Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

11-Jul-2016

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

REPORT OF A SURVEY ON REGULATORY AND TESTING ISSUES FOR THE SENSITISATION POTENTIAL OF MICRO-ORGANISMS: SURVEY RESULTS (2014)

Series on Pesticides
No. 84

JT03399219

ENV/JM/MONO(2016)37
Unclassified
English - Or. English

OECD Environment, Health and Safety Publications
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Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2016

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FOREWORD

This document is the report of an OECD survey on Regulatory and Testing Issues for the Sensitisation Potential of Micro-organisms.

A number of plant protection and biocidal products that are based on or derived from micro-organisms are currently available on the market and, like chemical based products, must undergo an authorisation procedure. Since micro-organisms differ from chemical active substances, test methods routinely used for chemical active substances are not always applicable to micro-organisms. A micro-organism is in general defined as any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including lower fungi, viruses, bacteria, yeasts, moulds, algae, protozoa and microscopic parasitic helminths.

Micro-organisms have the potential to provoke sensitisation reactions by inhalation as well as through dermal exposure. However, it has been argued that the available skin sensitisation study protocols routinely used for testing chemical active substances (Buehler, Guinea Pig Maximisation Test [GPMT], Local Lymph Node Assay [LLNA]) might not be useful. However, none of the currently available methods for testing dermal sensitisation are validated for micro-organisms and if conducted, results may be difficult to interpret. At present, there are also no validated test methods for respiratory sensitisation. Evidence that the micro-organism can induce respiratory hypersensitivity is usually based on human experience. Consequently, no studies are currently required to address sensitisation and all micro-organisms should thus be regarded as potential sensitisers, until further guidance is available.

The purpose of the OECD survey was to collect OECD member country opinions and requirements on available skin sensitisation studies so that commonalities or differences can be identified and options to help Member countries with this issue can be developed. The survey therefore invited countries to present their own opinion.

The discussion has already led to the adoption of certain requirements in some OECD member countries. For example, in the EU it was agreed that the following warning phrase should be added to the label of plant protection products and biocidal products containing micro-organisms: ‘Micro-organisms may have the potential to provoke sensitising reactions’.

The survey questionnaire (in Annex 3) was sent to OECD member countries on July 2014 with a deadline for responses by 24 October 2014.

This document was approved by the OECD BioPesticides Steering Group on 19 May 2015 and by the OECD Working Group on Pesticides on 28 March 2016.

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public.

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INTRODUCTION

1. In general, an active substance is defined as a substance or a micro-organism that has an action on or against harmful organisms. Due to the ability of micro-organisms to proliferate, there is a clear difference between chemicals and micro-organisms used in plant protection products and biocidal products. Hazards arising are not necessarily of the same nature as those presented by chemicals, especially in relation to the capacity of micro-organisms to persist and multiply in different environments. These differences between micro-organisms and chemicals should be taken into account in the assessment of active substances. Moreover, micro-organisms consist of a wide range of different organisms, all with their own unique characteristics and modes of action, that have to be taken into consideration when assessing the sensitising potential of the micro-organism.

2. The provisions of the classification and labelling framework for chemicals (Globally Harmonised System of Classification and Labelling of Chemicals, GHS) cannot be used for micro-organisms and thus they cannot be classified or labelled under this framework. However, the chemical constituents in a plant protection product or biocidal product containing micro-organisms may trigger classification and labelling according to GHS and other specific labelling requirements can apply. The warning phrase "Micro-organisms may have the potential to provoke sensitising reactions" – or a similar sentence – should always be applied to the active substance (micro-organism) and to the plant protection products or biocidal products.

3. A microbial plant protection product or biocidal product can be formulated in different ways in order to be most efficient. Biological properties, formulation and how the product is applied must be taken into account when assessing exposure and possible risk. OECD member countries must take into account the fact that in addition to the active micro-organism, any co-formulants might have an impact on the characteristics of the plant protection product or biocidal product.

