seem to be the more appropriate approach.
- If there are one or more *1B* results and all other outcomes are either *POS* or *NC/1B*, the median EC3 of the *1B* results is taken as the MSPE.
- If there are one or more *NC* results and all other test outcomes are *NC/1B*, the MSPE is *NC*.

Based on the calculated MSPE, classification results were then assigned to the reference substances according to the rules presented in Table 1 below.

Table 1: Criteria for the assignment of (borderline) classifications to LLNA reference substances based on the MSPE (NA = not applicable).

<table>
<tr><th rowspan="2">MSPE</th><th colspan="3">Classification mode</th></tr>
<tr><th>GHS_{BIN}[$]</th><th>$GHS_{SUB}$[$]</th><th>GHS_{BORDER}[$]</th></tr>
<tr><td>MSPE < 1.7%</td><td rowspan="5">1</td><td rowspan="2">1A</td><td>1A</td></tr>
<tr><td>1.7% ≤ MSPE ≤ 2.0%</td><td rowspan="3">1</td></tr>
<tr><td>POS</td><td>na</td></tr>
<tr><td>2.0% < MSPE ≤ 2.4%</td><td rowspan="2">1B</td></tr>
<tr><td>MSPE > 2.4</td><td>1B</td></tr>
<tr><td>NC/1B</td><td>na</td><td>na</td><td>NC/1B</td></tr>
<tr><td>NC</td><td>NC</td><td>NC</td><td>NC</td></tr>
</table>

[$] See text for explanation.

[12] In analogy to the "Acute Toxicity Estimate" (ATE) in the GHS.

[13] Only those with a sufficiently high test concentration were included, cf. previous subsection.

In binary GHS classification mode (termed "GHS_{BIN}", i.e. classification as sensitiser or not classified), all potential and clear positives were classified as *1* and all clear negatives as *NC*. Binary classification was not applicable (na) if the MSPE was *NC/1B*.

In standard GHS sub-categorisation mode (termed "GHS_{SUB}", i.e. *1A*/*1B*/*NC*), potential positives with an SPE ≤ 2.0% were considered strong sensitisers (*1A*), while those with an SPE > 2.0% were considered moderate/weak sensitisers (*1B*). GHS_{SUB} classification was not applicable, if the MSPE was *POS* or *NC/1B*.

To better account for borderline results, the rightmost column in Table 1 finally shows the GHS classification expanded with two borderline sub-categories (termed "GHS_{BORDER}") as follows:

- *1* for potential positives with 1.7%[14] ≤ SPE ≤ 2.4%, because in this range a reliable determination of the GHS sub-category is not possible, and
- *NC/1B* (cf. section 3.2.4).

4.3 WoE score approach

As another alternative method for sensitivity analysis, the so-called “Weight-of-evidence score” (WoE score) method was applied. This arithmetic mean-based method was used by the Human Data Sub-Group (HDSG) for their analysis of Human Predictive Patch Test (HPPT) data. In that system, first each individual test result receives a numerical score based on the SPE, as shown in Table 2 below. Note that individual test results with the ambiguous outcome of *NC/1* (which did not contribute meaningful information to the assessment) did not receive a numerical score, nor were they included in the WoE classification.

Table 2: Numerical scores assigned to different classification outcomes based on the SPE

SPE	NC	NC/1B	> 2.4%	2% < SPE ≤ 2.4%	POS	1.7% ≤ SPE ≤ 2%	< 1.7%
Score	0	0.50	1.00	1.25	1.50	1.75	2.00

Next, all individual scores were added up and divided by the number of test results to obtain the overall (mean) Weight-of-Evidence (WoE) score, which was rounded to the second decimal. In analogy to Table 2, the corresponding overall classification was then determined acc. to Table 3.

Table 3: Overall classification based on LLNA data as derived from the rounded overall (mean) WoE score

<table>
<tr><th rowspan="2">Overall WoE score</th><th colspan="3">Classification mode</th></tr>
<tr><th>GHS_{BIN}</th><th>GHS_{SUB}</th><th>GHS_{BORDER}</th></tr>
<tr><td>1.76-2.00</td><td rowspan="5">1</td><td rowspan="2">1A</td><td>1A</td></tr>
<tr><td>1.51-1.75</td><td rowspan="3">1</td></tr>
<tr><td>1.50[§]</td><td>na</td></tr>
<tr><td>1.26-1.49</td><td rowspan="2">1B</td></tr>
<tr><td>0.76-1.25</td><td>1B</td></tr>
<tr><td>0.26-0.75</td><td>na</td><td>na</td><td>NC/1B</td></tr>
<tr><td>0-0.25</td><td>NC</td><td>NC</td><td>NC</td></tr>
</table>

[§] For substances with an overall score of 1.50, which were derived exclusively from studies with an SPE value *POS*, a GHS sub-category was not available ("NA").

[14] The upper boundary of the borderline range of 2.4% was selected to correspond with the upper limit of the "1A" range for potential positives used in section 3.2.2. This value is + 26% relative to the cut-off of 2% on a log scale, i.e. log(2.4)/log(2) = 1.26. The lower boundary was then selected to be symmetrical with the upper limit resulting in a value of 1.67% (because log(1.67)/log(2) = 0.74) which was then rounded to 1.7%.

4.4 Determination of the overall classification result

The above calculations resulted in three classification sets (GHS_{BIN}, GHS_{SUB}, and GHS_{BORDER}) for each of the MLLP, MSPE, and WoE score approaches. The latter parameters as well as the resulting overall classifications are reported alongside an overview of the available studies in Table 7 (section 6).

Overall, MLLP (where available) and MSPE values showed very good agreement, demonstrating that only small adaptations were applied in the modified approach. For 171/196 reference substances, both values were available. In 152 or 89% of these cases, MLLP and MSPE values were exactly identical. In eleven of the nineteen cases where they differed, the resulting classifications were the same, while in eight cases, the MSPE suggested classification as *1B* or that the results were too uncertain to classify vs. *NC* proposed based on the MLLP[15]. Of the 25 substances for which an MLLP was not available, 21 had the MSPE *NC/1B*, two were positive with MSPE values of 10% (exclusion was confirmed later by EG DASS) and 25% (later confirmed by the EG DASS as *1B*), and for the remaining two also an MSPE could not be determined.

The overall reference classifications resulting from the MLLP, the MSPE, and the WoE approaches, were identical in the great majority of cases. Nevertheless, in some cases diverging results were noted between these three approaches, as shown in Table 4 below.

Table 4: Overview of those reference substances for which the classifications resulting from the MLLP, MSPE, and WoE score approaches were different from each other and/or from the overall reference classification (na = not available)

Name	CAS no.	EC no.	MLLP			MSPE			WoE score			Overall ref. classification		
			GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}
α-Amylcinnamic alcohol	101-85-9	202-982-8	na			1	1B		1	1B		1	1B	NC/1B
Aniline	62-53-3	200-539-3	NC			1	1B		na		NC/1B	1	1B	
Benzocaine	94-09-7	203-486-6	NC			1	1B		na		NC/1B	na		NC/1B
Benzyl benzoate	120-51-4	204-402-9	1	1B		1	1B		1	1B		1	1B	NC/1B
Benzyl butyl phthalate	85-68-7	201-622-7	NC			1	1B		1	1B		NC		NC/1B
Cinnamonitrile	1885-38-7	217-552-5	na		NC/1B	1	1B		na		NC/1B	na		NC/1B
Clofibrate	637-07-0	211-277-4	NC			1	1B		1	1B		NC		NC/1B
Coumarin	91-64-5	202-086-7	NC			1	1B		NC			na		NC/1B
DNBS, sodium salt	885-62-1	212-943-7	1	1A	1	1	1A	1	1	na	1	1	1A	1
Ethylene diamine (free base)	107-15-3	203-486-6	NC			na		NC/1B	na		NC/1B	1	1B	1
Formaldehyde	50-00-0	200-001-8	1	1B		1	1B		1	1B	1	1	na	1
Hexyl salicylate	6259-76-3	228-408-6	1	1A		1	1A		1	1B		1	na	1
2-Hexylidene-cyclopentanone	17373-89-6	241-411-7	1	1B	1	1	1B	1	1	1B		1	1B	1
2-Hydroxyethyl acrylate	818-61-1	212-454-9	1	na	1	1	na	1	1	na	1	1	1A	1
Isobergamate	68683-20-5	272-06-0	NC			1	1B		na		NC/1B	na		NC/1B
Methyl pyruvate	600-22-6	209-987-4	1	1B	1	1	1B	1	1	1B		1	1B	1
2-Methyl-decanenitrile	69300-15-8	273-960-3	NC			1	1B		NC			NC		
Methyliso-thiazolinone	2682-20-4	220-239-6	1	1A		1	1A		1	1A	1	1	1A	1
Neomycin sulfate	1405-10-3	215-773-1	NC			NC			na		NC/1B	na		NC/1B

[15] The EG DASS confirmed two of these as 1B, and three as NC, which underscores the importance of the sensitivity analysis.

Sometimes, also the results were the same in all three approaches, but other issues required clarification. For example, the outcome of individual study results might have been judged differently within the group. In all of these cases, these questions were resolved via an expert decision by the EG DASS (with the reasoning documented in (section 6). The overall decision process for obtaining the LLNA reference classifications is shown in Figure 3.

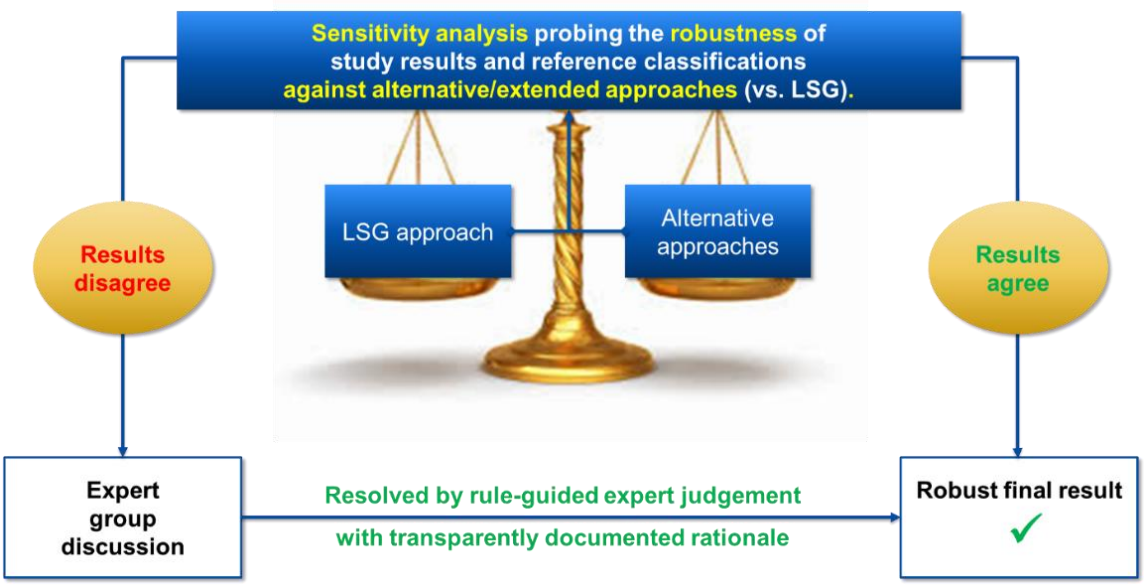

Figure 3: Schematic representation of the overall decision process for arriving at the LLNA reference classifications: The original LSG approach was challenged with slightly modified/extended, alternative evaluation strategies for sensitivity analysis. If the results agreed, they were considered robust. If not, the respective reference substances were brought forward to the EG DASS for further discussion. In the majority of cases, such substances had either borderline potency or the test results by themselves did not provide for an unambiguous classification result. They were then resolved by rule-guided expert judgement and the rationale was documented. If no consensus could be achieved by the group, such substances were excluded from the reference data set.

5 Reproducibility of LLNA-based reference classifications and consideration of uncertainties

The first version of the guideline document presented to the EG DASS proposed to benchmark DA predictivity against LLNA reproducibility. In their comments to this first draft, some EG DASS members criticised the method used to calculate LLNA reproducibility for significantly underestimating LLNA performance with respect to this parameter, as well as the fact that reproducibility was not a suitable benchmark for DA performance anyway. In a later assessment presented to the EG DASS, one group member used an alternative assessment of LLNA reproducibility, which is documented and discussed in this section.

The results reported in this section cannot claim to represent *the* reproducibility of LLNA-based classifications in absolute terms. First of all, the number of substances in the curated database with more than one test result was low, e.g. only around 20 substances had three or more test results. It is clear that in order to draw firm conclusions, a much larger number of substances would be needed. It is also clear that reproducibility is a function of both the test and the evaluation system used, i.e. with data curated to lesser standards, or following other decision rules than those applied here, different results might have been obtained.

Nevertheless, the approach reported below represents an attempt to estimate LLNA reproducibility based on the high-quality dataset acquired in this project. It also tries to closely follow a logic typically applied in the regulatory context when, for a given endpoint, multiple test results are available and need to be combined in a weight-of-evidence assessment:

1. Exclude all results from the assessment, which are not considered reliable enough (cf. section 3).
2. Combine those studies with a clear, unambiguous test result into an overall result (cf. MLLP/MSPE/WoE approaches in section 4).
3. Analyse whether studies with an ambiguous test result are in contradiction with the conclusion under 2. For example, a study resulting in *NC/1B* neither contradicts an *NC*, nor a *1B* result, but it is not in line with a *1A* result.
4. Draw the overall conclusion.

It must also be noted that, in the meantime, the EG DASS has already decided to follow the above suggestion not to use LLNA reproducibility for DA benchmarking. Nevertheless, the assessment is reported here for the following reasons:

- As with any bioassay, a certain variability in the results can be expected for the LLNA. Recent publications such as Dumont et al. (2016) or Hoffmann (2015) have investigated this variability more closely. While a detailed review of these papers is beyond the scope of the current report, it is noted that based on these analyses, far-reaching conclusions about the reliability of the LLNA have been drawn either by the authors themselves or by others, such as in the first drafts of the guideline document prepared for the EG DASS.
- The LLNA has been the gold standard *in vivo* OECD test for skin sensitisation for almost two decades. If new evidence became available that this test in fact performs significantly less reliably than originally assumed, this would have important consequences for risk assessment conclusions in both the past and the present.

- Therefore, it seems important that in an official OECD publication any such information be appraised in a critical, but unbiased way before potentially premature conclusions are drawn. One of the intentions of the present report is to create trust with the regulatory community that high scientific standards were applied in this work. It is therefore of particular importance to avoid any impression that the performance of previously established standard tests is belittled in an attempt to lower the bar for new testing and assessment strategies. As for the rest of this project, the use of well-curated reference data is a key pre-requisite for this purpose. And while LLNA reproducibility might not be directly relevant for the EG DASS work anymore, it may still be a point of reference for future assessments with a different focus (i.e. on other topics than DA performance assessment).

5.1 Reproducibility calculations

For the substances with multiple test results[16], reproducibility of the LLNA-based GHS classifications was determined for each classification mode in the following way:

- GHS_{BIN}: Reproducibility was calculated as the fraction of all valid test results giving an unambiguous classification result (*1* or *NC*) correctly predicting the overall call. Studies resulting in an SPE of *NC/1B* were excluded from this evaluation, since for them GHS_{BIN} was not applicable.
- GHS_{SUB}: Reproducibility was calculated as the fraction of all valid test results giving an unambiguous classification result (*1A*, *1B*, or *NC*) correctly predicting the overall call. Studies resulting in an SPE of *1* were excluded from this evaluation, since for them GHS_{SUB} was not applicable. For the same reason, studies resulting in *NC/1B* were omitted if the overall classification was *1B* or *NC.* They were, however, counted as contradictory if it was *1A*.

It is important to understand that these reproducibilities refer to the LLNA-based GHS classifications. They do not represent the reproducibility of the EC3/SPE values. As shown by other authors, the latter can be quite variable, but this is comparatively less important for clear *1A* or *1B* results, where even e.g. a 50% increase or decrease in the EC3 might still result in the same sub-categorisation. However, as shown by the results given in Table 7, section 6, a low reproducibility often indicates that the substance may have a skin sensitisation potential in the borderline area between *1A* and *1B*[17] or that it is borderline between a weak sensitiser and a substance not requiring classification.

The results obtained in this way can be seen as a surrogate probability that a new (valid) LLNA test result will confirm a classification previously established based on other LLNA results.

When this approach was presented to the EG DASS, some experts criticised that by not including all test results, but only those producing a classification result (whether binary or sub-categorised), reproducibility would appear higher than it actually was. However, the logic behind the approach taken was explained above and is essentially the same as for any other assessment in the regulatory arena: only valid test results (in the sense of: fit for the purpose of giving a classification result) are included in the assessment.

5.2 Discussion of the calculated reproducibilities

If, for a given substance, an infinite number of LLNAs could be performed, this would provide the "true" reproducibility of the LLNA-based GHS classification for that substance. Unfortunately, this is not possible, and reproducibility must be estimated from a limited number of test results. Therefore, sampling error must be taken into account. Obviously, sampling error can be reduced by increasing

[16] For obvious reasons, reproducibility cannot be calculated, if only one substance is available.

[17] Alternatively it could indicate variability in the composition of the test material or in other experimental parameters.

the number of test results per substance, but, on the other hand, this would leave fewer and fewer substances to include in the calculations.

In Table 5, reproducibility for the two classification modes GHS_{BIN} and GHS_{SUB} is reported as a function of the minimum number of test results required for inclusion in the calculation. These results show that classifications based on the curated LLNA data are highly reproducible.

For both classification modes, only a very slight dependency of reproducibilities on the number of tests available was noted. Binary classifications (GHS_{BIN}) were ca. 97% reproducible, while GHS classifications including sub-categorisation (GHS_{SUB}) had a reproducibility of ca. 91%.

Table 5: Reproducibility of LLNA-based GHS_{BIN} and GHS_{SUB} classification modes in relation to the number of available test results per substance

Classification mode	Number of test results available	No. of substances	Reproducibility (%)		
			Mean	Median	SD
GHS_{BIN}	≥ 2	47	97.6	100	11
	≥ 3	25	97.5	100	12
	≥ 4	20	96.9	100	14
	≥ 5	19	96.7	100	14
GHS_{SUB}	≥ 2	41	91.9	100	17
	≥ 3	19	91.8	100	17
	≥ 4	14	91.2	100	18
	≥ 5	14	91.2	100	18

Another way to calculate reproducibility based on the available data is by calculating a weighted average. This means that for each substance, first the individual reproducibility of the overall reference classification was multiplied by the number of tests available for that substance. These products were added up for all substances and that sum was then divided by the total number of test results (for all substances). In that way, a reproducibility value based on e.g. six test results received twice the weight of a reproducibility value calculated based on only three experiments.

The weighted mean reproducibilities (considering all substances with at least two test results) were found to be 96.9% for GHS_{BIN} and 90.0% for GHS_{SUB}, i.e. about the same as or slightly lower than the respective non-weighted reproducibilities.