4. The human health tests routinely used for chemicals are not always applicable to micro-organisms. For validation of chemical test methods, OECD guidance (OECD No 34; ENV/JM/MONO(2005)14)1 is in place. Although, the aforementioned OECD guidance, as well as the Guidance Document for such analytical methods [EU SANCO/3030/99]2 are not directly applicable to micro-organisms, some of the principles still can be used for the assessment of micro-organisms. If non-standardised tests are applied to assess sensitisation the quality of the methods need to be reported in detail and examined, for example, as regards relevance, representativeness, sensitivity, specificity, reproducibility, inter-laboratory validation and predictivity.

5. In terms of confirming the identity of micro-organisms, preferably a combination of both phenotypic and genotypic methods has to be used. Considering that full genome sequencing nowadays is a fairly straightforward analysis conducted at a reasonable cost, this should be the recommended method to confirm the identity of active micro-organisms. This information can also be used to check other properties of the micro-organisms (e.g. relevant toxins, metabolites). In general, the presence of such genes does not necessarily mean that the phenotype will be expressed; an absence of genes could be considered a strong indication that the property in question is not acquired by micro-organisms. However, it is always important to keep in mind what level of evidence is needed from a regulatory point of view versus the information which can be generated for a scientific point of view (i.e., nice to know).

6. The amount of analyses to be performed for identification will vary depending on the specific micro-organism in question. As an example, the identification of Bacillus strains may be more cumbersome compared to other micro-organism due to the close relation of species within this genus.

SURVEY RESULTS AND ANALYSIS

7. Nine responses were received to the OECD survey from Austria (AT), Canada (CA), Germany (DE), Denmark (DK), Hungary (HU), Japan (JP), the Netherlands (NL), New Zealand (NZ), and Sweden (SE). Responses to questions that were easily tabulated are summarized in the table in Annex 1. Detailed responses to all questions including any additional details provided in response to the questions in the table in Annex 1 are summarized in Annex 2. After analysing the results the following observations can be made:

- The majority of the respondents (8 of 9) generally accept dossiers without skin sensitisation studies for the relevant micro-organism.

- The majority of the respondents (8 of 9) would label the product containing micro-organisms with phrases such as:

  "Contains `*strain name of the microorganism'*, may cause a sensitising reaction"

  "May cause an allergic reaction"

  "May cause sensitisation"

  "Micro-organisms may have the potential to provoke sensitising reactions"

  "POTENTIAL SENSITISER" or

  "considered to be sensitiser".

- There was wide variation in the details of the responses to question 1 c, concerning the kind of personal protective equipment (PPE) that would be needed to protect the operator during mixing and loading and during application. The majority of the respondents said that, in general, it depends on the exposure when handling the specific product and the corresponding formulation type. If significant occupational exposure is expected from all routes, full PPE is required (gloves, long sleeved shirt, pants, eye goggle, respiratory protection etc.). The PPE requirements may be reduced to a protective level deemed appropriate for the application and level of hazard.

- Most respondents (5 of 9) consider protective equipment for re-entry workers as not necessary. Three respondents recommend gloves and optional respiratory protection. And some stated that a re-entry interval may potentially be required.

- Eight of nine respondents do not accept negative results in a Buehler test for micro-organisms as justification for the non-classification of the micro-organism as a 'potential sensitiser'; moreover seven of nine respondents do not accept negative results in a Buehler test for products containing micro-organisms as justification for not labelling the product with specific warning phrases.

- In the case of a positive Buehler test, Guinea Pig Maximisation test or Local Lymph Node Assay, most respondents would label the micro-organism with safety precautionary sentences as mentioned above (second point). The use of specific hazard phrases depends on study results. Labelling with GHS hazards statement H317 *May cause an allergic skin reaction* or statement H334 *May cause allergy or asthma symptoms or breathing difficulties if inhaled* is not considered appropriate (EU).

- Most respondents (6 of 9) do not accept a negative result of a Maximisation test for micro-organisms or products containing micro-organisms (5 of 9) as justification for non-classification of the micro-organism as a 'potential sensitiser' or as justification for not labelling the product with specific warning phrases. A frequently used explanation is that the Buehler test and a Maximisation study only address the dermal route of exposure. Sensitisation may occur through other routes (e.g. inhalation).

- Seven of nine respondents do not accept negative results in a LLNA test for micro-organisms as justification for non-classification of the micro-organism as a 'potential sensitiser'; in addition six of nine respondents do not accept negative results in a LLNA test for products containing micro-organisms as justification for not labelling the product with specific warning phrases. The LLNA test is essentially a dermal sensitisation study and would present the same limitations as the Buehler and Maximisation tests.

- In regard to the question concerning whether there are any specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment) some respondents indicated they already have specific requirements for labelling products containing micro-organisms (e.g. EU agreement).

- In response to the last question regarding whether the need for protective equipment for a product containing micro-organisms excludes the use by non-professionals, nearly all respondents answered "no" or "not in general".

RECOMMENDATIONS

8. Based on the responses, it is apparent that a few open points have to be addressed with respect to the assessment of sensitising potential of a microbial plant protection product or biocidal product:

1) Harmonised guidance and tests for plant protection products or biocidal products containing micro-organisms are needed. As a result, data requirements may have to be adjusted.
2) Applicability of existing skin sensitisation tests has to be determined:

   None of the existing tests are validated for micro-organisms. Open points include:
   a) Is the Guinea Pig Maximisation Test predictive?
   b) Is the Local Lymph Node Assay applicable?
   c) Dermal bioavailability has to be ensured in the Buehler, Maximisation Test and LLNA.

3) Options for testing respiratory sensitisation have to be identified:
   a) No test system is currently available. It has been suggested that blood markers can be applied in inhalations studies. If so, which one?
   b) Is the potential of the respiratory sensitisation higher for micro-organisms than for chemicals?
4) Is it necessary to classify each micro-organism as a potential sensitiser, or can classification be specific for each micro-organism, e.g. based on available information from existing literature indicating sensitising potential?
5) Establishment of different markers to get a specific profile of the sensitising potential of the concerned micro-organism.

REFERENCES

1. OECD (2005). Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. OECD Series on Testing and Assessment, Guidance Document 34. ENV/JM/MONO(2005)14

2. SANCO/3030/99 rev. 4, 11/07/00, Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414.

ANNEX 1: SUMMARY TABLE OF RESPONSES TO QUESTIONS

Austria	Canada	Germany	Denmark	Hungary	Japan	Netherlands	New Zealand	Sweden
1 a) Do you accept the dossier if no skin sensitisation study is provided for the micro-organism (MO)?								
Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
2) Negative Buehler test (micro-organism, product). For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?								
MO: No, product: No	MO: No, product: No	MO: No, product: No	MO: No, product: No	MO: No, product: Yes	MO: No, product: No	MO: No, product: No	MO: Yes, product: Yes	MO: No, product: No
3) Positive Buehler test (micro-organism) If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?								
MO: No	MO: No	MO: Yes	MO: No	MO: Yes	MO: Yes	MO: No	MO: Yes	MO: No
4) Negative Maximisation test (micro-organism, product). For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?								
MO: No, product: No	MO: No, product: No	MO: Yes, product: Yes	MO: No, product: Yes	MO: Yes, product: Yes	MO: No, product: No	MO: No, product: No	MO: Yes, product: Yes	MO: No, product: No
5) Positive Maximisation test (micro-organism). If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?								
MO: No	MO: No	MO: No	MO: No	MO: Yes	MO: Yes	MO: No	MO: Yes	MO: No
6) Negative LLNA (micro-organism, product). For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?								
MO: No, product: No	MO: No, product: No	MO: No, product: No	MO: No, product: Yes	MO: Yes, product: Yes	MO: No, product: No	MO: No, product: No	MO: Yes/No, product: Yes/No	MO: No, product: No
7) Positive LLNA (micro-organism). If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?								
MO: No	MO: No	MO: No	MO: Yes/No	MO: Yes	MO: Yes	MO: No	MO: Yes/No	MO: No
8 a) In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?								
No	Yes	Yes	Yes	No	No	Yes	No	Yes
8 b) If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?								