It is concluded that for the data available in this project, LLNA-based classifications were ca. 97% (GHS_{BIN}) and ca. 90% (GHS_{SUB}) reproducible. These figures are still remarkably higher than those originally provided in the first draft of the Guideline document. There are some generic reasons for this:

- While trying to reduce sampling error, for many substances reproducibility calculations are still based on only a handful of results. Therefore, the estimates might be somewhat off-target with respect to “true” reproducibility.
- The first drafts of the Guideline document used lower numbers based on a paper published by Dumont et al. (2016), however, the parameter to determine reproducibility applied in that publication, i.e. the concordance between individual LLNA results, is not the same as reproducibility of a given reference classification result. The concordance approach will necessarily produce lower numbers, as e.g. a substance with nine *1A* results and one *1B* result

would be considered "discordant", where it would be called 90% reproducible in the approach followed in the present report, provided the reference result was *1A*[18].

- In the present project, data were curated to very high quality standards and then evaluated according to strict and transparent rules, whereas authors of previous papers on the issue, or regulatory decision makers, might have used less reliable LLNA data and therefore the classifications they used may have been less reliable than the ones derived in this project.

At any rate, the median reproducibilities and standard deviations reported in Table 5 indicate that a closer look into those substances with less than 100% reproducibility might reveal additional insights.

Starting with the GHS_{BIN} classifications of 47 substances with a positive (*1*) reference classification and more than one test result, only two substances had a reproducibility < 100% (aniline: 38% and benzyl benzoate: 50%).

For aniline, ten tests resulting in *NC*, and six tests resulting in *1B* are available. The MLLP is *NC*, but the MSPE is 50%, because some of the tests with high SIs at the HCT of 50% were *NC* under the standard LSG approach, but were considered *POS* under the modified approach. This situation also led to the consensus decision by the EG DASS that aniline should receive the overall reference classification of *1B*. Because the results from the MLLP approach were used to determine the overall study outcome, (*NC* in the majority of cases), reproducibility of the EG DASS consensus decision - based on the modified approach (and further arguments, e.g. the use of uncommon solvents) - was lower than 50%. Nevertheless, aniline is a real *NC/1B* borderline chemical and a low reproducibility of the results is therefore not astonishing (the same was observed for this chemical with respect to the human predictive patch test data). Moreover, the comparatively high number of test results available for aniline explains the discrepancy between the median and the weighted reproducibilities observed for GHS_{BIN}. For the second chemical, benzyl benzoate, a similar situation was found: only two test results were available, one resulting in *NC* and one resulting in *1B*. Again, the NC result (under the MLLP approach) was identified as a potential positive under the MSPE approach and, again, a consensus decision was made by the EG DASS that the overall classification for this chemical should be *1B*.

Overall, these results show that reproducibility of LLNA-based classifications is a function of the decision logic applied in the evaluation of the LLNA test results. If the LSG had not accepted results with maximum SI values < 3 and tested up to 50% as negative, but had followed the modified approach instead, the SPE would have changed to *NC/1B* for 9/10 *NC* results. In that case (1 x *NC*, 9 x *NC/1B*, 6 x *1B*), 15/16 studies (94%) would have reproduced the overall classification *1B*.

For the GHS_{SUB} classification, 11/16 *1A* chemicals with more than one test result suitable for sub-categorisation had a reproducibility of 100%, the other five were 4-amino-m-cresol (50%, 2 test results), cinnamaldehyde (95%, 20 test results), DNBS, sodium salt (67%, 3 test results) isoeugenol (79%, 42 tests), and methylisothiazolinone (50%, 2 tests). 4-Amino-m-cresol is a borderline *1A/1B* substance with two EC3 values available at 1.45 and 2.15%, respectively. For cinnamaldehyde, the comparatively small deviation from 100% may be considered to reflect normal variability, given that 19/20 test results gave EC results between 0.2 and 3.1%. With EC3 values of 0.3, 0.82, and 6.4%, DNBS, sodium salt can be considered an *1A/1B* borderline case. For isoeugenol, the situation is comparable to cinnamaldehyde, i.e. EC3 values span a comparatively small range of values not far from the *1A/1B* border. For methylisothiazolinone, with two EC3 values of 0.4 and 2.2%, the situation is comparable to that of 4-amino-m-cresol above.

For 16/22 substances with a GHS_{SUB} classification of *1B* and more than one test result suitable for sub-categorisation, these classifications were 100% reproducible. The reproducibilities for aniline (38%)

[18] Therefore, concordance could be seen as an estimate for the likelihood that a given LLNA outcome is reproduced by all future experiments, which is different from the likelihood that a test result will be reproduced by another test.

and benzyl benzoate (50%) have already been discussed above. For citral and α-hexylcinnamaldehyde, classifications were 94% and 97% reproducible, which seems acceptable as normal variability. For 3-(dimethylamino)propylamine, the six available EC3 values range from 1.7 to 7.1%, with the majority on the *1B* side, which is supported by a further *NC/1B* result. Still, overall, this is a borderline 1A/1B result. The sixth chemical, sodium lauryl sulfate (7 x *1B*, 2 x *1A*) is similar, with a reproducibility of 78%, but is known to cause problems in the LLNA due to irritancy, and therefore interpretation problems might have constituted an additional source of variability. The classifications for the three *NC* chemicals with more than one test result were all 100% reproducible.

In summary, under the conditions of this project, i.e. using rigorously curated LLNA data and following standardised assessment routines according to OECD and UN GHS protocols, reproducibility of LLNA-based GHS classifications in general is very high, i.e. in the order of 90% or greater. It is acknowledged, however, that the number of substances and test results used as the basis for this assessment was limited and therefore this number should be taken with a grain of salt. It could have been lower (but also higher) if more tests had been available.

Reproducibility was smaller for a few cases that must be considered borderline. It is not surprising that classification of extreme sensitisers (with very low EC3 values << 2%) or very weak sensitisers (with EC3 values >> 2%) should be more robust than those of sensitisers with EC3 values near the GHS *1A/1B* border. A more detailed analysis of the relationship between the potency of a substance in the LLNA and the reproducibility of its classification could produce fruitful insights for regulatory practice; however, this was outside of the scope of the present project.

6 Results: LLNA-based reference classifications

Table 6: Distribution of the LLNA reference classifications over the GHS hazard classes/sub-categories (N = 194)

Mode	GHS class/sub-category				
	1			NC/1B	NC
	1A	1	1B		
GHS_{BIN}	135			na	33
GHS_{SUB}	38	na	85		
GHS_{BORDER}	34	20	78	31	31

Two out of the 196 reference substances did not have reliable LLNA test results. The results for the remaining 194 substances are summarised in Table 6.

- GHS_{BIN}: An unambiguous classification could be obtained for 168 (85.7%) of the chemicals, of which 135 (80.4%) were classified as sensitisers (GHS Skin Sens. 1) and 33 (19.6%) were not classified (NC).
- GHS_{SUB}: For 123 substances with an unambiguous GHS_{BIN} classification as skin sensitisers, also GHS_{SUB} classifications could be obtained. Of these, 38 (30.9%) were classified as Skin Sens. 1A and 85 (69.1%) as Skin Sens. 1B.
- GHS_{BORDER}: Of the 38 substances with GHS_{SUB} = *1A*, four had GHS_{BORDER} = *1*, i.e. the sub-categorisation has to be considered somewhat uncertain. The same was true for four of the 85 substances with GHS_{SUB} = 1B. For 31 further substances there was some uncertainty about whether they were sensitisers or not (according to the GHS criteria), but a strong/extreme sensitisation potential appeared unlikely (GHS_{BORDER} = NC/1B). Three of these had GHS_{SUB} = 1B and two GHS_{SUB} = NC, whereas for the remaining 26 substances, the available study results did not allow for a reliable classification (both GHS_{BIN} and GHS_{SUB} unavailable) according to the rules applied in this report.

Table 7 provides an overview of how these classifications were obtained for the individual substances. Table 8 gives a detailed account of all individual study results used in the assessment.

Table 7: Final LLNA reference classifications and their reproducibilities (cf. sections 3, 4, and 5 of this report)[19]

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Abietic acid	514-10-3	208-178-3			1					15		1.00	1	1B		na		
Acetanisole	100-06-1	202-815-9	1							NC		0.00	NC			na		
2-Acetylcyclohexanone	874-23-7	212-858-5		1						na	NC/1B	0.50	na		NC/1B	na		
4-Allylanisole	140-67-0	205-427-8			1					18		1.00	1	1B		na		
Allyl phenoxyacetate	7493-74-5	231-335-2			1					3.1		1.00	1	1B		na		
4-Aminobenzoic acid	150-13-0	205-753-0		5						na	NC/1B	0.50	na		NC/1B	na		
4-Amino-m-cresol	2835-99-6	220-621-2				1			1	1.8		1.63	1	1A	1	100	50	
5-Amino-o-cresol	2835-95-2	220-618-6			1					7.7		1.00	1	1B		na		
2-Aminophenol	95-55-6	202-431-1							2	0.45		2.00	1	1A		100		
3-Aminophenol	591-27-5	209-711-2			1					3.2		1.00	1	1B		na		
α-Amylcinnamaldehyde	122-40-7	204-541-5			3					10.6		1.00	1	1B		100		
α-Amylcinnamic alcohol	101-85-9	202-982-8		1						na	25	1.00	1	1B	NC/1B	na		"Potential positive" study result under MSPE/WoE score approaches (SI of 2.9 at 25%, the HCT). Expert group consensus on 1B.
Anethole	104-46-1	203-205-5					1			POS		1.50	1	na	1	na		Confirmed by expert group
Aniline	62-53-3	200-539-3	10		6					NC	50	0,69	1	1B	NC/1B	38		4/10 NC studies are "potential positives" under the MSPE/WoE score approaches. Expert group consensus: 1B
Anisyl alcohol	105-13-5	203-273-6			2					7.1		1.00	1	1B		100		
2-(p-Anisyl)propanal	5462-06-6	226-749-5			1					23.6		1.00	1	1B		na		
Applelide	478695-70-4	639-080-2	1							NC		0.00	NC			na		
BADGE	1675-54-3	216-823-5							1	1.5		2.00	1	1A		na		
Bandrowski's base	20048-27-5	na							2	0.03		2.00	1	1A		100		
Benzaldehyde	100-52-7	202-860-4		1						na	NC/1B	1.00	na		NC/1B	na		

[19] Note that GHS_{SUB} and GHS_{BIN} classifications were obtained by the process explained in section 3: The modified approach in section 3.2 was applied as a sensitivity analysis for the approach taken by the LLNA sub-group. Where the results of these approaches disagreed, this was resolved via discussion in the EG DASS.