No	No	Yes	No	Yes	Yes	No	Yes	No
10. Non-professional use. Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?								
No	Not in general	Not in general	Not in general	Not in general	No	No	No (case-by-case basis)	In general Yes

ANNEX 2: DETAILED RESPONSES BY COUNTRY TO ALL QUESTIONS

Austria

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

We generically label as: Contains XXXXXXXXX. May cause an allergic reaction

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

Gloves, respiratory protection

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Gloves, optional respiratory protection

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: no
Product: no
Explanation / remarks: **Not considered sensitive enough**

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks: **We label generically as described above**

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: no
Product: no
Explanation / remarks: **We label generically as described above**

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No
Explanation / remarks: **We label generically as described above**

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: no
Product: no
Explanation / remarks: **We label generically as described above**

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No
Explanation / remarks: **We label generically as described above**

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

No

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed

(gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

No Answer

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

No

Canada

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes
Explanation / remarks:
In Canada, a dermal sensitization study is not required for microbial-based pesticides as noted in Regulatory Directive DIR2001-02, "Guidelines for the Registration of Microbial Pest Control Agents and Products" (http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2001-02/index-eng.php#a4.4-acute). Although dermal sensitization studies are occasionally submitted by registrants to support registration applications, Health Canada assumes that all microorganisms contain substances that can elicit hypersensitivity or allergic reactions upon repeated exposure in humans, regardless of the outcome of sensitization testing. Consequently, Health Canada requires that all labels for microbial products be clearly marked as being potential sensitizers.

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

The principal display (i.e., front) panel of the product label is required to include the signal words "POTENTIAL SENSITIZER". In addition, the Precautions section of the label's secondary display panel requires the statement, "May cause sensitization". Depending on the use pattern (e.g., indoor use or spray applications with high pressure equipment), handlers of the product (i.e., mixers, loaders and applicators) may be required to wear personal protective equipment (PPE), including a microbiological dust-mist respirator to minimize inhalation exposure and thus decrease the potential for sensitization.

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

For use scenarios in which significant occupational exposure is expected from all routes, full PPE are required to minimize exposure through all routes, including the wearing of a long-sleeved shirt, long pants, waterproof gloves, shoes plus socks, eye goggles and a dust-mist filtering respirator/mask (with any NIOSH-approved N-95, P-95, R-95 or HE type filter for biological products). For other use scenarios where occupational exposure is expected to be low via one or more routes (e.g., directed applications, tree injections or enclosed systems), the PPE requirements may be reduced to a protective level deemed appropriate for the application and level of hazard.

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Microbial product labels in Canada restrict workers from re-entering freshly treated areas for a minimum period of 4 hours after application or until sprays have dried or dusts have settled unless they wear appropriate PPE (i.e., equivalent to or a subset of that required for an applicator/mixer/loader).

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: no
Product: no
Explanation / remarks:
A negative dermal sensitization result does not address potential sensitivity through other significant routes of exposure (e.g., inhalation). Unbroken skin is an important natural barrier to microorganisms, as well as other complex macromolecules, therefore the potential for producing sensitizing reactions via this route is limited. Other routes such as oral and inhalation have a greater potential for producing sensitizing reactions because of the presence of specialized lymphoid tissues present on the mucosa (e.g., mucosa-associated lymphoid tissue). These lymphoid tissues transport antigens to the underlying tissues where they are processed by the host's immune system. Consequently, all Health Canada-approved microbial pesticide labels require precautionary statements respecting sensitization potential of the active microorganism regardless of the results of any dermal sensitization study.

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks:
All microbial pesticides are labelled in the same way with respect to sensitization potential regardless of the results of a dermal sensitization study. Although the required worker PPE can vary between products, these variations are due to different use scenarios only.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: no
Product: no
Explanation / remarks:
As noted in the response to Question #2 for the Buehler test, a Maximization study only addresses the dermal route of exposure. Sensitization may occur through other routes (e.g., inhalation).

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No
Explanation / remarks:
As noted in the response to Question #3 for the Buehler test, all microbial-based pesticides are labelled in the same way with respect to sensitization regardless of the results of a dermal sensitization study.

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: no
Product: no
Explanation / remarks:
Health Canada has not yet received an LLNA test in support of registration of a microbial-based pesticide. As the LLNA test is essentially a dermal sensitization study, it would present the same limitations as the Buehler and Maximisation tests. Furthermore, the validity of the test method for microbial-based products must be established.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No
Explanation / remarks:
As noted in the responses to Questions #3 and #5, all microbial-based pesticides are labelled in the same way with respect to sensitization regardless of the results of any dermal sensitization test, including the LLNA.

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes
Explanation / remarks:
As noted in the responses to Question #1b and 1c, the principal display panel of the label for all microbial-based pesticides must contain the signal words "POTENTIAL SENSITIZER" and the secondary display panel must contain the statement "May cause sensitization".
For use scenarios in which significant occupational exposure is expected from all routes, the secondary display panel of microbial product labels further instructs handlers (i.e., mixers, loaders and applicators) to wear full PPE, including a long-sleeved shirt, long pants,

waterproof gloves, shoes plus socks, eye goggles and a dust-mist filtering respirator/mask (with any N-95, P-95, R-95 or HE filter for biological products) to minimize exposure. For other use scenarios where occupational exposure is expected to be low via one or more route of exposure (e.g., directed applications, tree injections, enclosed systems), the PPE requirements may be reduced.

Statements on the label's secondary display panel also restrict workers from re-entering freshly treated areas for a minimum period of 4 hours or until sprays have dried or dusts have settled unless they wear appropriate PPE (i.e., equivalent to or a subset of that required for a mixer/loader/applicator).

In addition to the above-noted principal and secondary panel statements, general precautionary and personal hygiene statements are also required on microbial product labels to further reduce repeated, long term exposures to the active microorganism that could in turn lead to the development of hypersensitivity/allergic reactions. Examples of such statements are: i) "Avoid contact with skin and eyes or clothing"; ii) "Avoid breathing dust or spray mist"; iii) "Wash thoroughly with soap and water after handling; and iv) "Remove contaminated clothing and wash before reuse."

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks:
As previously noted, all microbial-based pesticides are labelled as potential sensitizers; however, the microbial label statements are different than the standard chemical label statements. That said, if the study were to address a toxicological requirement, then data on the active microorganism would be used to label the end-use product containing this microorganism if there was no study done with the product itself.
Remarks: See response to Question #8a above for a description of label statements required by Health Canada.

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

See responses to Questions #1c and #1d above.

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

In general, domestic/residential use of microbial pesticides by homeowners does not require the wearing of PPE. Although all microbial-based products are assumed to be potential sensitizers and are labelled as such (including domestic use products), PPE is not currently required for handling domestic use products as the frequency of exposure is typically much lower than that for professional applicators applying commercial or restricted product formulations.

Germany[1]

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes, but we would regard the micro-organism as skin sensitising if no test is available.
All products containing micro-organisms will be labelled with a warning phrase. This label phrase is independent of a possible classification of co-formulants.
Non-submission of a skin sensitisation study with the product could be accepted in individual cases if sufficient data for the co-formulants are available (In this case, for classification with R43/H317 only the co-formulants are considered.)

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

We agree with the labeling phrase: "Micro-organisms may have the potential to provoke sensitising reactions."

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

Professional user:
During Mixing/Loading depending on formulation type:
Liquid formulation: gloves, coverall, face-shield, apron
Solid formulation (e.g. WP): gloves, coverall, respiratory protection
Solid formulation (e.g. WG): gloves, coverall, no respiratory protection
During application depending on concentrations of sensitising ingredients and application scenarios (low crop versus high crop): e. g. gloves, coverall, face-shield, respiratory protection
Personal Protective Equipment (PPE) for the use of Plant Protection Products in Germany is certified according to a BVL Guidance.
Non-professional user:
Since PPE for non-professional users is normally not supported product-integrated measures are preferred to reduce exposure. If the product is labelled with R43 use of long sleeved shirts, long trousers and protective gloves might be possible under specific circumstances.