[20] Numerical values in %

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
1,2-Benzisothiazol-3(2H)-one	2634-33-5	220-120-9			2	1				4.8		1.08	1	1B		100		
Benzocaine	94-09-7	202-303-5	14	5	4		1	1		NC	25	0.62	na		NC/1B	na		Four of the *NC/1B* and three of the *NC* results were "potential positives" under the MSPE and WoE score approaches.
Benzoic acid	65-85-0	200-618-2		1						na	NC/1B	0.50	na		NC/1B	na		
p-Benzoquinone	106-51-4	203-405-2							1	1A		2.00	1	1A		na		
Benzyl alcohol	100-51-6	202-859-9	1							NC		0.00	NC			na		
Benzyl benzoate	120-51-4	204-402-9	1		1					17.0	33.5	1,00	1	1B	NC/1B	na		Negative study result is "potential positive" under MSPE/WoE approaches (SI of 2.7 at 50%, the HCT). Expert group consensus: 1B.
Benzyl bromide	100-39-0	202-847-3							1	0.2		2.00	1	1A		na		
Benzyl butyl phthalate	85-68-7	201-622-7	1							NC	50	1.00	NC		NC/1B	na		"Potential positive" study result under MSPE/WoE score approaches (SI of 2.5 at 50%, the HCT). Extrapolation suggests EC3 > 100%.
Benzyl cinnamate	103-41-3	203-109-3			1					18.4		1.00	1	1B		na		
Benzyl salicylate	118-58-1	204-262-9			1					2.9		1.00	1	1B		na		
Benzylidene acetone	122-57-6	204-555-1					1			POS		1.50	1	na	1	na		
BGE	2426-08-6	219-376-4			1					30.9		1.00	1	1B		na		
Bis-GMA	1565-94-2	216-367-7			1					45		1.00	1	1B		na		
Bourgeonal	18127-01-0	242-016-2			1					9.5		1.00	1	1B		na		
1-Bromobutane	109-65-9	203-691-9		1						na	50	0.50	na		NC/1B	na		
1-Bromohexane	111-25-1	203-850-2			1					10		1.00	1	1B		na		
Bromothalonil	35691-65-7	252-681-0							1	0.9		2.00	1	1A		na		
Butan-1-ol	71-36-3	200-751-6	1							NC		0.00	NC			na		
2-Butoxyethyl acetate	112-07-2	203-933-3	1							NC		0.00	NC			na		
Butyl acrylate	141-32-2	205-480-7			1					11.2		1.00	1	1B		na		
L-Carvone	6485-40-1	218-827-2			1					13		1.00	1	1B		na		
CD-3	25646-71-3	247-161-5							1	0.60		2.00	1	1A		na		
Chloramine-T	127-65-1	204-854-7					1			POS		1.50	1	na	1	na		
3-Chloro-p-anisaldehyde	4903-09-7	225-532-2	1							NC		0.00	NC			na		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Chlorobenzene	108-90-7	203-628-5		1						NC/1B		0.50	na		NC/1B	na		
Chlorothalonil	1897-45-6	217-588-1							1	0.004		2.00	1	1A		na		
Chlorpromazine	50-53-3	200-045-8					1			POS		1.50	1	na	1	na		
Cinnamaldehyde	104-55-2	203-213-9			1		1	1	18	1.0	1.1	1.94	1	1A		100	95	
Cinnamic alcohol	104-54-1	203-212-3			2		1			23.1		1.00	1	1B		100		
Cinnamonitrile	1885-38-7	217-552-5	1							NC	10	100	na		NC/1B	na		"Potential positive" study result under MSPE/WoE score approaches
Citral	5392-40-5	226-394-6		1	15	1			1	5.8	6.05	1.04	1	1B		100	94	
Citronellol	106-22-9	203-375-0			1					43.5		1.00	1	1B		na		
Clofibrate	637-07-0	211-277-4	1							NC	50.0	1.00	NC		NC/1B	na		"Potential positive" study result under MSPE/WoE score approaches (SI of 2.9 at 50%, the HCT). Extrapolation suggests EC3 > 100%.
Coumarin	91-64-5	202-086-7	1	1						NC	5	0.25	na		NC/1B	na		The *NC/1B* result was a "potential positive" under the MSPE and WoE score approaches.
Cyclamen aldehyde	103-95-7	203-161-7			1					22.3		1.00	1	1B		na		
trans-Dec-2-enal	3913-81-3	223-474-2			1					2.5		1.00	1	1B		na		
DEET	134-62-3	205-149-7	1							NC		0.00	NC			na		
Diacetyl	431-03-8	207-069-8			1					11.3		1.00	1	1B		na		
2,5-Diaminotoluene sulfate	615-50-9	210-431-8							1	0.4		2.00	1	1A		na		
Dibenzoyl peroxide	94-36-0	202-327-6							5	1A		2.00	1	1A		100		
Dibenzyl ether	103-50-4	203-118-2			1					6.3		1.00	1	1B		na		
Dibutyl phthalate	84-74-2	201-557-4	1							NC		0.00	NC			na		
N,N-Dibutylaniline	613-29-6	210-335-6			1					19.6		1.00	1	1B		na		
1,1-Dichloroethene	75-35-4	200-864-0	1							NC		0.00	NC			na		
Diethyl maleate	141-05-9	205-451-9				1	1			2.1		1.38	1	1B	1	na		
Diethyl phthalate	84-66-2	201-550-6	1							NC		0.00	NC			na		
Diethyl sulfate	64-67-5	200-589-6			1					3.3		1.00	1	1B		na		
Diethylenetriamine	111-40-0	203-865-4					1			POS		1.50	1	na	1	na		
3,4-Dihydrocoumarin	119-84-6	204-354-9			1					5.6		1.00	1	1B		na		
Dihydroeugenol	2785-87-7	220-499-0			1					6.8		1.00	1	1B		na		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Dihydromyrcenol	18479-58-8	242-362-4		1						NC/1B		0.50	na		NC/1B	na		
Dimethyl fumarate	624-49-7	210-849-0							1	0.35		2.00	1	1A		na		
3-Dimethylaminopropylamine	109-55-7	203-680-9		1	3	1		2		3.5		1.18	1	1B		100	67	
Diphenylcyclopropenone	886-38-4	212-948-4							1	1A		2.00	1	1A		na		1A confirmed by expert group
Disodium 2-[4-[[2-cyano-3-[4-[methyl(2-sulphonatoethyl)amino]-phenyl]-1-oxoallyl]amino]phenyl]-6-methylbenzothiazole-7-sulphonate	2498-95-5	219-694-3		1						na	NC/1B	0.50	na		NC/1B	na		
DMSO	67-68-5	200-664-3			1					72		1.00	1	1B		na		
DNBS, sodium salt	885-62-1	212-943-7			1			1	1	2		1.50	1	1A	1	100	67	One additional study (EC3 = 16%) excluded, since the solvent used (water) was considered inappropriate
DNCB	97-00-7	202-551-4							20	0.054		2.00	1	1A		100		
EGDMA	97-90-5	202-617-2			1					28		1.00	1	1B		na		
Ethyl acrylate	140-88-5	205-438-8		1	2					32.75		0.83	1	1B		100		
Ethyl benzoylacetate	94-02-0	202-295-3		1						na	NC/1B	0.50	na		NC/1B	na		
Ethyl vanillin	121-32-4	204-464-8	2							NC		0.00	NC			100		
2-Ethylbutanal	97-96-1	202-623-5			1					76		1.00	1	1B		na		
Ethylene brassylate	105-95-3	203-347-8		1						na	NC/1B	0.50	na		NC/1B	na		
Ethylene diamine (free base)	107-15-3	203-468-6		2		1				NC	NC/1B	0.75	1	1B		na		Expert group consensus: 1B
2-Ethylhexyl acrylate	103-11-7	203-080-7			1					36.8		1.00	1	1B		na		
Eugenol	97-53-0	202-589-1			12		5			11.6		1,00	1	1B		100		
Farnesal	502-67-0	242-957-9			1					12		1.00	1	1B		na		
Farnesol	4602-84-0	225-004-1			2					4.8		1.00	1	1B		100		
2-Fluoro-5-nitroaniline	369-36-8	206-720-3	1							NC		0.00	NC			na		
Formaldehyde	50-00-0	200-001-8			8		3		7	3.8	2.8	1,47	1	na	1	100	na	Lacking information on whether concentrations were based on formaldehyde or formalin (37% CHO in water). Unsuitability for sub-categorisation confirmed by expert group
Furil	492-94-4	207-766-7		1						na	NC/1B	0.50	na		NC/1B	na		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Geraniol	106-24-1	203-377-1			6					16.1		1.00	1	1B		100		
Glutaraldehyde	111-30-8	203-856-5					3		4	0.08		2.00	1	1A		100		Unclear whether reported test concentrations relate to pure glutaraldehyde or to 50% glutaraldehyde in water. 1A confirmed by expert group.
Glycerol	56-81-5	200-289-5	2							NC		0.00	NC			100		
Glyoxal	107-22-2	203-474-9					1		1	1.4		2.00	1	1A		na		Unclear whether reported test concentrations relate to pure glyoxal or to 40% glyoxal in water. However, 1A applies in both cases and was confirmed by the expert group.
Helional	1205-17-0	214-881-6			1					16.4		1.00	1	1B		na		
Hepta-2,4-dienal	5910-85-0	227-627-4			1					4		1.00	1	1B		na		
n-Hexane	110-54-3	203-777-6	1							NC		0.00	NC			na		
trans-Hex-2-enal	6728-26-3	229-778-1			2					4.05		1.00	1	1B		100		
Hexyl salicylate	6259-76-3	228-408-6		1					1	0.18		1.25	1	na	1	na		Expert group consensus: Unsuitable for sub-categorisation because of unclear influence of solvents used
α-Hexylcinnamaldehyde	101-86-0	202-983-3		1	27		1		1	10.8	10.6	1.05	1	1B		100	96	NC/1B result is a "potential positive" under MSPE/WoE score approaches (SI of 2.8 at 10%, HCT)
2-Hexylidenecyclopentanone	17373-89-6	241-411-7				1				2.4		1.25	1	1B	1	na		Expert group consensus: 1B
HHPA	85-42-7	201-604-9							1	0.84		2.00	1	1A		na		
Hydratropaldehyde	93-53-8	202-255-5			1					6.3		1.00	1	1B		na		
Hydrocortisone	50-23-7	200-020-1								na			na			na		
Hydroquinone	123-31-9	204-617-8							17	0.19		2.00	1	1A		100		For two of these studies, no reliable EC3 could be established, but as positive responses below 2% were observed, they were counted as *1A*.
4-Hydroxybenzoic acid	99-96-7	202-804-9	2							NC		0.00	NC			100		
Hydroxycitronellal	107-75-5	203-518-7			8					21.1		1.00	1	1B		100		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
2-Hydroxyethyl acrylate	818-61-1	212-454-9					4			POS		1.50	1	1A	1	100	na	Expert group consensus: 1A
2-Hydroxypropyl methacrylate	923-26-2	213-090-3	1							NC		0.00	NC			na		
Imidazolidinyl urea	39236-46-9	254-372-6			1					24		1.00	1	1B		na		
Iodocarb	55406-53-6	259-627-5							1	0.9		2.00	1	1A		na		
1-Iodohexane	638-45-9	211-339-0	1							NC		0.00	NC			na		
Isobergamate	68683-20-5	272-066-0		1						na	NC/1B	0.50	na		NC/1B	na		
Isobornyl acetate	125-12-2	204-727-6		1						na	NC/1B	0.50	na		NC/1B	na		
p-Isobutyl-α-methylhydrocinnamaldehdye	6658-48-6	229-695-0			1					9.5		1.00	1	1B		na		
2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol	63500-71-0	613-238-0		1						na	NC/1B	0.50	na		NC/1B	na		
Isoeugenol	97-54-1	227-678-2			7	2	4	6	27	1.3	1.4	1.76	1	1A		100	79	Expert group consensus: 1A
α-Isomethylionone	127-51-5	204-846-3			1					21.8		1.00	1	1B		na		
Isopropanol	67-63-0	200-661-7	1							NC		0.00	NC			na		
Isopropyl myristate	110-27-0	203-751-4			1					44		1.00	1	1B		na		
Kanamycin	59-01-8	200-411-7	1							NC		0.00	NC			na		Expert group consensus NC: chemical does not dissolve and cannot be tested higher
Kathon CG	55965-84-9	611-341-5; 911-418-6							9	0.008		2.00	1	1A		100		
Lactic acid	50-21-5	200-018-0	1							NC		0.00	NC			na		Expert group consensus NC: chemical is irritant at higher concentrations
Lauryl gallate	1166-52-5	214-620-6							1	1A		2.00	1	1A		na		
Lilial	80-54-6	201-289-8			5					8.6		1.00	1	1B		100		
D-Limonene	5989-27-5	227-813-5			2					52.5		1.00	1	1B		100		
Linalool	78-70-6	201-134-4			3					35.5		1.00	1	1B		100		
Maleic anhydride	108-31-6	203-571-6							1	0.16		2.00	1	1A		na		
2-Mercaptobenzothiazole	149-30-4	205-736-8					4	1	1	1.35		1.88	1	1A		na		Expert group consensus: 1A
2-Methoxy-p-cresol	93-51-6	202-252-9			1					5.4		1.00	1	1B		na		
1-(4-Methoxyphenyl)pent-1-en-3-one	104-27-8	203-190-5			1					9.3		1.00	1	1B		na		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Methyl acrylate	96-33-3	202-500-6			1					20		1.00	1	1B		na		
Methyl 3-bromoproprionate	3395-91-3	222-247-5	1							NC		0.00	NC			na		
Methyl dihydrojasmonate	24851-98-7	246-495-9		1						na	NC/1B	0.50	na		NC/1B	na		
Methyl methacrylate	80-62-6	201-297-1			2					75		1.00	1	1B		100		
Methyl methanesulphonate	66-27-3	200-625-0			1					8.1		1.00	1	1B		na		
Methyl non-2-ynoate	111-80-8	203-909-2					1			POS		1.50	1	na	1	na		Expert group consensus: Not suitable for sub-categorisation, because test result is 1A or 1B, depending on extrapolation method used.
Methyl oct-2-ynoate	111-12-6	203-836-6							1	0.5		2.00	1	1A		na		
Methyl pyruvate	600-22-6	209-987-4				1				2.4		1.25	1	1B	1	na		
Methyl o-toluate	89-71-4	201-932-2		1						na	NC/1B	0.50	na		NC/1B	na		
1-(3-Methyl-2-benzofuranyl)ethanone	23911-56-0	429-100-6		1						na	100	0.50	na		NC/1B	na		
α-Methylcinnamaldehyde	101-39-3	202-938-8			1					4.5		1.00	1	1B		na		
6-Methylcoumarin	92-48-8	202-158-8		2						na	NC/1B	0.50	na		NC/1B	na		
2-Methyldecanenitrile	69300-15-8	273-960-3	1							NC	100	1.50	NC			na		
6-Methylhepta-3,5-dien-2-one	1604-28-0	216-507-7		1						na	100	0.50	na		NC/1B	na		
5-Methylhexane-2,3-dione	13706-86-0	237-241-8			1					26.0		1.00	1	1B		na		
Methylisothiazolinone	2682-20-4	220-239-6				1			1	1.3		1.63	1	1A	1	100	50	Expert group consensus: 1A
4-Methyl-2-nitroanisole	119-10-8	204-296-4	1							NC		0.00	NC			na		
Methylparaben	99-76-3	202-785-7	1							NC		0.00	NC			na		
2-Methylundecanal	110-41-8	203-765-0			1					10		1.00	1	1B		na		
Metol	55-55-0	200-237-1							1	0.8		2.00	1	1A		na		
1-Naphthol	90-15-3	201-969-4							1	1.3		2.00	1	1A		na		
Neomycin sulfate	1405-10-3	215-773-1		1						na	NC/1B	0.50	na		NC/1B	na		
4-Nitrobenzyl bromide	100-11-8	202-820-6							1	0.05		2.00	1	1A		na		
2-Nitro-p-phenylenediamine	5307-14-2	226-164-5							1	0.4		2.00	1	1A		na		
cis-6-Nonenal	2277-19-2	218-900-9			1					23		1.00	1	1B		na		
Octanoic acid	124-07-2	204-677-5	1							NC		0.00	NC			na		
OTNE	54464-57-2	259-174-3			3					14.2		1.00	1	1B		100		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
Oxalic acid	144-62-7	205-634-3			1					15		1.00	1	1B		na		
Oxazolone	15646-46-5	239-713-9							7	0.002	0.003	2.00	1	1A		100		
Penicillin G	61-33-6	200-506-3			7		2			31.3		1,11	1	1B		100		
Pentachlorophenol	87-86-5	201-778-6			1					20		1.00	1	1B		na		
Perillaldehyde	2111-75-3	218-302-8			1					4.04		1.00	1	1B		na		
3-Phenoxypropanenitrile	3055-86-5	221-278-1	1							NC		0.00	NC			na		
Phenyl benzoate	93-99-2	202-293-2			1				1	POS		1.50	1	na	1	na		Expert group consensus: Not suitable for sub-categorisation
Phenylacetaldehyde	122-78-1	204-574-5			1		1			3		1,25	1	1B		100		
p-Phenylenediamine	106-50-3	203-404-7					4		10	0.11		2.00	1	1A		100		
1-Phenylpropane-1,2-dione	579-07-7	209-435-2					1			POS		1.50	1	na	1	na		
Phthalic anhydride	85-44-9	201-607-5							1	0.16		2.00	1	1A		na		
Propyl gallate	121-79-9	204-498-2							1	1A		2.00	1	1A		na		Expert group consensus: 1A, due to very high SI at lowest conc. tested (5%)
Propylene glycol	57-55-6	200-338-0	1							NC		0.00	NC			na		
3-Propylidenephthalide	17369-59-4	241-402-8			1					3.7		1.00	1	1B		na		
Propylparaben	94-13-3	202-307-7		1						na	NC/1B	0.50	na		NC/1B	na		
Pyridine	110-86-1	203-809-9			1					72		1.00	1	1B		na		
Resorcinol	108-46-3	203-585-2			1					6.3		1.00	1	1B		na		
Saccharin	81-07-2	201-321-0	1							NC		0.00	NC			na		
Safranal	116-26-7	204-133-7			1					7.5		1.00	1	1B		na		
Salicylic acid	69-72-7	200-712-3		1	1					12.2	18.6	1,00	1	1B		na		The NC/1B result is a "potential positive" under MSPE/WoE score approaches (SI of 2.5 at 25%, the HCT). Expert group consensus: 1B
Sodium lauryl sulfate	151-21-3	205-788-1			7				2	3.7		1.22	1	1B		100	78	
Squaric acid	2892-51-5	220-761-4					1			POS		1.50	1	na	1	na		
Sulfanilamide	63-74-1	200-563-4	1							NC		0.00	NC			na		
Sulfanilic acid	121-57-3	204-482-5		3						na	NC/1B	0.50	na		NC/1B	na		
L-Tartaric acid	87-69-4	201-766-0		1						na	NC/1B	0.50	na		NC/1B	na		
Tetrachlorosalicylanilide	1154-59-2	214-576-8							2	0.027		2.00	1	1A		100		

Name	CASRN	EC no.	SPE count[20]							MLLP	MSPE	WoE score	Overall classification			Reproducibility		Remarks
			NC	NC/1B	> 2.4	2.0 < SPE ≤ 2.4	POS	1.7 ≤ SPE ≤ 2.0	< 1.7				GHS_{BIN}	GHS_{SUB}	GHS_{BORDER}	GHS_{BIN}	GHS_{SUB}	
2,2,6,6-Tetramethyl-heptane-3,5-dione	1118-71-4	214-268-3			1					27		1.00	1	1B		na		
Thioglycerol	96-27-5	202-495-0								na			na			na		
Thiram	137-26-8	205-286-2			1					5.2		1.00	1	1B		na		
α-Tocopherol	59-02-9	200-412-2			1					7.4	9.2	1.00	1	1B		na		
Triethanolamine	102-71-6	203-049-8	1							NC		0.00	NC			na		
Trimellitic anhydride	552-30-7	209-008-0			1					9.2		1.00	1	1B		na		
Tropolone	533-75-5	208-577-2			1					4.3		1.00	1	1B		na		
Undec-10-enal	112-45-8	203-973-1			1					6.8		1.00	1	1B		na		
Vanillin	121-33-5	204-465-2	1							NC		0.00	NC			na		
4-Vinylpyridine	100-43-6	202-852-0					1			POS		1.50	1	na	1	na		

Appendix 1: Curated LLNA data used in this evaluation

Table 8: Detailed overview of the individual study results used for this evaluation

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Abietic acid	514-10-3	208-178-3	na	AOO	na	na	5	1.5	15	n	na			Not among the publications quoted in Ashby et al. 1995. Assumed to be an unpublished study.	Unknown, cited in Ashby et al. (1995)
							10	2.0							
							25	5.2							
Acetanisole	100-06-1	202-815-9	100	AOO	CBA/Ca	4	10	1.3	NC	n	na				Ryan et al. (2000
							25	1.0							
							50								
2-Acetylcyclohexanone	874-23-7	212-858-5	na	ACE	na	na	10	0.8	NC/1B	n	na				P&G, unpublished
							20	0.7							
							40	0.8							
4-Allylanisole	140-67-0	205-427-8	na	AOO	na	na	10	1.2	18	n	na				Unilever unpublished
							25	4.7							
							50	4.5							
							100	8							
Allyl phenoxyacetate	7493-74-5	231-335-2	99.5	DEP:EtOH 3:1	na	4	0.5	0.8	3.1	n	na				RIFM, unpublished
							1	1.3							
							2.5	1.6							
							5	7.5							
							10	8.1							
4-Aminobenzoic acid	150-13-0	205-753-0	99	AOO	CBA/Ca	4 or 5	0.5	1.2	NC/1B	n	na				Loveless et al. (1996)
							1								
							2.5	1.1							
							5	1.6							
							10	1.4							
					CBA/JHsd		0.5	1.1							
							1	0.6							
							2.5	0.7							
							5	0.8							
							10	0.6							
							0.5	1.1							
							1								
							2.5	1.2							
							5	1.1							
							10	1.0							

[21] Rounded off to first decimal (original values were used for EC3 calculation)

[22] Criteria which must be fulfilled for an extrapolated EC3 value in order to be considered reliable (cf. section 3.1.1; p = pass, f = fail, na = not applicable)

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
4-Aminobenzoic acid, ctd.	150-13-0	205-753-0	99	AOO	CBA/JHsd	4 or 5	0.5	1.6	NC/1B	n	na				Loveless et al. (1996)
							1	0.8							
							2.5	0.9							
							5	0.7							
							10								
					na	na	2.5	1.1						Dose levels and SIs are available from Schneider & Akkan (2004)	Unilever, unpublished
							5	1.6							
							10	1.4							
4-Amino-m-cresol	2835-99-6	220-621-2	95.8	DMSO	CBA/J	5	0.5	0.9	1.45	n	na				SCCP (2005)
							1.5	3.1							
							5	6.5							
							10	6.7							
							0.5	1.5	2.15						
							1.5	1.7							
							3	4.7							
							5	6.9							
5-Amino-o-cresol	2835-95-2	220-618-6	na	AOO	BALB/c	8	2.5	1.5	7.7	n	na				NICEATM[23]
							5	2.8							
							10	3.2							
2-Aminophenol	95-55-6	202-431-1	na	AOO	na	na	0.1	1.4	0.5	n	na				Gerberick et al. (2007)
							0.25	2.9							
							0.5	3							
							1	5.7							
							2.5	13.1							
							0.5	3.5	0.4	y	p			Not among the publications quoted in Ashby et al. 1995. Assumed to be an unpublished study.	Unknown, cited in Ashby et al. (1995)
							1	5							
							2.5	7.4							
3-Aminophenol	591-27-5	209-711-2	na	AOO	na	na	2.5	2.8	3.2	n	na				Ashby et al. (1995)
							5	3.5							
							10	5.7							
α-Amylcinnamaldehyde	122-40-7	204-541-5	92.1	DEP:EtOH 3:1	CBA/Ca	4	1	1.7	7.6	n	na				RIFM, unpublished
							2.5	1.6							
							5	1.8							
							10	4.1							
							25	10.2							

[23] https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/immunotoxicity/llna/index.html, last accessed 2021-07-10

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
α-Amylcinnamaldehyde, ctd.	122-40-7	204-541-5	> 98	AOO	CBA/Ca	4	1	1.5	10.6	n	na			The paper shows the SIs in a graph. SIs reported in Gerberick et al. (2005) seem to be correct.	Elahi et al. (2004), also cited in Gerberick et al. (2005)
							2.5	1.7							
							5	2.2							
							10	2.8							
							25	8.2							
			na		na	na	10	2.1	11.2					Unclear, whether TG 429 was followed.	Smith & Hotchkiss (2001)
							25	13							
α-Amylcinnamic alcohol	101-85-9	202-982-8	na	EtOH:DEP	na	na	1	1.2	NC/1B	n	na			Expert group consensus on 1B classification based on dose-response curve with SI of 2.9 at the highest concentration tested	Kern et al. (2010)
							2.5	0.8							
							5	1.4							
							10	1.7							
							25	2.9							
Anethole	104-46-1	203-205-5	na	AOO	na	na	4.5	13.5	POS	y	p	f	p	Expert group consensus to use it only for binary classification. Different extrapolation methods provide different answers (1A or 1B)	Unilever, unpublished
							9	24.7							
							22.6	37.3							
Aniline	62-53-3	200-593-3	na	MEK	CBA/Ca	4	10	1.7	13.25	n	na			5 days treatment	Basketter et al. (1991)
							25	7.7							
							50	7.5							
							100	1.5							
				AOO			10	1.9	16.6						
							25	4.4							
							50	3.6							
							100	1.7							
				AOO	na	na	25	2.1	37						Smith & Hotchkiss (2001)
							100	7.6							
				MEK	CBA/Ca	4	10	1.5	50						Basketter et al. (1991)
							25	1.7							
							50	3.0							
				AOO			5	1.3	77.8					4 days treatment. EC3 calculated since it was missing from original publication.	
							10	1.2							
							25	2.1							
							50	1.5							
							100	4.2							
							5	1.1	89					5 days treatment	
							10	0.9							
							25	2.0							
							50	1.9							
							100	3.3							
							25	2.6	NC					4 days treatment	
							50	1.6							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Aniline, ctd.	62-53-3	200-593-3	na	AOO	CBA/Ca	4	10	0.8	NC	n	na			4 days treatment	Basketter et al. (1991)
							25	0.9							
							50	1.0							
				MEKPO			10	1.4							
							25	1.8							
							50	2.9							
				AOO			10	1.1						5 days treatment	
							25	2.5							
							50	1.3							
				ACE			10	1.2							
							25	1.5							
							50	1.7							
				MEKPO			10	1.6						6 days treatment	
							25	2.2							
							50	2.4							
				PO			10	1.0							
							25	1.1							
							50	1.6							
				AOO			10	1.2							
							25	1.8							
							50	1.4							
							10	1.9							
							25	2.4							
							50	2.7							
							5	1.4							
							10	1.1							
							25	1.8							
							50	1.9							
							100	0.7							
Anisyl alcohol	105-13-5	203-273-6	na	EtOH:DEP	CBA/Ca	4	2.5	1.8	5.9	n	na			Study report available. EC3 value modified from 5.3 to 5.9 as reported in the study and in the NICEATM database	RIFM, unpub-lished, cited in Kern et al. (2010)
							5	2.8							
							10	3.9							
							25	5.1							
							50	5.3							
				AOO			5	2.4	8.3						P&G, unpublished
							10	3.3							
							25	10.9							
2-(p-Anisyl)propanal	5462-06-6	226-749-5	98.5	DEP:EtOH 3:1	na	5	7.5	1.5	23.63	n	na				RIFM, unpublished
							15	2.0							
							30	3.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Applelide	478695-70-4	639-080-2	na	AOO	CBA/Ca	4	25	1.3	NC	n	na				RIFM, unpublished
							50	2.3							
							100	2.4							
BADGE	1675-54-3	216-367-7	100	AOO	CBA/Ca	4	1	2.0	1.5	n	na				Warbrick et al. (2001)
							3	6.0							
							10	17.4							
Bandrowski's base	20048-27-5	na	89	AOO	CBA/Ca	4	0.01	1.1	0.02	n	na				White et al. (2006)
							0.025								
							0.05	3.1							
							0.1	5.7							
							0.25	5.6							
							0.01	1.2	0.04						
							0.025	1.8							
							0.05	4.1							
							0.1	5.4							
							0.25	4.4							
Benzaldehyde	100-52-7	202-860-4	na	AOO	na	na	1	2.1	NC/1B	n	na				P&G, unpublished
							2.5	1.7							
							5	2.2							
							10	1.8							
							25	2							
1,2-Benzisothiazol-3(2H)-one	2634-33-5	220-120-9	na	DMF	na	na	10	3.8	2.3	y	p			Unclear, whether TG 429 was followed. The study is not reported in the publications quoted in Ashby et al. 1995. It is assumed this is an unpublished study.	Unknown, cited in Ashby et al. (1995)
							30	4.4							
							50	4.9							
			100		CBA/Ca	4	3	2.7	4.8	n	na				Botham et al. (1991)
							10	3.8							
							30	4.5							
							50	5.0							
							3	1.6	32.4						
							10	1.2							
							30	2.8							
							50	4.5							
Benzocaine	94-09-7	202-303-5	na	DMF	na	na	1	1.9	1.8	n	na			Unclear, whether TG 429 was followed	Basketter et al. (1995)
							5	7.4							
							25	3.0							
							10	3.2	POS						
							25	2.5							
							50	2.2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Benzocaine, ctd.	94-09-7	202-303-5	na	DMF	na	na	5	3.2	4.54	n	na			Unclear, whether TG 429 was followed	Basketter et al. (1995)
							10	2.4							
							12.5	3.6							
							15	1.8							
							25	2.4							
							1	1.7	4.7						
							5	3.1							
							12.5	2.4							
							25	1.4							
				AOO	CBA/Ca	3	2.5	1.0	7.9					Modified LLNA. *ex vivo* ^{3}H-thymidine incorporation. Labelling and excision on day 4	Kimber & Weisenberger (1989)
							5	1.6							
							10	3.8							
				DMF	na	na	10	2.2	42					Unclear, whether TG 429 was followed	Smith & Hotchkiss (2001)
							50	3.2							
			98	ACE	CBA/J	5	5	1.3	NC/1B					4 days treatment. labelling and excision from 18 to 24 h after fourth treatment	Gerberick et al. (1992)
							10	1.0							
							20	1.3							
			na	DMF	na	na	1	1.4						Unclear, whether TG 429 was followed	Basketter et al. (1995)
							5								
							12.5	2.2							
							25	1.5							
							1	1.6							
							5	1.5							
							12.5	2.4							
							25	1.0							
							2.5	1.4							
							5	2.3							
							10	2.1							
							25	1.4							
							2.5	1.7							
							5	1.8							
							10	2.1							
							25	2.4							
					CBA/Ca	4	2.5	2.0	NC						Warbrick et al. (2000)
							5	2.8							
							10	2.4							
							25	1.3							
							50	2.0							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Benzocaine, ctd.	94-09-7	202-303-5	na	ACE	CBA/Ca	4	2.5	1.9	NC	n	na				Warbrick et al. (2000)
							5	3.0							
							10	1.5							
							25	2.0							
							50								
				AOO			2.5	2.1							
							5	1.8							
							10	2.7							
							25	1.8							
							50	1.2							
							10							Radioactive labelling and excision on day 4	Kimber et al. (1991)
							25	1.3							
							50	1.4							
							10	2.3							
							25	1.3							
							50								
							10	1.8							
							25	1.3							
							50	0.9							
						na	10	1.5							
							25	1.3							
							50	0.9							
							10	1.7						Labelling and excision on day 5 or 6. Acc. to the reference, the majority of chemicals had a purity above 98% but specific purities are not reported.	Basketter and Scholes (1992)
				ACE	na		25	2.0							
							50	0.9							
							10	1.9							
							25	1.5							
							50	1.2							
				AOO			10	1.7						Unclear, whether TG 429 was followed	Basketter et al. (1995)
							25	2.0							
							50	0.9							
				DMF			10	1.3							
							25	1.6							
							50	1.2							
				DMSO	CBA/Ca	4	2.5	1.1							Warbrick et al. (2000)
							5								
							10	1.7							
							25								
							50	1.8							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Benzocaine, ctd.	94-09-7	202-303-5	na	Acetone: saline 1:1	CBA/Ca	4	2.5	1.5	NC	n	na				Warbrick et al. (2000)
							5	1.3							
							10	2.1							
							25								
							50	1.7							
				MEK			2.5	1.2							
							5	1.8							
							10	1.4							
							25	1.7							
							50								
Benzoic acid	65-85-0	200-618-2	97	ACE	CBA/J	5	5	0.8	NC/1B	n	na			4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							10	0.9							
							20	0.8							
p-Benzoquinone	106-51-4	203-405-2	na	AOO	CBA/Ca	4	0.5	36.4	1A	y	f		p		Basketter & Scholes (1992)
							1	42.3							
							2.5	52.3							
Benzyl alcohol	100-51-6	202-859-9	na	EtOH:DEP	CBA/Ca	4	2.5	1.0	NC	n	na			Corrected SI for 2.5% dose. Study report available. Tested up to 50% with SI ≤ 2.5.	RIFM unpublished
							5	0.9							
							10	0.5							
							25	0.6							
							50	1.2							
Benzyl benzoate	120-51-4	24-402-9	na	AOO	na	na	5	2.3	17	n	na				Smith & Hotchkiss (2001)
							25	3.5							
			99.8	DEP:EtOH 3:1		4	2.5	0.7	NC						RIFM, unpublished
							5								
							10	0.8							
							25	1.7							
							50	2.7							
Benzyl bromide	100-39-0	202-847-3	na	AOO	CBA	na	0.25	3.5	0.2	y	p				Unilever, unpublished
							0.5	11.5							
							1	16.1							
							2.5	16.4							
							5	25.1							
Benzyl butyl phthalate	85-68-7	201-622-7	na	AOO	CBA/Ca	4	0.5	1.2	NC	n	na			Extrapolation indicates EC3 > 100	DK EPA report GM7919-58
							5	1.5							
							50	2.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Benzyl cinnamate	103-41-3	203-109-3	na	EtOH:DEP	CBA/Ca	4	2.5	0.8	18.4	n	na				RIFM, unpublished
							5	1.9							
							10	2.1							
							25	3.7							
							50	5.9							
Benzyl salicylate	118-58-1	204-262-9	99.8	DEP:EtOH 3:1	na	4	2.5	2.6	2.9	n	na				RIFM, unpublished
							5	5.5							
							10	6							
							25	18.9							
							50	26.2							
Benzylidene acetone	122-57-6	204-555-1	99	AOO	CBA/J	4	10	8.5	POS	y	p		f		Ryan et al. (2000)
							25	13.6							
							50	12.8							
BGE	2426-08-6	219-376-4	na	AOO	CBA/Ca	4	10	1.4	30.9	n	na				Basketter et al. (1994)
							25	2.2							
							50	5.6							
Bis-GMA	1565-94-2	216-367-7	> 95	AOO	CBA/CaJ	3 or 5	35	2	45	n	na				Kostoryz et al (2006)
							75	5.9							
Bourgeonal	18127-01-0	242-016-2	99	70% EtOH	na	4	10	3.3	9.5	y	p			Changed EC3 from 7.6 to 9.5 as for RIFM indication	RIFM unpublished
							25	8.3							
							50	19.8							
							100	34.3							
1-Bromobutane	109-65-9	203-691-9	≥ 96	AOO	CBA/Ca	na	5	1.1	NC/1B	n	na				Basketter et al. (1992)
							10	1.2							
							25	1							
1-Bromohexane	111-25-1	203-850-2	na	AOO	na	na	1	1.7	10	n	na			No information on doses and Sis in Estrada et al (2003). EC3 corresponds in both publications	Estrada et al. (2003), also cited in Gerberick et al. (2005)
							10	2.9							
							50	18.6							
Bromothalonil	35691-65-7	252-681-0	na	AOO	na	na	0.5	1.4	0.9	n	na				Unilever, unpublished
							1	3.4							
							2.5	3.5							
							5	5.4							
Butan-1-ol	71-36-3	200-751-6	100	water	CBA/J	5	5	1.6	NC	n	na			Expert group consensus: 20% max dose sufficient due to evidence of skin irritation	Ryan et al. (2000)
							10	1.2							
							20	1.4							
2-Butoxyethyl acetate	112-07-2	203-933-3	na	AOO	CBA/Ca	4	10	1.2	NC	n	na				DK EPA report GM7919-58
							25	0.7							
							50	1.2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Butyl acrylate	141-32-2	205-480-7	99.7	AOO	CBA/Ca	4	2.5	1.3	11.2	n	na				Dearman et al. (2007)
							5	1.4							
							10	2.5							
							25	8.7							
L-Carvone	6485-40-1	218-827-2	98	AOO	CBA/Ca	4	6	1.3	13	n	na				Nilsson et al. (2005)
							12	2.6							
							20	6.2							
CD-3	25646-71-3	247-161-5	na	DMSO	CBA	na	0.1	1.2	0.6	n	na				Ryan et al. (2000)
							1	4.5							
							5	5.9							
							10	6.3							
Chloramine-T	127-65-1	204-854-7	na	DMSO	CBA/Ca	4	5	7.7	POS	y	na		f		Basketter & Scholes (1992)
							10	7.5							
							25	10.7							
3-Chloro-p-anisaldehyde	4903-09-7	225-532-2	na	AOO	CBA/Ca	4	10	1.6	NC	n	na			Fit is too bad to extrapolate. Negative slope	DK EPA report GM7919-58
							25	1.8							
							65	1.2							
Chlorobenzene	108-90-7	203-628-5	na	AOO	na	na	5	1.1	NC/1B	n	na				Ashby et al. (1995)
							10	1.7							
							25	1.6							
Chlorothalonil	1897-45-6	217-588-1	99	DMF	CBA/Ca	4	0.003	2.1	0.004	n	na				Boman et al (2000)
							0.01	9.4							
							0.03	13.8							
							0.1	18.4							
							0.3	27.2							
Chlorpromazine	50-53-3	200-045-8	na	DMF	CBA/Ca	4	10	11.8	POS	y	p		f		Basketter et al. (1994)
							25	13.7							
							50	8.9							
Cinnamaldehyde	104-55-2	203-213-9	na	EtOH:DEP 3:1	na	4	0.1	2.0	0.2	n	na				RIFM, unpublished
							0.3	3.9							
							1	10.4							
							3	13.0							
							10	24.5							
				EtOH:DEP 3:1 + 0.1% Tocopherol			0.1	1.9							
							0.3	4.7							
							1	5.9							
							3	26.7							
							10	24.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Cinnamaldehyde, ctd.	104-55-2	203-213-9	99	DMF	CBA/Ca	4	0.1	0.8	0.5	n	na				Wright et al. (2001)
							0.25	1.5							
							0.5	3.1							
							1	4.5							
							2.5	8.3							
							5	8.6							
							10	10.7							
							25	11.1							
			na	EtOH:DEP 3:1 + 2% Toco-pherol	na		0.1	1.2	0.6						RIFM, unpublished
							0.3	1.6							
							1	4.5							
							3	6.2							
							10	8.5							
				EtOH:DEP 3:1 + 0.1% TrlC			0.1	1.3	0.7						
							0.3	1.6							
							1	4.1							
							3	9.6							
							10	21.5							
				EtOH:DEP 3:1 + AO mix			0.1	2.3							
							0.3	2.0							
							1	3.6							
							3	9.3							
							10	16.2							
				DMF	CBA/Ca		1	4.3		y	p				Montelius et al (1994)
							5	9.8							
							25	12.8							
				EtOH:DEP (3:1) + 2% Toco-pherol	na		0.1	0.9	0.8	n	na				RIFM, unpublished
							0.3	1.8							
							1	3.7							
							3	6.6							
							10	11.9							
			99	DMSO	CBA/Ca		0.1	0.7	0.9					Changed EC3 from 1.3 to 0.9% for DMSO.	Wright et al. (2001)
							0.25	1.7							
							0.5	2.3							
							1	4.4							
							2.5	7.6							
							5	7.6							
							10	8.5							
							25	11.3							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Cinnamaldehyde, ctd.	104-55-2	203-213-9	na	EtOH:DEP (3:1)	na	4	0.1	1.1	0.9	n	na				RIFM, unpublished
							0.3	0.9							
							1	3.3							
							3	6.9							
							10	13.4							
				EtOH:DEP (3:1) + 0.1% Tocopherol			0.1	1.08	1.1						
							0.3	1.85							
							1	2.58							
							3	9.42							
							10	13.1							
			99	MEK	CBA/Ca		1	2.8							Wright et al. (2001)
							2.5	6.2							
							5	8.5							
							10	14.6							
							25	13.2							
				50% EtOH			1	2.1	1.2						
							2.5	9.5							
							5	10.3							
							10	13.6							
							25	21.9							
			na	EtOH:DEP 3:1 + AO mix	na		0.1	1.04	1.3						RIFM, unpublished
							0.3	1.26							
							1	2.63							
							3	5.39							
							10	10.7							
			99	PG	CBA/Ca		1	2.1	1.4						Wright et al. (2001)
							2.5	5.8							
							5	8.2							
							10	16.3							
							25	17							
			98	EtOH:DEP 3:1 + 0.1%TrlC	na		0.1	0.5						Changed EC3 from 1.3 to 1.4 as for RIFM indication	RIFM unpublished
							0.3	1.4							
							1	2.2							
							3	6.7							
							10	9.2							
			na	AOO		na	1	2.4						Changed maximum dose from NA to 2.5%. Intermediate dose not reported.	Smith & Hotchkiss (2001)
							2.5	4.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Cinnamaldehyde, ctd.	104-55-2	203-213-9	99	10% EtOH	CBA/Ca	4	1	2.7	1.6	n	na				Wright et al. (2001)
							2.5	3.5							
							5	4.8							
							10	5.2							
							25	5.8							
				AOO			1	2.2	1.7						
							2.5	3.9							
							5	4.6							
							10	7.6							
							25	5.4							
							0.5	1.4	3.1						Basketter et al (2001)
							1	0.9							
							2.5	1.9							
							5	7.1							
							10	15.8							
			na				5	12.5	POS	y	p		f	Labelling and excision on day 5 or 6. Acc. to the reference, the majority of chemicals had a purity above 98% but specific purities are not reported.	Basketter and Scholes (1992)
							10	18.4							
							25	15.4							
Cinnamic alcohol	104-54-1	203-212-3	na	AOO	na	na	10	1.8	21	n	na				Estrada et al (2003)
							25	3.5							
							50	3.9							
							90	5.7							
			98.2				10	1.7	25.2						Basketter et al. (2012)
							25	2.9							
							50	12.0							
			96.5		CBA/Ca	4	na	na	POS					Doses and SIs presented in graph	Elahi et al. (2004)
Cinnamonitrile	1885-38-7	217-552-5	99.5	DEP:EtOH 3:1	na	4	2.5	1.20	NC	n	na				RIFM, unpublished
							5	2.30							
							10	2.50							
							25	na[24]							
							50								
Citral	5392-40-5	226-394-6	93.4	EtOH:DEP 3:1 + 0.1% Toco-pherol	na	4	0.3	1.8	1.5	n	na				RIFM, unpublished
							1	2.5							
							3	4.7							
							10	23.8							
							30	58.7							

[24] Systemic toxicity was observed at these concentrations.