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

[1] The answers are primarily experiences and results from the plant protection area. In the area of biocides there are just little approved microorganisms.

No protective equipment needed.

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: no
Product: no
Explanation / remarks:
1. Buehler Test is not validated/adopted for micro-organisms or products.

2. In Buehler test no access to intradermal compartment/blood/lymphatics is possible. Thus, a microorganism with potential allergens could not pass the intact dermal barrier. This is different to chemicals or low molecular weight proteins that could penetrate the epidermis/dermis, bind to proteins etc.

3. Buehler Test is not validated/adopted for respiratory sensitization. The test is based on a different MoA (dermal) than the MoA (with IgE) for respiratory sensitization.

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes
Explanation / remarks:
Micro-organism: Yes, the labelling phrase 'Micro-organisms may have the potential to provoke sensitising reactions' would apply. However, this would also apply if there is no test available.
Product: Yes, if a test with the product is positive normally the product would be classified/labelled accordingly. (In exceptional cases only labelling with. 'Micro-organisms may have the potential to provoke sensitising reactions' may be sufficient.)
Explanation: Products: For labelling with H334 additional information on respiratory effects is necessary, e. g. from inhalation tests or from medical data.

Remark: In contrast to medical products that have to be manufactured and charge-tested for "endotoxin-free" purity, biocidal or PSM a.s. and products are not. Therefore, microbial derived endotoxins such as LPS, found as contaminants in PSM and biocides that are not produced in an endotoxin-free way, are very likely to evoke a positive result in tests where endotoxins have access to blood or lymphatic circulation. Even if access to deeper epidermal layers of whole microorganism is unlikely, we could not exclude migration of cell wall compartments.

So it is not possible to discriminate between a positive result because of an allergen or because of an endotoxin in the case of micro-organisms.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: Yes, regarding dermal sensitisation
Product: Yes, regarding dermal sensitisation
Explanation / remarks:
If GPMT is negative, we accept for a non-sensitizer. However, since microorganisms bear endotoxins, it is unlikely that a GPMT is negative. Thus, we evaluate studies presented with caution.

In addition, it should be reminded that to date no adequate test system analysing respiratory sensitisation is available.

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Micro-organism: No, we would label the product with the warning phrase 'Micro-organisms may have the potential to provoke sensitising reactions'.

Product: Yes, normally the product would be classified/labelled accordingly. (In exceptional cases only labelling with. 'Micro-organisms may have the potential to provoke sensitising reactions' may be sufficient.)

Explanation: **Products: For labelling with H334 additional information on respiratory effects is necessary, e. g. from inhalation tests or from medical data.**
Remark: **According to OECD TG406 the Guinea Pig Maximisation Test (GPMT) of Magnusson and Kligman uses Freunds Complete Adjuvant (FCA). In detail, for induction at day 0 in "Injection 3" the test substance at the selected concentration formulated in a 1:1 with FCA is given to the guinea pigs. This means in the case of a microbial test substance that two different microbial stimuli are given in parallel as FCA itself consists of inactivated and dried mycobacteria (usually M. tuberculosis). From the current scientific knowledge, it is not possible to discriminate specific effects of microbial ligands on their receptors, "Pathogen recognition receptors" (PRRs). From recent literature we know that receptors, such as Toll-like receptor 2, 4 and 5 recognize petidoglycan, lipopolysaccharide from bacterial cell wall and the flagellin molecule from bacterial flagellum as well as allergens. Importantly, it could not be excluded that one ligand from microorganism A will enhance or attenuate sensitivity for a different ligand of a microorganism B by such means as surface receptor upregulation or cytoplasmatic cross talk. Microbial binding Toll-like receptors are of highest importance in human diseases and this is recognized by its crucial**

role as the central mode of action in sepsis. Complex microbial interactions on the immune system are a major issue of current studies as summarized in the article of Nicholas J. Gay (Nature Reviews Immunology, august 2014, Vol. 14). Thus, a test system using bacterial products (GPMT) is expected to be positive even in case of known human non-allergens derived from bacteria or other microorganism. So it is not possible to discriminate between a positive result because of an allergen or because of an endotoxin.
However, as a worst case assumption we would consider the micro-organism a skin sensitiser.