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Citral, ctd.	5392-40-5	226-394-6	99.5	EtOH:DEP 3:1 + AO Mix	na	4	0.3	1.7	2.1	n	na				RIFM, unpublished
							1	2.0							
							3	3.8							
							10	13.9							
							30	28.3							
				3:1 EtOH:DEP + 0.1% TrIC			0.3	1.8	3.7						
							1	1.8							
							3	2.2							
							10	10.6							
							30	31.1							
				EtOH:DEP 3:1			0.3	1.9	4.6						
							1	1.8							
							3	2.3							
							10	5.6							
							30	23.5							
			92.6	EtOH:DEP + AO Mix			0.3	0.9							
							1	0.7							
							3	1.4							
							10	8.4							
							30	29.0							
			na	AOO		na	5	2.9	5.1					Indicated as Citral PQ extra. Could not find this study in any of the publications quoted. It is assumed this is an unpublished study.	Unknown, cited in Ashby et al. (1995)
							10	6.4							
							25	12.9							
			na	EtOH:DEP 3:1	na	4	0.3	0.6	5.3						RIFM, unpublished
							1	1.2							
							3	1.6							
							10	5.8							
							30	27.7							
				AOO	CBA/Ca		5	2.2	5.7						Basketter et al. (1991)
							10	5.1							
							25	20.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Citral, ctd.	5392-40-5	226-394-6	95.9	EtOH:DEP 3:1 + 0.1% TrlC	na	4	0.3	0.9	5.8	n	na				RIFM unpublished
							1	1.3							
							3	0.9							
							10	6.3							
							30	22.8							
			98.5	DEP:EtOH 3:1	CBA/Ca		1	0.9	6.3						
							2.5	2.2							
							5								
							10	5.2							
							25	6.1							
			na				2.5	2.3	6.3						
							5								
							10	5.1							
							25	11.4							
							50	22.2							
				AOO			5	2.1	6.5					Changed maximum conc. tested to 25%	Basketter et al. (1991)
							10	5							
							25	9.3							
			99.5	EtOH:DEP 3:1 + 0.1% Toco-pherol	na		0.3	0.8	6.8						RIFM unpublished
							1	1.7							
							3	2.0							
							10	3.9							
							30	9.2							
			na	AOO	CBA/Ca		5	0.9	12						Basketter et al. (1991)
							10	2.2							
							25	6.2							
							5	0.9	12.6						
							10	2.4							
							25	4.7							
					na	na	5	1.2	13.2					EC3 value changed to 13.2 as for original reference. Original reference does not report the concentrations and SIs. It is assumed these are P&G unpublished data.	Patlewicz et al. (2002)
							10	2.1							
							25	6.3							
			98.9	DEP:EtOH 3:1		4	5	1.22	26.8						RIFM unpublished
							10	1.38							
							25	1.85							
							50	18.3							
							100	38.8							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Citral, ctd.	5392-40-5	226-394-6	98.9	DEP:EtOH 3:1	na	4	0.5	1.1	NC/1B	n	na				RIFM unpublished
							1	1.3							
							2.5	1.0							
							5	1.3							
							10	1.2							
Citronellol	106-22-9	203-375-0	na	DEP:EtOH 3:1	na	na	2.5	1.6	43.5	n	na				P&G unpublished
							5	1.2							
							10	1							
							25	1.3							
							50	3.6							
Clofibrate	637-07-0	211-277-4	na	ACE	na	na	10	2.1	NC	n	na				P&G unpublished
							25	1.7							
							50	2.9							
Coumarin	91-64-5	202-086-7	na	AOO	CBA/J	4 or 5	5	2.7	NC/1B	n	na				Gerberick et al. (2005)
							10	2.0							
							25	2.3							
			99.9	DMF	Balb/c	4	10	1.9	NC						Vocanson et al. (2006)
							25	1.8							
							50	2.4							
Cyclamen aldehyde	103-95-7	203-161-7	As-sumed 100	AOO	CBA/Ca	4	1	1.4	22.3	n	na				Basketter et al (2001)
							2.5	1.3							
							10	1.8							
							25	3.3							
							50	51.6							
trans-Dec-2-enal	3913-71-1	223-474-2	na	AOO	na	na	0.5	1.3	2.5	n	na				Patlewicz et al. (2002)
							1	1.1							
							2.5	3							
							5	6							
							10	9.5							
DEET	134-62-3	205-149-7	na	ACE	na	na	1	0.4	NC	n	na				P&G unpublished
							5	0.5							
							10	0.5							
							20	0.5							
							40	1.1							
							60	1.3							
Diacetyl	431-03-8	207-069-8	na	na	na	na	5	1.4	11.3	n	na				Roberts et al. (1999)
							10	2.8							
							25	5.2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
2,5-Diaminotoluene sulfate	615-50-9	210-431-8	99.5	AOO	CBA/Ca/01a/Hsd	5	0.5	4.4	0.4	y	p				Wella unpublished
							1.5	10.4							
							2.8	19.4							
Dibenzoyl peroxide	94-36-0	202-327-6	70	ACE	CBA/Ca	5	0.5	14.6	1A	y	f		p	Not clear how the EC3 is calculated original publication reports EC3 <0.5.	Kimber et al. (1998)
							1	17.2							
							2.5	18.1							
							5	20.2							
							10	21.8							
					CBA/JHsd		0.5	24.4						According to 429 use of ^{125}I-UdR instead of 3H-TdR. IDR not clear how the EC3 is calculated original publication reports EC3 <0.5.	
							1	22.1							
							2.5	33.7							
							5	31.4							
							10	26.5							
							0.5	18.7						Not clear how the EC3 is calculated, original publication reports EC3 < 0.5. Calculated EC3 very far from the lowest tested concentration and lowest SI high.	
							1	21.0							
							2.5	24.9							
							5	24.8							
							10	18.6							
					CBA/Ca		0.5	23.4			p	f			
							1	22.8							
							2.5	21.8							
							5	22.5							
							10	16.8							
					CBA/ JHsd		0.5	14.7							
							1	7.9							
							2.5	10.9							
							5	20.5							
							10	17.3							
Dibenzyl ether	103-50-4	203-118-2	98.5	DEP:EtOH 3:1	na	4	1	0.9	6.3	n	na				RIFM unpublished
							2.5	2.2							
							5	2.2							
							10	5.2							
							25	6.1							
Dibutyl phthalate	84-74-2	201-557-4	na	AOO	CBA/Ca	4	10	1.4	NC	n	na			Extrapolation indicates EC3 >100	DK EPA report GM7919-58
							25	1.8							
							50	2.2							
N,N-Dibutylaniline	613-29-6	210-335-6	na	AOO	na	na	5	2	19.6	n	na				DK EPA report GM7919-58
							10	1.9							
							50	6.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
1,1-Dichloroethene	75-35-4	200-864-0	100	AOO	CBA/Ca	4	10	0.8	NC	n	na				Warbrick et al. (2001)
							25	0.8							
							50	0.9							
Diethyl maleate	141-05-9	205-451-9	na	AOO	CBA/Ca	4	1	2.1	2.1	n	na				Basketter et al. (1999)
							2.5	3.3							
							5	3.5							
							10	7.5							
							25	16							
			97				25	16.3	POS	y	p		f	Lowest SI is high and negative slope	Ryan et al. (2000)
							50	22.6							
							100	13.1							
Diethyl phthalate	84-66-2	201-550-6	99	AOO	CBA/Ca	4	25	1	NC	n	na				Ryan et al. (2000)
							50	1.3							
							100	1.5							
Diethyl sulfate	64-67-5	200-589-6	na	AOO	na	na	1	0.8	3.3	n	na				Ashby et al. (1995)
							2.5	1.9							
							10	12							
Diethylenetriamine	111-40-0	203-865-4	na	AOO	CBA/Ca	na	5	6.4	POS	y	f				Basketter et al (1994)
							10	6.1							
3,4-Dihydrocoumarin	119-84-6	204-354-9	na	AOO	na	na	2.5	1.6	5.6	n	na				Ashby et al. (1995)
							5	2.5							
							10	6.6							
Dihydroeugenol	2785-87-7	220-499-0	na	AOO	na	na	5.1	2.7	6.8	n	na				Smith & Hotchkiss, 2001
							10.1	3.6							
							25.3	7.8							
Dihydromyrcenol	18479-58-8	242-362-4	na	DEP:EtOH 3:1	CBA/Ca	4	0.5	0.9	NC/1B	n	na				RIFM unpublished
							1	0.8							
							2.5	0.8							
							10	0.9							
							25	1.4							
Dimethyl fumarate	624-49-7	210-849-0	> 97	DMF	CBA/J	5	0.03	1.4	0.35	n	na				Basketter et al. (2013)
							0.1	1.5							
							0.3	2.2							
							1	12.5							
							3	22.6							
3-(Dimethylamino)propylamine	109-55-7	203-680-9	99	DMF	CBA/Ca	4	0.5	1.5	NC/1B	n	na				Wright et al. (2001)
							1	1.7							
							2.5	4.4							
							5	6.4							
							10	15.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
3-(Dimethylamino)propylamine, ctd.	109-55-7	203-680-9	99	MEK	CBA/Ca	4	0.5	1.6	1.8	n	na				Wright et al. (2001)
							1	2.1							
							2.5	3.8							
							5	6.8							
							10	12.6							
				AOO			0.5	1.3	2.2						
							1	1.1							
							2.5	3.5							
							5	7.0							
							10	13.9							
				DMSO			0.5	1.4	3.5						
							1	1.3							
							2.5	2.1							
							5	5.4							
							10	9.0							
				90% EtOH			0.5	1.0	4.1						
							1	1.5							
							2.5	1.6							
							5	3.8							
							10	5.9							
				50% EtOH			0.5	1.0	7.1						
							1	0.9							
							2.5	1.7							
							5	1.2							
							10	5.5							
				PG			0.5	1.5	NC/1B	na					
							1	1.0							
							2.5	1.3							
							5	1.4							
							10	2.2							
							0.1	1.5							
							0.3	2.2							
							1	12.5							
							3	22.6							
Diphenylcyclopropenone	886-38-4	212-948-4	98	ACE	CBA/Ca	4	0.3	24.5	1A	y	na		f		Ryan et al. (2000)
							1	24.7							
							3	31.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Disodium 2-[4-[[2-cyano-3-[4-[methyl(2-sulphonatoethyl)-amino]phenyl]-1-oxoallyl]-amino]phenyl]-6-methylbenzo-thiazole-7-sulphonate	2498-95-5	219-694-3	na	1% aqueous Pluronic(R)	CBA	5	5	0.8	NC/1B	n	na				ECHA[25]
							10	1.1							
							25	1.0							
DMSO	67-68-5	200-664-3	na	AOO	na	na	25	2.7	72	n	na			There is no information on the primary source for this study. Estrada et al (2003) only report the EC3 without providing information on the doses and SIs. Possibly P&G in-house data	Estrada et al (2003)
							50	2.3							
							100	3.9							
DNBS, sodium salt	885-62-1	212-943-7	na	DMF	na	4 or 5	1	4.0	0.83	y	p			No extrapolation done in the report (Ryan et al. (2002) report EC3 < 1), but calculated to be 0.83	Ryan et al (2002)
							10	16.3							
							20	18.5							
				DMSO			1	1.7	2	n	na				
							10	13.7							
							20	16.1							
				1% aqueous Pluronic(R)			1	0.9	6.4						
							10	4.4							
							20	11.6							
DNCB	97-00-7	202-551-4	99	ACE	CBA/J	5	0.001	0.8	0.012	n	na			4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							0.05	10.7							
							0.1	21.1							
			98.9	DMSO	CBA/Ca	4	0.01	2.4	0.015						Betts et al. (2005)
							0.025	4.2							
							0.05	7.3							
							0.1	14.7							
							0.25	14.7							
			na	AOO		4 or 5	0.01	2	0.027						Kimber et al. (1995)
							0.025	2.3							
							0.05	5.3							
							0.1	10							
							0.25	35.5							
						4	0.02	2	0.029						Montelius et al (1994)
							0.1	10.5							
							0.1	23							

[25] https://echa.europa.eu/registration-dossier/-/registered-dossier/17095

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
DNCB, ctd.	97-00-7	202-551-4	99	AOO	CBA/JHsd	4 or 5	0.01	2.5	0.033	n	na			Use of ^{125}I-UdR instead of ^{3}H-TdR. EC3 (0.03) originally calculated by fitted quadratic equations. EC3 recalculated by applying the linear method (0.033).	Loveless et al. (1996)
							0.025	2.9							
							0.05	3.2							
							0.1	7.1							
							0.25	25							
			98.9		CBA/Ca	4	0.01	1.4	0.036						Betts et al. (2006)
							0.025	2.2							
							0.05	4.0							
							0.1	9.8							
							0.25	16.2							
			na		CBA/J	4 or 5	0.01	0.8	0.046					4 days treatment. Labelling and excision on day 4	Kimber et al. (1995)
							0.025	1.8							
							0.05	3.3							
							0.1	8.7							
							0.25	40.9							
			99		CBA/Ca		0.01	1.5	0.048					EC3 (0.05) originally calculated by fitted quadratic equations. EC3 recalculated by applying the linear method (0.048).	Loveless et al. (1996)
							0.025	1.9							
							0.05	3.1							
							0.1	6.5							
							0.25	25							
					CBA/JHsd		0.01	1.0	0.051					4 days treatment, labelling and excision on day 5. EC3 (0.06) originally calculated by fitted quadratic equations. EC3 recalculated by applying the linear method (0.051).	
							0.025	1.2							
							0.05	2.8							
							0.1	13							
							0.25	78							
					CBA/Ca		0.01	1.2	0.053					EC3 (0.06) originally calculated by fitted quadratic equations. EC3 recalculated by applying the linear method (0.053).	
							0.025	0.9							
							0.05	2.9							
							0.1	4.5							
							0.25	13							
					CBA/JHsd		0.01	1.5	0.055					4 days treatment, labelling and excision day 5. EC3 (0.04) originally calculated by fitted quadratic equations. Apparently a mistake in the calculation since EC3 cannot be lower than 0.05. Recalculated by applying linear method (0.055).	
							0.025	1.8							
							0.05	2.4							
							0.1	8.9							
							0.25	38							
			na		CBA/J		0.01	1.3	0.057						Kimber et al. (1995)
							0.03	1.5							
							0.05	2.1							
							0.1	7.7							
							0.25	43.9							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
DNCB, ctd.	97-00-7	202-551-4	na	AOO	BALB/c	5	0.03	1.6	0.06	n	na				Fukuyama et al. (2008)
							0.1	4.9							
							0.3	15.8							
							1	24.6							
					CBA/Ca	4 or 5	0.01	1.1	0.062						Kimber et al. (1995)
							0.03	1.4							
							0.05	2.5							
							0.1	4.6							
							0.25	11.5							
					BALB/C	4	na	na	0.0765					Concentrations and SIs shown in graph. EC3 values recorded in molar concentrations in the paper. The value was converted into %. Criteria are difficult to evaluate due to the graph format but visually the slope ratio is probably > 2.	Basketter et al. (1997)
					CBA/Ca		0.1	4.7	0.087	y	p			Radioactive labelling and excision on day 4	Kimber et al. (1991)
							0.25	15.8							
							0.5	26.8							
			99		CBA/J	4 or 5	0.01	0.8	0.096	n	na			Labelling and excision on day 5. Use of ^{125}I-UdR	Kimber et al. (1995)
							0.025	1.2							
							0.05	1.7							
							0.1	3.1							
							0.25	22.5							
						4	0.1	10.3	1A	y	p	f	p	Radioactive labelling and excision on day 4	Kimber et al. (1991)
							0.25	29.7							
							0.5	49.6							
							0.1	6.2							
							0.25	15.7							
							0.5	24.0							
					CBA/Ca		0.1	5.9							
							0.25	19.9							
							0.5	36.7							
EGDMA	97-90-5	202-617-2	na	MEK	na	na	10	1.2	28	n	na				Unilever, unpublished
							25	2.4							
							50	7							
Ethyl acrylate	140-88-5	205-438-8	98.5	AOO	CBA/Ca	4	10	1.2	28.7	n	na				Warbrick et al. (2001)
							25	2.7							
							50	5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Ethyl acrylate, ctd.	140-88-5	205-438-8	99.95	AOO	CBA/Ca	4	2.5	1.3	36.8	n	na				Dearman et al. (2007)
							5	1.5							
							10	1.4							
							25	2.1							
							50	4.0							
			99	ACE	B6C3F1	5	10	0.9	NC/1B	n	na			Labelling and excision on day 5	NTP, unpublished
							20	1.2							
							30	0.9							
Ethyl benzoylacetate	94-02-0	202-295-3	na	ACE	na	na	10	0.9	NC/1B	n	na				P&G, unpublished
							20								
							40	1.2							
Ethyl vanillin	121-32-4	204-464-7	97	AOO	CBA/Ca	4	2.5	0.7	NC	n	na				Basketter et al (2001)
							5	1.1							
							10	0.7							
							25	0.4							
							50	0.3							
			na		CBA/J		2.5	1.9							ECHA[26]
							5	1.7							
							10	1.4							
							25	1.4							
							50	1.6							
2-Ethylbutanal	97-96-1	202-623-5	na	AOO	na	na	25	1.2	76	n	na				Patlewicz et al (2002)
							50	0.8							
							75	2.4							
							100	16.3							
Ethylene brassylate	105-95-3	203-347-8	na	ACE	CBA/Ca	4	1	1.0	NC/1B	n	na				RIFM unpublished
							10	2.2							
							30	2.4							
Ethylene diamine (free base)	107-15-3	203-468-6	na	AOO	CBA/Ca	na	0.1	1.1	2.2	n	na				Kimber et al. (1998)
							0.25	1.2							
							0.5	1.6							
							1	1.9							
							2.5	3.3							
							5	6.1							
							10	17.4							

[26] https://echa.europa.eu/it/registration-dossier/-/registered-dossier/13700/7/5/2

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Ethylene diamine (free base), ctd.	107-15-3	203-468-6	na	ACE/ water 3:1	CBA/Ca	na	0.1	0.8	NC/1B	n	na				Kimber et al. (1998)
							0.25	1.7							
							0.5	1.1							
							1	1.2							
							2.5	1							
				ACE	CBA/J	5	1	1.1						4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							5	1.1							
							10	2.2							
2-Ethylhexyl acrylate	103-11-7	203-080-7	99.95	AOO	CBA/Ca	4	2.5	1.3	36.8	n	na				Dearman et al. (2007)
							5	1.5							
							10	1.4							
							25	2							
							50	3.97							
Eugenol	97-53-0	202-589-1	99	ACE	CBA/J	5	25	5.4	POS	y	p	f	f	4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							50	10.6							
							75	10.5							
			na	AOO	CBA/Ca	4	25	4.8				p		Radioactive labelling and excision on day 4	Kimber et al. (1991)
							50	9.3							
							100	7.6							
							25	7.2				f			
							50	10.2							
							100	8.2							
							25	44.7							
							50	70.3							
							100	68.1							
							25	5.5					na		
							50	14.1							
			98	AOO	CBA/JHsd	4 or 5	2.5	1.5	3.8	n	na			Use of ^{125}I-UdR instead of ^{3}H-TdR. EC3 of 6.0 calculated by fitted quadratic equation. The original EC3 does not match the data. Recalculated with standard interpolation	Loveless et al. (1996)
							5	1.3							
							10	4.6							
							25	14							
							50	6.1							
			99.9	EtOH:DEP 3:1	CBA/Ca	4	1	1.1	5.3						Lalko et al. (2004)
							3	2.2							
							10	4.7							
							30	8.6							
							50	18.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Eugenol, ctd.	97-53-0	202-589-1	99.9	DEP:EtOH 3:1	CBA/Ca	4	2.5	1.2	5.4	n	na				Lalko & Api (2006)
							5	2.7							
							10	6.0							
							25	14.3							
							50	19.4							
			98	AOO		4 or 5	2.5	2.0	7.5					EC3 of 5.8 calculated by fitted quadratic equation. Recalculated with standard interpolation	Loveless et al. (1996)
							5	2.8							
							10	3.2							
							25	13.0							
							50	17.0							
			99.9	EtOH:DEP 3:1		4	1	0.8	10.5						Lalko et al. (2004)
							3	1.7							
							10	2.8							
							30	9.2							
							50	10.6							
				EtOH			1	1.6	10.7						
							3	1.4							
							10	2.7							
							30	10.3							
							50	15.1							
			98	AOO	CBA/JHsd	4 or 5	2.5	1.1	12.5					4 days treatment, labelling and excision day 5. EC3 of 8.9 calculated by fitted quadratic equation. The original EC3 is clearly a mistake since at 10% the response is negative. Recalculated with standard interpolation.	Loveless et al. (1996)
							5	1.7							
							10	1.8							
							25	9.1							
							50	12.4							
					CBA/Ca		2.5	1.6	12.9					EC3 of 14.5 calculated by fitted quadratic equation. Recalculated with standard interpolation	
							5	1.5							
							10	2.4							
							25	5.5							
							50	16							
			na		na	4	10	2.4							Bertrand et al. (1997)
							25	55							
							50	16.1							
					BALB/c		5	0.6	13.8						Hilton et al. (1996)
							10	1.5							
							25	4							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Eugenol, ctd.	97-53-0	202-589-1	99.9	DEP	CBA/Ca	4	1	2	15.1	n	na				Lalko et al. (2004)
							3	1.1							
							10	1.8							
							30	6.5							
							50	6.4							
			98	AOO	CBA/JHsd	4 or 5	2.5	2.4	16.6					4 days treatment, labelling and excision day 5. EC3 of 13.8 calculated by fitted quadratic equation. Recalculated with standard interpolation.	Loveless et al. (1996)
							5	2.1							
							10	1.2							
							25	5.3							
							50	9.6							
Farnesal	502-67-0	242-957-9	na	AOO	na	na	1	0.6	12	n	na			Conc. and SI values taken from secondary reference. EC3 corresponds in both sources	Patlewicz et al. (2002), also cited in Gerberick et al. (20059
							2.5	1.1							
							5	1.7							
							10	2.5							
							25	7.0							
Farnesol	4602-84-0	225-004-1	0.98	AOO	na	4	5	3.8	4.1	y	p				RIFM unpublished
							10	6.7							
							25	12.7							
							5	2.8	5.5	n	na				
							10	4.7							
							25	17.6							
2-Fluoro-5-nitroaniline	369-36-8	206-720-3	na	AOO	CBA/Ca	4	5	1.5	NC	n	na			"Vehicle trial preparations indicated that the preferred vehicle AOO (4:1) provided a good dosing solution up to 40% (w/v).	DK EPA report GM7919-58
							10								
							25	1.6							
							40	1.2							
Formaldehyde	50-00-0	200-001-8	na	AOO	CBA/Ca	4	0.1	1.0	0.35	n	na				Basketter et al (2001)
							0.5	1.9							
							1	3.2							
							5	5.2							
							10	8.6							
							0.1	0.8	0.4					EC3 value corrected from 2.8 to 0.4	
							0.19	2.5							
							0.38	2.6							
							0.95	6.2							
							1.9	12							
				DMF			na	na	0.41					The EC3 value is reported in mol/L in the original publication. Conversion from mol/L to % should lead to an EC3 of 0.41%. SI values are reported in graph in the original publication	Hilton et al. (1998)