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: no
Product: no
Explanation / remarks:
1. LLNA is not validated/adopted for micro-organisms or products.

2. In LLNA, no access to intradermal compartment/blood/lymphatics is possible. Thus, a microorganism with potential allergens could not pass the intact dermal barrier. This is different to chemicals or low molecular weight proteins that could penetrate the epidermis/dermis, bind to proteins etc.

3. Furthermore, several scientific reports support the assumption that the mouse could not be used for allergy testing if the MoA involves Toll-like receptors. For instance, it was shown that one of the most important human contact allergens, nickel, is not detected by mouse LLNA because mice have a receptor lacking two non-conserved histidines comparing to the human receptor. In line with these observations, most of microbial antigens/superantigens/allergens are recognized by Toll-like receptors. Thus, a mouse test is expected to be negative for the allergen even in case it is a known allergen for humans.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Micro-organism: No, the labelling phrase 'Micro-organisms may have the potential to provoke sensitising reactions' would apply. However, this would also apply if there is no test available.

Product: Yes, normally the product would be classified/labelled accordingly. (In exceptional cases only labelling with. 'Micro-organisms may have the potential to provoke sensitising reactions' may be sufficient.)
Explanation: **Products: For labelling with H334 additional information on respiratory effects is necessary, e. g. from inhalation tests or from medical data.**

Remark: **In contrast to medical products that have to be manufactured and charge-tested for "endotoxin-free" purity, biocidal or PSM a.s. and products are not. Therefore, microbial derived endotoxins such as LPS, found as contaminants in PSM and biocides that are not produced in an endotoxin-free way, are very likely to evoke a positive result in tests where endotoxins have access to blood or lymphatic circulation. In this case it is not possible to discriminate between a positive result because of an allergen or because of an endotoxin**

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes (EU agreement)
Remark: **Labelling with the phrase 'Micro-organisms may have the potential to provoke sensitising reactions' applies.**

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes, the labelling phrase 'Micro-organisms may have the potential to provoke sensitising reactions' would apply.

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

<u>Professional user:</u> During Mixing/Loading depending on formulation type:
Liquid formulation: gloves, coverall, face-shield, apron
Solid formulation (e.g. WP): gloves, coverall, respiratory protection
Solid formulation (e.g. WG): gloves, coverall, no respiratory protection
During application depending on concentrations of sensitising ingredients and application scenarios (low crop versus high crop): e. g. gloves, coverall, face-shield, respiratory protection
Personal Protective Equipment (PPE) for the use of Plant Protection Products in Germany is certified according to a BVL Guidance.

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

Not in general, but a qualitative risk assessment should be performed considering sensitisation rate, frequency and degree of exposure etc.
Normally, PPE for non-professional users is not supported. Therefore, product-integrated measures are preferred to reduce exposure. If the product is labelled with R43 use of long sleeved shirts, long trousers and protective gloves might be possible under specific circumstances.

Denmark

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

Hazard Pictogram: None
Signal word: None
H-phrases: None
P-phrases: P102 Keep out of reach of children,
P261 Avoid breathing dust and spray
(the sentence depend on the application of the product)
P302 + P352 IF ON SKIN: Wash with plenty of soap and water
P501 Dispose of contents/container in accordance with local regulations for waste
Safety precautions:
Contains "strain name of the microorganism"; may have the potential to provoke sensitising reactions.
Keep away from food, drink and animal feeding stuffs
Avoid contact with skin and (eyes, if irritation)

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

It depends on the exposure when using the specific product depending on the amount, dustability, aerosols and… E.g.:

- **If the product has a low degree of dustability and are provided as granules for incorporating in soil only gloves will be needed. (disposable gloves will be sufficient)**
- **For professional users who are mixing a large amount of powder into water and for spray application (hand held) we would recommend to wear suitable protective clothing, gloves, eye protection (in some cases) and respiratory protection. However, this will not be included in the label**

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

No protective equipment required.