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Formaldehyde, ctd.	50-00-0	200-001-8	na	ACE	CBA/Ca	4	0.09	1.1	0.66	n	na			Could not cross-check SI values since the primary reference shows them only in a graph. However, they seem to correspond to what's reported by the secondary source.	Hilton et al. (1998), also cited in Gerberick et al. (2005)
							0.19	2.3							
							0.37	2.3							
							0.93	3.9							
							1.85	1.85							
				AOO			5	3.7	0.99	y	p			Radioactive labelling and excision on day 4	Kimber et al. (1991)
							10	4.0							
							25	5.8							
				DMF	CBA/J or CBA/Ca	4 or 5	1	6.7	1A	y	p	f	p		Ryan et al. (2002)
							10	13.2							
							20	17.7							
				DMSO			1	7.5							
							10	16.0							
							20	17.6							
				AOO	CBA/Ca	4	5	9.0	POS		f				Basketter et al (2001)
							10	10.6							
							25	11.9							
							5	6.8			p			Radioactive labelling and excision on day 4	Kimber et al. (1991)
							10	6.1							
							25	6.6							
							5	4.6							
							10	4.7							
							25	4.2							
				PG			0.38	1.1	2.8	n	na				Basketter et al (2001)
							0.95	1.6							
							1.9	1.5							
							3.8	3.2							
							9.5	8.5							
			36.5 - 38	1% Pluronic L92®	CBA/J	5	1	1.1	3.8					Formaldehyde 36.5%	BASF unpublished[27]
							5	3.8							
							20	10.6							
			na		CBA/J or CBA/Ca	4 or 5	1	2	4.2						Ryan et al. (2002)
							10	4.8							
							20	8.8							
			36.5-38	1% Pluronic L92®	CBA/J	5	1	1.6	5.6					Formaldehyde 36.5%	Dow Chemical, unpublished[26]
							5	2.6							
							20	12							

[27] ECPA LLNA project submitted to NICEATM

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Formaldehyde, ctd.	50-00-0	200-001-8	36.5-38	1% Pluronic L92®	CBA/J	5	1	1.0	8	n	na				Bayer, unpublished[26]
							5	2.2							
							20	6.2							
							1	1.1	8.2						Dupont, unpublished[26]
							5	2.5							
							20	4.8							
							1	0.9	12.3						Syngenta/RCC, unpublished[26]
							5	1.3							
							20	4.8							
			na	water	CBA/J or CBA/Ca	4 or 5	1	1.2	14.5						Ryan et al. (2002)
							10	2.5							
							20	3.6							
Furil	492-94-4	207-766-7	na	AOO	na	na	5	1.2	NC/1B	n	na				Roberts et al. (1999)
							10	1.7							
							25	2.2							
Geraniol	106-24-1	203-377-1	98.5	EtOH	CBA/Ca	4	1	1.5	5.6	n	na				Lalko et al. (2004)
							3	2.2							
							10	4.3							
							30	7.3							
							50	11.6							
				DEP:EtOH 3:1			2.5	1.7	11.4						Lalko & Api (2006)
							5	2.4							
							10	2.8							
							25	4.8							
							50	6.0							
				DEP			1	1.7	11.8						Lalko et al. (2004)
							3	1.7							
							10	2.8							
							30	5.0							
							50	7.8							
				DEP:EtOH 3:1			1	0.9	20.4						
							3	1.3							
							10	2.3							
							30	3.7							
							50	3.8							
				EtOH:DEP 3:1			1	1	26						
							3	1							
							10	1.3							
							30	3.4							
							50	3.9							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Geraniol, ctd.	106-24-1	203-377-1	na	AOO	CBA/Ca	4	12.5	0.9	57	n	na				Basketter et al. (1994)
							25	1.2							
							50	2.6							
Glutaraldehyde	111-30-8	203-856-5	na	AOO	CBA/Ca	4	0,,04	1.6	0.07	n	na			Glutaraldehyde (52% aqueous)	Basketter et al (2001)
							0.05	2.4							
							0.13	4.9							
							0.26	5.1							
							0.52	11.3							
			"Grade I"	DMF		na	0.1	4.9	0.07	y	p				Azadi et al. (2004)
							0.75	16.4							
							2.5	31.5							
							0.1	3.5	0.089						
							0.75	12.7							
							2.5	25.5							
			na	PG		4	0.26	1	1.5	n	na			Glutaraldehyde (52% aqueous)	Basketter et al (2001)
							0.52	1.3							
							1.3	2.4							
							2.6	6.9							
				DMF		na	na	na	POS					Concentrations and SIs shown in graph. Criteria are difficult to evaluate due to graph format but the slope ratio is probably greater than 2.	Hilton et al. (1998)
				ACE						y					
				DMF: water 1:1	CBA/J	5	3.1	9.8			p	f	p	4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							6.2	21.4							
							12.5	22.9							
Glycerol	56-81-5	200-289-5	99	DMF	CBA/Ca	4	25	1.1	NC	n	na				Ryan et al. (2000)
							50	0.7							
							100	0.5							
			na		CBA/J	5	10	0.8						4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							25	0.6							
							50	0.9							
Glyoxal	107-22-2	203-474-9	na	AOO	na	na	1	2.5	1.4	n	na				Patlewicz et al. (2002)
							2.5	4.2							
							5	5.2							
							10	10.3							
							25	15.8							
				DMF			5	18.1	POS	y	p	f		Not clear how the EC3 was calculated the publication only reports positive or negative outcomes.	Basketter et al. (1994)
							10	13.6							
							25	12.2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Helional	1205-17-0	214-881-6	na	EtOH:DEP	CBA/Ca	4	2.5	1	16.4	n	na			Study provided by P&G. GLP study report available	RIFM, unpublished
							5	2.7							
							10	2.4							
							25	3.8							
							50	8.3							
Hepta-2,4-dienal	5910-85-0	227-627-4	na	AOO	na	na	0.5	1.1	4	n	na			No information available on doses and Sis in the Estrada et al (2003) paper. The EC3 corresponds in both publications	Estrada et al (2003), also cited in Gerberick et al. (2005)
							1	1.4							
							2.5	1.9							
							5	3.7							
							10	8.1							
n-Hexane	110-54-3	203-777-6	na	AOO	CBA/Ca	4	25	0.8	NC	n	na				Basketter et al. (1998)
							50	0.8							
							100	2.2							
trans-Hex-2-enal	6728-26-3	229-778-1	98.5	DEP:EtOH 3:1	na	4	0.5	0.8	2.6	n	na				RIFM, unpublished
							1	1.4							
							2.5	2.8							
							5	8.4							
							10	12.6							
			na	AOO		na	0.5	1.2	5.5						Estrada et al (2003)
							1	1.2							
							2.5	2.3							
							5	2.6							
							10	6.4							
Hexyl salicylate	6259-76-3	228-408-6	98.5	DEP:EtOH 3:1	na	4	0.05	1.9	0.18	n	na				RIFM, unpublished
							0.25	3.6							
							0.5	5.6							
							1	10.8							
							2.5	10.8							
			na	DMF		na	0.7	0.9	NC/1B						P&,G unpublished
							3.5	0.88							
							14	0.91							
							28	0.72							
α-Hexylcinnamaldehyde	101-86-0	202-983-3	85	ACE	CBA/CaOlaHsd	5	3	4.6	1.2	y	p				BASF ,unpublished[28]
							10	6.6							
							30	9.9							
					CBA/J		1	1.8	2.7	n	na				
							3	3.2							
							10	3.7							

[28] Submitted to NICEATM by C. Hastings

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
α-Hexylcinnamaldehyde, ctd.	101-86-0	202-983-3	na	AOO	CBA/Ca	4	2.5	2.2	4.4	n	na				Basketter et al. (1999)
							5	3.2							
							10	7.1							
							25	13.9							
							50	17.6							
			85	ACE	DBA/2	5	5	3	5						Woolhiser et al. (2000)
							25	6.9							
							50	12							
			na	AOO	CBA/Ca	4	2.5	1.7	6.6						Basketter et al. (1999)
							5	2.1							
							10	4.4							
							25	8.1							
							50	14.5							
			95	1% Pluronic L92(R)	CBA/J	5	3	1.2	6.7						BASF unpublished[29]
							10	4.6							
							30	18							
			85	AOO	CBA/JHsd	4 or 5	2.5	1.1	6.8					4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							5	2.2							
							10	4.4							
							25	9.8							
							50	20							
			95	1% Pluronic L92	CBA/J	5	3	1.9	7						Bayer unpublished[28]
							10	4.2							
							30	9.2							
			85	AOO	CBA/Ca	4 or 5	2.5	1.3	7.6						Loveless et al. (1996)
							5	1.5							
							10	10							
							25	25							
							50	50							
					CBA/JHsd		2.5	1.3	7.9					Use of ^{125}I-UdR instead of ^{3}H-TdR	
							5	1.3							
							10	4.2							
							25	8.8							
							50	17							
				ACE	CBA/J	5	1	1.84	8						BASF unpublished[30]
							3	2.35							
							10	3.26							

[29] ECPA LLNA project submitted to NICEATM

[30] Submitted to NICEATM by C. Hastings

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
α-Hexylcinnamaldehyde, ctd.	101-86-0	202-983-3	85	AOO	CBA/Ca	4 or 5	2.5	1.4	8.8	n	na				Loveless et al. (1996)
							5	2.1							
							10	3.3							
							25	8.3							
							50	14							
			na			4	2.5	1.3	10.6					Corrected EC3 from 10.9 to 10.6 as reported in the paper	Basketter et al. (1999)
							5	2.1							
							20	2.7							
							25	7.8							
							50	13.4							
			85			4 or 5	2.5	1.7							Dearman et al. (2001)
							5	2.2							
							10	2.8							
							25	8.2							
			95	1% Pluronic L92	CBA/J	5	3	1.1	10.8						Dupont unpublished[31]
							10	2.5							
							30	15.6							
			85	AOO	CBA/JHsd	4 or 5	2.5	1.3	11					4 days treatment, labelling and excision day 5 EC3 of 8.4 calculated by fitted quadratic equation. It seems the value does not fit the data. Recalcualted by Canada to be 11%.	Loveless et al. (1996)
							5	1.1							
							10	2.5							
							25	10							
							50	17							
			na		CBA/Ca	4	2.5	1.7	11.3						Basketter et al. (1999)
							5	2.1							
							10	2.4							
							25	7.2							
							50	14.1							
			85	ACE	CBA	5	5	2.5	11.3						Woolhiser et al. (2000)
							25	4.1							
							50	9.4							
			na	AOO	CBA/Ca	4	2.5	1	11.5						Basketter et al. (1999)
							5	1.4							
							10	2							
							25	8.7							
							50	11.6							
			85			4 or 5	5	1.6	11.7						Dearman et al. (2001)
							10	2.5							
							25	6.8							

[31] ECPA LLNA project submitted to NICEATM

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
α-Hexylcinnamaldehyde, ctd.	101-86-0	202-983-3	85	AOO	CBA/Ca	4 or 5	5	1.4	11.7	n	na				Dearman et al. (2001)
							10	2.7							
							25	5.3							
			95	Pluronic L92 (1%)	CBA/J	5	3	1.9	12						Dow Chemical unpublished[32]
							10	2.2							
							30	10.3							
			85	ACE	BALB/c		5	1.7	12.9						Woolhiser et al. (2000)
							25	5							
							50	10.9							
				AOO	CBA/Ca	4	1	1.0	14.7						Basketter et al (2001)
							2.5	1							
							5	1.5							
							10	1.8							
							25	5.7							
			95	Pluronic L92 (1%)	CBA/J	5	3	1.3	17.6						Syngenta/RCC unpublished[31]
							10	2.2							
							30	4.3							
			85	ACE	C57BL:6		5	1.4	21.8						Woolhiser et al. (2000)
							25	3.3							
							50	5.1							
					B6C3F1		5	1	25.5						
							25	2.9							
							50	8							
					SJL		5	1.4	33.8						
							25	2.4							
							50	4.1							
					CBA		10	4.3	POS	y	p		f		BASF unpublished[33]
							30	7.3							
							50	7.1							
				AOO	CBA/CaOl aHsd		2.5	1.1	NC/1B	n	na				
							5	1.2							
							10	2.8							
2-Hexylidenecyclopentanone	17373-89-6	241-411-7	na	DEP:EtOH 3:1	na	5	0.1	1.2	2.4	n	na				RIFM unpublished
							0.5	1.5							
							2.5	3.1							
							5	2.5							

[32] ECPA LLNA project submitted to NICEATM

[33] Submitted to NICEATM by C. Hastings

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
HHPA	85-42-7	201-604-9	98	AOO	BALB/c	4	0.25	0.92	0.84	n	na				Dearman et al. (2000)
							0.5	2.08							
							1	3.43							
							2.5	7.85							
							5	13.2							
Hydratropaldehyde	93-53-8	202-255-5	na	AOO	na	na	0.5	2.0	6.3	n	na			SI values from Gerberick et al. (2005). The EC3 corresponds in both publications	Patlewicz et al. (2002), also cited in Gerberick et al. (2005)
							1	2.2							
							2.5	1.0							
							5	2.2							
							10	5.2							
Hydrocortisone	50-23-7	200-020-1													
Hydroquinone	123-31-9	204-617-8	> 99	ACE	CBA/Ca	4	0.05	1.3	0.07	n	na				Lea et al. (1999)
							0.1	5.6							
							0.25	13							
							0.5	15.3							
							1	24.1							
							0.05	1.8	0.08						
							0.1	3.9							
							0.25	9.3							
							0.5	25.7							
							1	25.1							
				MEK			0.05	2.2							
							0.1	3.6							
							0.25	14							
							0.5	19.8							
							1	30.9							
							0.05	1.9	0.1						
							0.1	2.9							
							0.25	13.9							
							0.5	23							
							1	24.5							
				AOO			0.05	1.3	0.11						
							0.1	2.7							
							0.25	9.2							
							0.5	14.7							
							1	25.8							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Hydroquinone, ctd.	123-31-9	204-617-8	> 99	AOO	CBA/Ca	5	0.1	2.8	0.11	n	na				Kimber et al. (1998)
							0.25	5.8							
							0.5	13.7							
							1	15.2							
							2.5	13.1							
						5	0.1	2.5	0.12	n	na			EC3 value recalculated	Kimber et al. (1998)
							0.25	5.8							
							0.5	6.0							
							1	8.4							
							2.5	12.2							
							0.1	2.4	0.12						
							0.25	7.0							
							0.5	11.1							
							1	15.9							
							2.5	15							
				DMF		4	0.05	1.3	0.19						Lea et al. (1999)
							0.1	1.2							
							0.25	4.3							
							0.5	11.2							
							1	12.1							
							0.05	0.8	0.19						
							0.1	1.8							
							0.25	3.7							
							0.5	7.3							
							1	8.0							
							0.05	1.6	0.23						
							0.1	1.8							
							0.25	3.2							
							0.5	7.7							
							1	10.9							
				DMSO			0.05	1.1	0.33						
							0.1	0.9							
							0.25	2.6							
							0.5	4.0							
							1	4.2							
							0.05	1.2	0.37						
							0.1	1.2							
							0.25	1.9							
							0.5	4.2							
							1	6.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Hydroquinone, ctd.	123-31-9	204-617-8	> 99	ACE: saline 1:1	CBA/Ca	5	0.05	0.7	1.3	n	na			The authors performed a first study up to 1%. Then they did a second study with 3 concentrations, i.e. 2.5%, 5% and 10%. This entry reports the combination of the two studies. The study was performed in the same laboratory, using the same mouse strain, same vehicle and experimental schedule.	Lea et al. (1999)
							0.1	1							
							0.25	0.9							
							0.5	1.9							
							1	1.9							
							2.5	6.8							
							5	10.9							
							10	11.1							
				PG			0.05	1.5	1.67					Combination of two studies as above. Changed value from NC as in Hoffmann et al. to 1.67.	
							0.1	1							
							0.25	1							
							0.5	1.1							
							1	1							
							2.5	5.5							
							5	13.7							
							10	19.4							
				AOO	CBA/JHsd		0.1	3.6	1A	y	p		f		Kimber et al. (1998)
							0.25	4.8							
							0.5	12							
							1	15.3							
							2.5	23.2							
							0.1	3.2						Use of ^{125}I-UdR instead of ^{3}H-TdR. No EC3 value reported in the publication with the note: dataset inappropriate for derivation of EC3 value by extrapolation. It is unclear, why. Nevertheless it shows a clear effect at very low concentration.	
							0.25	14.9							
							0.5	23.7							
							1	25.3							
							2.5	33.4							
				ACE: saline 1:1	CBA/Ca	4	0.05	1.4	NC/1	n	na				Lea et al. (1999)
							0.1	0.8							
							0.25	1.2							
							0.5	1.39							
							1	1.9							
				PG			0.05	0.7							
							0.1	0.9							
							0.25	1.2							
							0.5	1.9							
							1	2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
4-Hydroxybenzoic acid	99-96-7	202-804-9	99.9	DMSO	CBA/CaOlaHsd	4	5	0.9	NC	n	na			Reported that 25% solution in DMSO is the technically highest possible concentration. Extrapolation indicates EC3 > 100	ECHA[34]
							10	0.9							
							25	1.0							
			na		na	na	5	1.4						Not among the publications quoted in Ashby et al. 1995. Assumed to be an unpublished study. Reported that 25% solution in DMSO is the technically highest possible concentration.	Unknown, cited in Ashby et al. (1995)
							10	1.5							
							25	1.3							
Hydroxycitronellal	107-75-5	203-518-7	na	DMF	CBA/Ca	4	1	1.3	18.8	n	na				Montelius et al (1994)
							5	2.1							
							25	3.4							
			98.7	DEP:EtOH 3:1			1	1.1	19.3						Lalko et al. (2004)
							3	0.9							
							10	2.1							
							30	4							
							50	6.2							
				DEP			1	1.3	19.7						
							3	1.5							
							10	1.8							
							30	4.2							
							50	5.3							
			na	AOO			25	3.6	20	y	p			Labelling and excision on day 5 or 6. Reference indicates that majority of reported compounds were more than 98% pure. No information on purity for individual substances.	Basketter and Scholes (1992)
							50	5.9							
							100	8.5							
			98.7	EtOH:DEP 3:1			1	1.6	22.2	n	na				Lalko et al. (2004)
							3	1.6							
							10	1.4							
							30	4							
							50	5.8							
			na	AOO			10	1.7	23						Basketter et al. (1994)
							25	3.2							
							50	6.7							
			98.7	EtOH			1	1.3	26.4						Lalko et al. (2004)
							3	1.0							
							10	1.6							
							30	3.3							
							50	7.2							

[34] https://echa.europa.eu/it/registration-dossier/-/registered-dossier/15944/7/5/2, last accessed 2021-07-10

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Hydroxycitronellal, ctd.	107-75-5	203-518-7	100% assum-ed	AOO	CBA/Ca	4	2.5	2.2	33	n	na				Basketter et al (2001)
							5	1.0							
							10	0.8							
							25	1.1							
							50	4.0							
2-Hydroxyethyl acrylate	818-61-1	212-454-9	na	AOO	CBA/Ca	4	10	12.8	POS	y	na	f	f	The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported.	Scholes et al. (1992)
							25	8.6							
							50	9.9							
							5	10.7	POS		p		p		
							10	14.8							
							25	18.1							
				DMF			10	13.8	POS				f		
							25	11							
							50	11.7							
				AOO			10	9	POS				na	Labelling and excision on day 5 or 6. The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported.	Basketter and Scholes (1992)
							25	8.2							
							50	na[35]							
2-Hydroxypropyl methacrylate	923-26-2	213-090-3	na	AOO	CBA/Ca	4	10	1.1	NC	n	na			Tested up to 50% with SI ≤ 2.5. The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported. Extrapolation indicates EC3 >100	
							25	1.2							
							50	1.3							
Imidazolidinyl urea	39236-46-9	254-372-6	na	DMF	CBA/Ca	4	10	1.7	24	n	na			The publication reports that the vast majority of the compounds reported were more than 98% pure. No specific information of the purity of each single compound available	
							25	3.1							
							50	5.5							
Iodocarb	55406-53-6	259-627-5	na	AOO	na	na	0.1	0.7	0.9	n	na				Siebert (2004)
							1	3.4							
							5	4.2							
							10	12							
1-Iodohexane	638-45-9	211-339-0	na	AOO	na	na	10	0.9	na	n	na			Tested up to 50% with SI ≤ 2.5. Extrapolation indicates EC3 >100	Unilever unpublished
							25	1.2							
							50	1.5							
Isobergamate	68683-20-5	272-066-0	na	DEP:EtOH 3:1	na	5	0.5	1.2	NC/1B	n	na				RIFM, unpublished
							1	1.0							
							2.5	1.3							
							5	1.2							
							10	1.6							

[35] Due to toxicity

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Isobornyl acetate	125-12-2	204-727-6	na	DEP:EtOH 3:1	CBA/Ca/ Ola/Hsd	4	1	1	NC/1B	n	na				RIFM unpublished
							2.5	1							
							5	1.2							
							10	1.4							
							25	1.7							
p-Isobutyl-α-methylhydrocinnamaldehdye	6658-48-6	229-695-0	99	70% EtOH	na	4	10	3.3	9.5	n	na				RIFM unpublished
							25	8.3							
							50	19.8							
							100	34.3							
2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol	63500-71-0	613-238-0	na	DEP:EtOH 3:1	CBA/J	5	7.5	0.73	NC/1B	n	na				RIFM unpublished
							15	0.74							
							30	0.63							
Isoeugenol	97-54-1	227-678-2	99	AOO	CBA/Ca	5	0.5	0.9	0.5	n	na			Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	6.3							
							5	31.0							
					CBA		0.5	2.3	0.6						
							1	1.6							
							5	23.6							
							0.5	1.6							
							1	2.2							
							5	19.0							
							0.5	1.8							
							1	2.9							
							5	23.2							
							0.5	1.5							
							1	2.5							
							5	29.8							
							0.5	1.6							
							1	4.3							
							5	24.4							
					CBA/Ca		0.5	1.2	0.7						
							1	4.2							
							5	18.4							
							0.5	1.5	0.8						
							1	2.6							
							5	19.2							
					CBA		0.5	1.1							
							1	1.8							
							5	23.2							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Isoeugenol, ctd.	97-54-1	227-678-2	99	AOO	CBA	5	0.5	1.5	0.8	n	na			Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	3							
							5	19.2							
				DMSO	CBA/Ca	4	0.5	1.9	0.9						Wright et al. (2001)
							1	3.2							
							2.5	7.4							
							5	20							
							10	17.1							
				AOO	CBA/Ca	5	0.5	1.3	1.0					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	2.2							
							5	13.1							
					CBA		0.5	1.6							
							1	1.6							
							5	14.7							
							0.5	1.6							
							1	1.4							
							5	14.7							
							0.5	0.7							
							1	2.3							
							5	13.8							
							0.5	1.1							
							1	1.9							
							5	15.3							
					CBA/Ca	4	0.5	1.8							Wright et al. (2001)
							1	2.9							
							2.5	7.7							
							5	11.1							
							10	11.7							
				MEK			0.5	0.9							
							1	3.2							
							2.5	5							
							5	4.9							
							10	8.1							
				AOO	CBA/Ca	5	0.5	0.8	1.1					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	1.6							
							5	14.1							
					CBA		0.5	1	1.2						
							1	1							
							5	12.8							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Isoeugenol, ctd.	97-54-1	227-678-2	99	AOO	CBA/Ca	5	0.5	1.2	1.3	n	na			Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	3.2							
							5	8.7							
			98			4 or 5	0.25	1.5							Loveless et al. (1996)
							0.5	2.2							
							1	2.5							
							2.5	4.9							
							5	10.0							
					CBA/JHsd		0.25	1.2	1.4					Use of ^{125}I-UdR instead of ^{3}H-TdR	
							0.5	1.7							
							1	2.6							
							2.5	4.3							
							5	11							
			99	DMF	CBA/Ca	4	0.5	2.6							Wright et al. (2001)
							1	2.7							
							2.5	3.7							
							5	7.5							
							10	11.6							
				AOO		5	0.5	1.3	1.5					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	3.3							
							5	14.7							
					CBA		0.5	2.0	1.6						
							1	1.4							
							5	7.6							
							0.5	1.6							
							1	2.2							
							5	7.5							
			98		CBA/JHsd	4 or 5	0.25	2.9	1.7					4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							0.5	1.7							
							1	2.3							
							2.5	3.8							
							5	6.8							
			99		CBA/Ca	5	0.5	1.2	1.8					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	1.4							
							5	19.3							
							0.5	1.0							
							1	1.3							
							5	7.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Isoeugenol, ctd.	97-54-1	227-678-2	99	EtOH (10%)	CBA/Ca	4	0.5	1.8	1.8	n	na				Wright et al. (2001)
							1	2							
							2.5	3.8							
							5	5.8							
							10	12.6							
				AOO		5	0.5	0.9	1.9					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	1							
							5	7.2							
					CBA		0.5	1.4	2						
							1	1.2							
							5	6.7							
					CBA/Ca		0.5	0.8	2.1						
							1	2.8							
							5	5.6							
			na			4	2.5	4.2	2.2	y	p			Radioactive labelling and excision on day 4	Kimber et al. (1991)
							5	11.8							
							10	21.3							
			99	PG		4	0.5	0.8	2.5	n	na				Wright et al. (2001)
							1	1.6							
							2.5	3							
							5	5.3							
							10	8.5							
				AOO	CBA	5	0.5	1.4	2.6					Studies carried out over a 4-year period as positive control.	Basketter & Cadby (2004)
							1	1.5							
							5	4.9							
							0.5	1.7							
							1	1.2							
							5	5							
			98		CBA/JHsd	4 or 5	0.25	0.7	2.9					4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							5	0.7							
							1	0.9							
							2.5	2.1							
							5	7.2							
					CBA/Ca		0.25	1	3.5						
							5	1.3							
							1	2.1							
							2.5	2.3							
							5	4.1							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Isoeugenol, ctd.	97-54-1	227-678-2	99	50% EtOH	CBA/Ca	4	0.5	1.0	5	n	na				Wright et al. (2001)
							1	1.2							
							2.5	2.0							
							5	3.0							
							10	5.4							
			na	AOO	BALB/c		5	2.8	6.4						Hilton et al. (1996)
							10	3.5							
							25	11							
				na	na	na	2.5	6.6	POS	y	p		f	Could not find the study in any of the publications quoted in Ashby et al. 1995.	Unknown, cited in Ashby et al. (1995)
							5	11.1							
							10	12.9							
				AOO	CBA/Ca	4	2.5	7.5						Radioactive labelling and excision on day 4	Kimber et al. (1991)
							5	13.1							
							10	25.3							
							2.5	7.8							
							5	13.1							
							10	14.6							
							2.5	9.9							
							5	17							
							10	29.5							
α-Isomethylionone	127-51-5	204-846-3	na	EtOH: DEP	CBA/Ca	5	2.5	0.6	21.8	n	na			Study provided by P&G. GLP study report available.	RIFM, unpublished
							5								
							10	1.5							
							25	3.4							
							50	4.6							
Isopropanol	67-63-0	200-661-7	na	AOO	na	4	10	1.7	NC	n	na				Basketter et al. (1998)
							25	1.1							
							50	1							
Isopropyl myristate	110-27-0	203-751-4	98	AOO	CBA/J	5	25	2.1	44	n	na				Ryan et al. (2000)
							50	3.3							
							100	3.4							
Kanamycin	59-01-8	200-411-7	na	AOO	na	na	5	2.2	NC	n	na				Basketter et al. (1996)
							10	0.8							
							25	1.0							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Kathon CG	55965-84-9	611-341-5; 911-418-6	na	AOO	CBA/Ca	4	7.5E-4	0.9	0.0049	n	na				Warbrick et al. (1999b)
							0.0015	1.2							
							0.0075	4.4							
							0.015	9.1							
							0.0375	8.5							
				MEK			0.0015	0.9	0.00675						
							0.0075	3.3							
							0.015	8.4							
							0.0375	14							
							0.075	17.6							
				DMF			0.0015	1.5	0.0075						
							0.0075	3							
							0.015	4.7							
							0.0375	10.3							
							0.075	28							
				DMSO			0.0015	1							
							0.0075	3							
							0.015	9.5							
							0.0375	6.4							
							0.075	10.3							
				ACE			0.0015	1.2	0.00762						
							0.0075	2.9							
							0.015	9.3							
							0.0375	17.7							
							0.075	23.5							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Kathon CG, ctd.	55965-84-9	611-341-5; 911-418-6	na	AOO	CBA/Ca	4	3.8E-3	1.3	0.0082	n	na				Basketter et al. (2003)
							0.0075	2.6							
							0.015	7							
							0.0375	10.9							
							0.075	14							
				PG			0.0015	2	0.0484						Warbrick et al. (1999b)
							0.01	8							
							0.02	2.1							
							0.04	2.3							
							0.08	4.7							
				PG			3.8E-3	0.8	0.063						Basketter et al. (2003)
							0.0075	0.8							
							0.015	0.8							
							0.0375	1.5							
							0.075	3.7							
				ACE	CBA/J	5	0.005	8.1	1A	y	p	f	p	4 exposures with labelling and excision on day 5	Gerberick et al (1992)
							0.05	27.8							
							0.1	48.2							
Lactic acid	50-21-5	200-018-0	na	DMSO	na	na	5	1	NC	n	na			Expert group consensus NC: chemical is an irritant at higher concentrations	Basketter et al. (1998)
							10	1.4							
							25	2.2							
Lauryl gallate	1166-52-5	214-620-6	na	DMSO	na	na	1	12.1	1A	y	p		f		P&G unpublished
							10	29.7							
							25	29.3							
							50	36							
Lilial	80-54-6	201-289-8	98.6	EtOH	na	4	1	1.6	3	n	na				RIFM, unpublished
							3	3.0							
							10	4.5							
							30	3.0							
							50	15.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Lilial, ctd.	80-54-6	201-289-8	98.6	DEP	na	4	1	1.9	4.2	n	na				RIFM, unpublished
							3	2.6							
							10	4.9							
							30	5.9							
							50	9.2							
			98.4	EtOH:DEP 3:1			0.3	0.9	8.6						
							1	1.1							
							3	1.6							
							10	3.3							
							30	8.5							
			98.6	DEP:EtOH 3:1			0.3	1.3	13.9						
							1	1.3							
							3	1.3							
							10	2.6							
							30	4.8							
			na	AOO			1	1.3	18.6						
							2.5	2.5							
							10	2.0							
							25	3.7							
							50	9.3							
D-Limonene	5989-27-5	227-813-5	na	AOO	CBA/J	4	1	1.6	36	n	na				Wei et al. (2010)
							25	2.3							
							100	7.1							
			99		CBA/Ca		25	1.8	69						Warbrick et al. (2001)
							50	2.4							
							100	4							
Linalool	78-70-6	201-134-4	97	AOO	CBA/Ca	4	25	2.5	30	n	na				Ryan et al. (2000)
							50	4.8							
							100	8.3							
			99.14	water-free DMF	na	5	25	2.5	35.5						RIFM unpublished
							50	3.7							
							100	4.3							
			97	AOO		4	25	1.9	46.2						Sköld et al. (2004)
							50	3.2							
							100	3.0							
Maleic anhydride	108-31-6	203-571-6	99	na	BALB/c	4	0.1	1.9	0.16	n	na				Dearman et al. (2000)
							0.25	1.9							
							0.5	6.3							
							1	14.0							
							2.5	16.0							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
2-Mercaptobenzothiazole	149-30-4	205-736-8	na	DMF	CBA/Ca	4	1	3.0	1.0	n	na				Montelius et al (1994)
							5	9.9							
							25	17.1							
			98				1	1.0	1.7						Basketter et al., (1993)
							3	3.0							
							10	10.0							
			na				10	4.5	POS	y	p	p	f	The paper indicates the majority of chemicals had a purity above 98%, but specific chemicals' purities are not reported.	Scholes et al. (1992)
							25	4.6							
							50	5.5							
							10	9.8				f			
							25	9.5							
							50	8.9							
							10	10.0							
							25	10.8							
							50	8.1							
							10	5.2							
							25	9.1							
							50	4.8							
2-Methoxy-p-cresol	93-51-6	202-252-9	na	AOO	na	na	4.2	1.8	5.4	n	na			There is no reference to this study in the Estrada publication, it only reports the EC3. It is assumed this is an unpublished study.	Unknown, cited in Estrada et al (2003)
							8.4	5.0							
							21	8.5							
1-(4-Methoxyphenyl)pent-1-en-3-one	104-27-8	203-190-5	99	AOO	CBA/J	4	10	3.5	9.3	y	y				Ryan et al. (2000)
							25	10.0							
							50	26.1							
Methyl acrylate	96-33-3	202-500-6	99.94	AOO	CBA/Ca	4	1	0.8	20	n	na				Dearman et al. (2007)
							2.5	0.8							
							5	1.3							
							10	1.6							
							25	3.8							
Methyl 3-bromoproprionate	3395-91-3	222-247-5	na	AOO	CBA/Ca	4	10	1.1	NC	n	na				DK EPA report GM7919-58
							25	0.9							
							50	1.3							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Methyl dihydrojasmonate	24851-98-7	246-495-9	na	AOO	CBA/J	5	1	1.7	NC/1B	n	na				RIFM, unpublished
							5	1.0							
							10	1.0							
							20	1.2							
							40	1.7							
							1	0.7							
							10	3.6							
Methyl methacrylate	80-62-6	201-297-1	99.96	ACE	CBA/Ca	4	10	1.5	60	n	na				Betts et al. (2006)
							30	2.3							
							50	2.0							
							75	4.4							
							100	7.3							
							10	1.4	90						
							30	1.5							
							50	1.5							
							75	2.1							
							100	3.6							
Methyl methanesulphonate	66-27-3	200-625-0	na	AOO	na	na	0.25	0.7	8.1	n	na				Ashby et al. (1995)
							1								
							10	3.6							
Methyl non-2-ynoate	111-80-8	203-909-2	99	EtOH	CBA/Ca	4	5	10.4	POS	y	p	f	p	Expert group consensus to use it only for binary classification. Different extrapolation methods provide different answers (1A or 1B)	Ryan et al. (2000)
							10	17.7							
							20	24.4							
Methyl oct-2-ynoate	111-12-6	203-836-6	na	EtOH:DEP	na	na	0.05	1.7	0.5	n	na				RIFM, unpublished
							0.1	1.7							
							0.25	1.8							
							0.5	3.3							
							1	8.7							
Methyl pyruvate	600-22-6	209-987-4	na	AOO	na	na	1	1.2	2.4	n	na				Patlewicz et al. (2004)
							2.5	3.1							
							5	4.7							
							10	8.0							
Methyl o-toluate	89-71-4	201-932-2	na	DEP:EtOH 3:1	CBA/J	5	7.5	1.13	NC/1B	n	na				ECHA[36]
							15	1.59							
							30	1.22							
1-(3-Methyl-2-benzofuranyl)ethanone	23911-56-0	429-100-6	na	ACE	CBA/Ca/ Ola/Hsd	4	1	0.67	NC/1B	n	na				RIFM unpu,blished
							10	1.57							
							30	1.87							

[36] https://echa.europa.eu/registration-dossier/-/registered-dossier/20425, last accessed 2021-07-10

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
α-Methylcinnamaldehyde	101-39-3	202-938-8	na	AOO	na	na	1	1.8	4.5	n	na			The Basketter 1999 paper reports only doses and SIs for Hexylcinnamaldehyde.	Basketter et al. (1999), also cited in Gerberick et al. (2005)
							2.5	1.5							
							5	3.4							
							10	3.3							
							25	15.3							
6-Methylcoumarin	92-48-8	202-158-8	na	ACE	na	na	5	1.0	NC/1B	n	na				Ashby et al. (1995)
							10								
							25	1.1							
					CBA/Ca	4	5	0.8							Basketter et al. (1994)
							10	1							
							25	0.8							
2-Methyldecanenitrile	69300-15-8	273-960-3	96.8	AOO	CBA/CaOlaHsd	5	25	2.1	NC	n	na				RIFM unpublished
							50	1.6							
							100	2.7							
6-Methylhepta-3,5-dien-2-one	1604-28-0	216-507-7	98.9	DEP:EtOH 3:1	na	5	0.1	0.5	NC/1B	n	na				RIFM, unpublished
							0.5	0.6							
							1	0.2							
							2.5	0.5							
							5	0.9							
5-Methylhexane-2,3-dione	13706-86-0	237-241-8	99	AOO	CBA/Ca	4	25	2.9	26	n	na				Ryan et al. (2000)
							50	6							
							100	14.3							
Methylisothiazolinone	2682-20-4	220-239-6	19.7% in water	AOO	CBA/Ca	4	0.05	1.5	0.4	n	na				Basketter et al (2003)
							0.1	1.5							
							0.2	1.8							
							0.49	3.8							
							0.99	2.5							
				PG			0.99	1.9	2.2						
							1.97	2.6							
							4.93	7.0							
							9.85	7.6							
4-Methyl-2-nitroanisole	119-10-8	204-296-4	na	AOO	CBA/Ca	4	10	1.1	NC	n	na				DK EPA report GM7919-58
							25	1.7							
							50	2.2							
Methylparaben	99-76-3	202-785-7	99	DMF	CBA/Ca	4	10	0.8	NC	n	na				Ryan et al. (2000)
							25	0.9							
							50	0.8							
							50	0.8							
							100	0.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
2-Methylundecanal	110-41-8	203-765-0	na	AOO	na	na	0.5	1.4	10	n	na			SI values from Gerberick et al. (2005). The EC3 corresponds in both publications	Patlewicz et al. (2002), also cited in Gerberick et al. (2005)
							1	1.3							
							2.5								
							5	2.4							
							10	3							
Metol	55-55-0	200-237-1	na	DMF	CBA/Ca	4	0.5	2.5	0.8	n	na			The publication reports that the vast majority of the compounds were more than 98% pure, but there is no information for the specific chemicals	Basketter and Scholes (1992)
							1	3.4							
							2.5	6.7							
1-Naphthol	90-15-3	201-969-4	na	AOO	na	na	0.1	1.4	1.3	n	na			No information available on doses and Sis in the Estrada et al (2003) paper. The EC3 corresponds in both publications	Estrada et al. (2003)
							0.25	1.0							
							0.5	1.2							
							1	1.5							
							2.5	8.5							
Neomycin sulfate	1405-10-3	215-773-1	95	25% EtOH	CBA/J	5	0.5	0.9	NC/1B	n	na				Gerberick et al. (1992)
							1								
							2								
4-Nitrobenzyl bromide	100-11-8	202-820-6	na	AOO	CBA	na	0.01	0.9	0.05	n	na				Unilever unpublished
							0.03	1.3							
							0.05	3.5							
							0.1	11.5							
2-Nitro-p-phenylenediamine	5307-14-2	226-164-5	na	AOO	na	na	0.1	1.8	0.4	n	na			The publication indicates: "LLNA sensitization study data conducted to the same conditions (e.g., same vehicle) where an EC3 value had been successfully determined were selected from Unilever's database".	Estrada et al (2003), also cited in Gerberick et al. (2005)
							0.25	2.2							
							0.5	3.3							
							1	7.9							
							2.5	11.9							
cis-6-Nonenal	2277-19-2	218-900-9	na	AOO	na	na	10	1.6	23	n	na				Estrada et al (2003)
							25	3.3							
							50	4.5							
							100	13.7							
Octanoic acid	124-07-2	204-677-5	na	AOO	CBA	4	10	0.7	NC	n	na				Basketter et al. (1998)
							25	1							
							50	1.6							
OTNE	54464-57-2	259-174-3	95.5	DEP:EtOH 3:1	na	5	2.5	1.4	6.07	n	na				RIFM, unpublished
							5	5							
							10	10							
							25	25							
							50	50							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
OTNE, ctd	54464-57-2	259-174-3	95.5	DEP:EtOH 3:1	na	5	2.5	1.1	14.2	n	na				RIFM, unpublished
							5	1.3							
							10	2							
							25	5.6							
							50	11.3							
			98.2			4	2.5	1.6	25.14						
							5	1.4							
							10	1.4							
							25	2.8							
							50	32.4							
Oxalic acid	144-62-7	205-634-3	na	DMF	na	na	5	2.4	15	n	na				Unilever unpublished
							10	2.8							
							25	3.4							
Oxazolone	15646-46-5	239-713-9	99	ACE	CBA/J	5	0.0001	1.6	0.0011	n	na			4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							0.005	8.7							
							0.05	55.2							
			≥ 90	AOO	CBA/Ca	4 or 5	0.0025	3.9	0.0014	y	p			4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							0.005	4.8							
							0.01	6							
							0.025	12							
							0.05	13							
					CBA/JHsd		0.0025	3.8	0.002					Use of ^{125}I-UdR instead of ^{3}H-TdR. 4 days treatment, labelling and excision day 5	
							0.005	6.2							
							0.01	7.7							
							0.025	15							
							0.05	23							
							0.0025	4	0.0025					4 days treatment, labelling and excision day 5	
							0.005	6.9							
							0.01	16							
							0.025	40							
							0.05	59							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Oxazolone, ctd.	15646-46-5	239-713-9	≥ 90	AOO	CBA/JHsd	4 or 5	0.0025	2.9	0.0026	n	na			4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							0.005	4.9							
							0.01	12							
							0.025	22							
							0.05	33							
					CBA/Ca		0.0025	3.4	1A	y	p		f		
							0.005	4.4							
							0.01	4.0							
							0.025	5.9							
							0.05	8.9							
			na		BALB/c	4	1	25.2		n	na			3 days treatment, labelling and excision day 4	Mandervelt et al. (1997)
							2	25.2							
							4	19							
Penicillin G	61-33-6	200-506-3	na	DMF	CBA/Ca	4	10	2.7	11.25	n	na			The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported.	Scholes et al. (1992)
							25	6.3							
							50	6.5							
				DMSO		5	2.5	1.3	16.1						Kimber et al. (1998)
							5	1.7							
							10	1.9							
							25	4.0							
							50	4.6							
						4	10	1.5	19.8					The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported.	Scholes et al. (1992)
							25	3.8							
							50	8.9							
						5	2.5	1	31.3						Kimber et al. (1998)
							5	1							
							10	1.4							
							25	2.1							
							50	6.6							
					CBA/JHsd		2.5	0.6	41.1					Use of ^{125}I-UdR instead of ^{3}H-TdR	
							5	0.8							
							10	1.3							
							25	1.9							
							50	3.6							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Penicillin G, ctd.	61-33-6	200-506-3	na	DMSO	CBA/JHsd	5	2.5	0.8	46.4	n	na				Kimber et al. (1998
							5	0.7							
							10	0.8							
							25	1.3							
							50	3.4							
							2.5	0.9	46.5						
							5	1.0							
							10	0.8							
							25	1.3							
							50	3.4							
				DMF	CBA/Ca	4	10	5.6	POS	y	p		f	The paper indicates the majority of chemicals had a purity above 98% but specific chemicals' purities are not reported.	Scholes et al. (1992)
							25	6.9							
							50	17.0							
							10	3.8							
							25	8.9							
Pentachlorophenol	87-86-5	201-778-6	na	DMSO	na	na	10	2.1	20	n	na				Basketter et al. (1996)
							25	3.5							
							50	5.4							
Perillaldehyde	2111-75-3	218-302-8	na	AOO	na	na	0.5	1.2	4.04	n	na			Primary reference only provides the EC3 values without indicating the source of the study. EC3 re-calculated since the EC3 previoulsy reported was above the highest tested dose.	Patlewicz et al. (2002), also cited in Gerberick et al. (2005)
							1	1.1							
							2.5	0.9							
							5	4.3							
3-Phenoxypropanenitrile	3055-86-5	221-278-1	na	AOO	CBA/Ca	4	10	1	NC	n	na			Tested up to 50% with SI ≤ 2.5. Fit is too bad to extrapolate. Negative slope	DK EPA report GM7919-58
							25	0.9							
							49	0.8							
Phenyl benzoate	93-99-2	202-293-2	na	AOO	CBA/Ca	4	1	2	1.2	n	na				Basketter et al. (1999)
							2.5	6.4							
							5	9.3							
							10	8.7							
							25	11.1							
					na	na	5	2.3	20						Unilever, unpublished
							10	2.1							
							25	3.5							
Phenylacetaldehyde	122-78-1	204-574-5	85	AOO	CBA/Ca	4	1	0.7	3	n	na				Basketter et al (2001)
							2.5	1.8							
							5	7.8							
							10	8.8							
							25	19.0							
			100				25	15.5	POS	y	p		f		Ryan et al. (2000)
							50	23.8							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
							100	24.1							
p-Phenylenediamine	106-50-3	203-404-7	97	AOO	CBA/c	4	0.05	2.6	0.06	n	na				Warbrick et al. (1999)
							0.1	4.7							
							0.25	10.3							
							0.5	15.5							
							1	14.2							
							0.05	2.29	0.07						
							0.1	4.42							
							0.25	17.0							
							0.5	23.2							
							1	38.0							
							0.05	1.9	0.09						
							0.1	4.4							
							0.25	17.3							
							0.5	23.8							
							1	22.5							
							0.05	1.99	0.09						
							0.1	3.29							
							0.25	10.2							
							0.5	2.5							
							1	26.4							
							0.05	1.45	0.13						
							0.1	3.6							
							0.25	9.72							
							0.5	16							
							1	17.0							
							0.05	1.95	0.13						
							0.1	2.35							
							0.25	5.4							
							0.5	8.8							
							1	9.56							
			na				0.01	0.9							White et al. (2006)
							0.025	1.5							
							0.05	1.3							
							0.1	1.9							
							0.25	7.1							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
p-Phenylenediamine, ctd.	106-50-3	203-404-7	na	AOO	CBA/c	4	0.01	0.7	0.16	n	na				White et al. (2006)
							0.025	1.0							
							0.05	1.0							
							0.1	2.0							
							0.25	4.4							
							0.05	1.9							Warbrick et al. (1999)
							0.1	2.3							
							0.25	4.0							
							0.5	5.3							
							1	6.6							
			97				0.05	1.1	0.2						
							0.1	2.2							
							0.25	3.5							
							0.5	7.6							
							1	4.6							
			na		CBA/Ca		2.5	21.0	POS	y	f			Radioactive labelling and excision on day 4	Kimber et al. (1991)
							5	26.0							
							10	75.3							
							2.5	12.8		y	p	f	p	Radioactive labelling and excision on day 4	Kimber et al. (1991)
							5	16.5							
							10	23.3							
							2.5	6.5					na		
							5	23.7							
							10	nd							
							2.5	18.6			f				
							5	20							
							10	37.4							
1-Phenylpropane-1,2-dione	579-07-7	209-435-2	na	AOO	CBA	na	5	12.8	POS	y	p	f			Roberts et al. (1999)
							10	17.7							
							25	20.1							
Phthalic anhydride	85-44-9	201-607-5	99	AOO	BALB/c	4	0.1	2.0	0.16	n	na				Dearman et al. (2000)
							0.25	4.8							
							0.5	4.8							
							1	6.0							
							2.5	10.8							
Propyl gallate	121-79-9	204-498-2	na	AOO	CBA/Ca	4	5	22.3	1A	y	p	f		Labelling and excision on day 5 or 6. The paper indicates the majority of chemicals had a purity above 98%, but specific chemicals' purities are not reported. Very strong response at 5% - expert group consensus 1A.	Basketter and Scholes (1992)
							10	18.3							
							25	33.6							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Propylene glycol	57-55-6	200-338-0	na	water	na	na	50	1.2	NC	n	na			The study is not reported in the publications quoted in Ashby et al. 1995. It is assumed this is an unpublished study.	Unknown, cited in Ashby et al. (1995)
							100	1.6							
3-Propylidenephthalide	17369-59-4	241-402-8	96	AOO	CBA/Ca	4 or 5	5	4.9	3.7	y	p				Ryan et al. (2000)
							10	9.1							
							25	15.1							
Propylparaben	94-13-3	202-307-7	na	AOO	na	na	5	1.4	NC/1B	n	na				Ashby et al. (1995)
							10	1							
							25	1.3							
Pyridine	110-86-1	203-809-9	na	AOO	na	na	25	1.1	72	n	na				Basketter et al. (1996)
							50	2.3							
							100	3.9							
Resorcinol	108-46-3	203-585-2	99.9	AOO	CBA/Ca	4	1	0.7	6.3	n	na				Basketter et al. (2007)
							5	2.2							
							10	5.2							
							25	8.4							
							50	10.4							
Saccharin	81-07-2	201-321-0	98	DMSO	CBA/Ca	4	25	1.3	NC	n	na			Extrapolation indicates EC3 > 100	Warbrick et al. (2001)
							50	1.3							
							75	1.5							
Safranal	116-26-7	204-133-7	na	AOO	na	na	0.5	0.7	7.5	n	na				Patlewicz et al. (2002)
							1	1.1							
							2.5	1.1							
							5	2.7							
							10	3.3							
Salicylic acid	69-72-7	200-712-3	99	ACE	CBA/J	5	1	0.9	12.2	n	na			4 days treatment, labelling and excision from 18 to 24 hours after fourth treatment	Gerberick et al. (1992)
							10	1.8							
							20	7.2							
				AOO	na	na	5	0.8	NC/1B						Basketter et al. (1998)
							10	1.5							
							25	2.5							
Sodium lauryl sulfate	151-21-3	205-788-1	99	DMF	CBA/JHsd	4 or 5	1	2.7	1.3	n	na			4 days treatment, labelling and excision day 5	Loveless et al. (1996)
							2.5	4.2							
							5	4.6							
							10	8.9							
							25	8.6							
			na		CBA/Ca	4	4	4.1	1.5	y	p				Montelius et al (1994)
							10	5.1							
							25	6.7							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22] 1	2	3	Comments	Primary source
Sodium lauryl sulfate. ctd.	151-21-3	205-788-1	na	DMSO	CBA/Ca	4	5	3.2	2.5	y	p				Basketter et al. (1994)
							10	4							
							25	4.2							
				DMF			5	4	2.7						Montelius et al (1994)
							10	5.1							
							25	7.8							
			99			4 or 5	1	1.5	3.7	n	na				Loveless et al. (1996)
							2.5	2.3							
							5	3.8							
							10	4.1							
							25	5.3							
					CBA/JHsd		1	1.2	3.8					Use of ^{125}I-UdR instead of ^{3}H-TdR	
							2.5	1.7							
							5	4.3							
							10	5.4							
							25	8.0							
			na	1% Pluronic L92	CBA/CaOlaHsd	6	5	3.05	4.9	y	p				Bayer, unpublished[37]
							10	4.78							
							25	8.46							
			99	DMF	CBA/Ca	4 or 5	1	0.9	14.4	n	na				Loveless et al. (1996)
							2.5	1.1							
							5	1.7							
							10	2.6							
							25	3.5							
					CBA/JHsd		1	1.6	17					4 days treatment, labelling and excision day 5	
							2.5	2.1							
							5	2.8							
							10	1.6							
							25	3.6							
Squaric acid	2892-51-5	220-761-4	99	DMSO	CBA/J	4	2.5	4	POS	n	na				Ryan et al. (2000)
							5	2.7							
							10	3.4							
Sulfanilamide	63-74-1	200-563-4	na	DMF	CBA/Ca	4	10	1.0	NC	n	na				Basketter et al. (1994)
							25	1.0							
							50	0.9							

[37] BGIA Project FP251 submitted to NICEATM

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Sulfanilic acid	121-57-3	204-482-5	99	DMF	CBA/Ca	4	5	1.5	NC/1B	n	na				Basketter et al. (1992)
							10	1.9							
							25	2.2							
							5	1.1							
							10	1.2							
							25	1.3							
							5	1.9							
							10	1.2							
							25	1.8							
L-Tartaric acid	87-69-4	201-766-0	na	DMF	na	na	5	1	NC/1B	n	na				Kern et al. (2010)
							10	0.9							
							25	1.5							
Tetrachlorosalicylanilide	1154-59-2	214-576-8	na	ACE	CBA/Ca	4	0.1	16	0.013	y	p		f		Scholes et al. (1991)
							0.25	27.8							
							0.5	40.5							
							0.25	11.2	0.04						Basketter et al. (1994)
							0.5	14.4							
							1	18							
2,2,6,6-Tetramethylheptane-3,5-dione	1118-71-4	214-268-3	na	ACE	na	na	10	2.1	27	n	na				P&G unpublished
							20	2.8							
							40	3.4							
Thioglycerol	96-27-5	202-495-0													
Thiram	137-26-8	205-286-2	na	AOO	na	na	2.5	2.4	5.2	n	na				Basketter et al. (1996)
							5	2.9							
							10	5.1							
α-Tocopherol	59-02-9	200-412-2	na	EtOH:DEP	CBA/Ca/01a/Hsd	4	0.3	0.6	7.4	n	na				RIFM, unpublished
							1	0.8							
							3	1.1							
							10	4.2							
							30	6.7							
Triethanolamine	102-71-6	203-049-8	na	AOO	BALB/c	5	10	1.2	NC	n	na			irritancy (ear thickness). 50% is indicated as maximum soluble concentration.SI ≤ 2.5	Anderson et al. (2009)
							25	1.8							
							50	2.4							
Trimellitic anhydride	552-30-7	209-008-0	na	AOO	na	na	1	1.1	9.2	n	na			No information available on doses and Sis in the Estrada et al (2003) paper. The EC3 corresponds in both publications	Estrada et al. (2003), also cited in Gerberick et al. (2005)
							2.5	2.0							
							5								
							10	3.2							
							25	4.6							
							50	1.36							
							90	1.02							

Substance	CAS RN	EC no.	Purity (%)	Vehicle	Strain	Animals/ group	Conc. (%)	SI[21]	EC3 [%]/ SPE	Extrapo-lated?	Criteria fulfilled?[22]			Comments	Primary source
											1	2	3		
Tropolone	533-75-5	208-577-2	na	DMF	na	na	0.5	1	4.3	n	na				P&G unpublished
							5	3.3							
							10	5.2							
							20	nd							
Undec-10-enal	112-45-8	203-973-1	na	AOO	na	na	5	1.7	6.8	n	na				Patlewicz et al (2002)
							10	5.3							
							25	7.5							
							50	8.7							
							75	8.8							
Vanillin	121-33-5	204-465-2	97	AOO	CBA/Ca	5	2.5	0.9	NC	n	na				Basketter et al (2001)
							5	1.4							
							10	1.5							
							25	1.2							
							50	1.4							
4-Vinylpyridine	100-43-6	202-852-0	na	AOO	na	na	2.5	7.4	POS	y	p		f		Ashby et al. (1995)
							5	14.2							
							10	14.8							

Abbreviations

1A	GHS sub-category classification result for a strong/extreme skin sensitiser
1B	GHS sub-category classification result for a moderate/weak skin sensitiser
ACE	Acetone
AOO	Acetone/olive oil
BfR	German Federal Institute for Risk Assessment
CosEU128	Reference substance list used by NICEATM/Cosmetics Europe in the Hoffmann et al./Kleinstreuer et al. publications from 2018 (cf. reference section)
DA	Defined Approach
DASS	Defined Approaches for Skin Sensitisation
DEP	Diethyl phthalate
DMF	N,N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
EC3	Estimated effect concentration of a test substance needed to produce a stimulation index of three
EG	Expert Group
EtOH	Ethanol
HC	Health Canada
HDSG	Human Data Sub-Group
HPPT	Human Predictive Patch Test
HCT	Highest concentration tested
IDR	Insufficient Dose Response
JRC	Directorate General Joint Research Centre of the European Commission
LLNA	Local Lymph Node Assay (as per OECD TG 429)
LPCT	Lowest Positive Concentration Tested
LSG	LLNA sub-group
MEK	Methyl ethyl ketone
MEKPO	Methyl ethyl ketone:paraffin oil
MLLP	Median-Like Location Parameter
MSPE	Median Sensitisation Potency Estimate
NC	Not classified (as a sensitiser)
NC/1	Ambiguous classification outcome: not classified or sensitiser
NC/1B	Ambiguous classification outcome: not classified or moderate/weak sensitiser, but not a strong sensitiser
NICEATM	United States NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Co-Operation and Development
PG	Propylene glycol
PO	Paraffin oil

POS	SPE for an individual LLNA outcome showing that a substance is a sensitiser (“positive”), but this result cannot be used for sub-categorisation
RIFM	Research Institute for Fragrance Materials
RIVM	Dutch National Institute for Public Health and the Environment
SCCP	Scientific Committee on Consumer Products
SI	Stimulation Index
SPE	Sensitisation Potency Estimate
TC	Teleconference
TrIC	Trolox C
WoE	Weight of evidence

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