2. Negative Buehler test (micro-organism, product)

For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: no
Product: no
Explanation / remarks:
We don't in general find the Buehler test sensitive enough to exclude sensitisation

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks:
None R or H-phrases used for microorganisms, However we always use the safety precautionary sentence:
"Contains "strain name of the microorgansism"; may have the potential to provoke sensitising reactions."

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: no, unless the product only contains of the microorganism and compounds you would not expect to have any effect.
Product: Yes

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No
Explanation / remarks:
None R or H-phrases used for microorganisms, however we always use the safety precautionary sentence: "Contains "strain name of the micro-organsism"; may have the potential to provoke sensitising reactions."

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: no, unless the product only contains of the microorganism and compounds you would not expect to have any effect.
Product: Yes

7. Positive LLNA (micro-organism)

If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes / no

Explanation / remarks:

None R or H-phrases used for microorganisms, However we always use the safety precautionary sentence: "Contains "strain name of the microorgansism"; may have the potential to provoke sensitising reactions."

8. Product labelling

8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes

Explanation / remarks:

We always use the safety precautionary sentence: "Contains "strain name of the microorganism"; may have the potential to provoke sensitising reactions."

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No

Explanation / remarks:

None R or H-phrases used for microorganisms, However we always use the safety precautionary sentence: "Contains "strain name of the microorganism"; may have the potential to provoke sensitising reactions."

9. Protective Equipment

9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Please, find answer in 1C

10. Non-professional use

Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

When no Hazard Pictograms is required for labelling the product can get authorisation for private users. However, it must not be necessary to use personal protective equipment to

demonstrate safe use. However, if applicants recommend gloves on the label for reasons of routine hygiene it is permitted.

If a company would like to have their product authorized for non-professional users as well, they will need to sell their product under another name. Furthermore it has to fulfill the "Criteria for pesticides that can be used by and sold to non-professional users". Please find these criteria in "Framework for the Assessment of Plant Protection Products", Annex 17, page 65. Please use the link below:

Danske vurderingsrammer for pesticider, april 2014 http://mst.dk/virksomhed-myndighed/bekaempelsesmidler/sproejtemidler/ansoeger/vurderingsrammer-for-miljoe-og-sundhed/

Hungary

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

Considered to be sensitizer

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

Gloves for all cases. If the product can be inhaled during the registered use, respiratory protection is also prescribed

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Not necessary

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: no
Product: Yes
Explanation / remarks:
Yes, only with 9 inductions

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes
Explanation / remarks:
Buehler test has a very weak predictivity. If the result is positive, the product is considered as sensitizer.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: Yes

Product: Yes

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: Yes

Product: Yes

Explanation / remarks:
This is considered to be the best available test for the sensitization potential.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes

Explanation / remarks:

Yes, see above point 6.

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

No

Explanation / remarks:

Normally SPo2 is applied and in case of positive test result PPE is prescribed

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes

Explanation / remarks:

Yes, in case the microorganism content in the product exceeds the concentration limit

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed

(gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

See answer in 1c and 1d.

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

Not every time. In case when only gloves are needed, non-professional use is also authorized.

Japan

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

The dossier without results of skin sensitisation study for products containing micro-organisms is not acceptable. The data of skin sensitisation study for products containing micro-organisms is required in any case. In principle, the study should be done based on the Japanese test guideline which recommends the use of intradermal injections for induction and challenge for male guinea pigs. Other study results may be acceptable on a case-by-case basis taking account of the scientific justification provided by the applicant.
Since skin sensitisation study is required not for micro-organism but for products containing micro-organisms in Japan, please note that responses to the following questions 3, 5 and 7 are based on assumptions and are not necessarily based on established rules or decisions made on actual cases.

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

N/A

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

If a product containing micro-organisms shows positive results in any sensitisation study, it is necessary to wear gloves, working clothes with long sleeves, pants and masks for respiratory protection.

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Basically, protective equipment is not required for re-entry workers.

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: No
Product: No
Explanation / remarks:
Only the data of skin sensitisation study for products is required. Even if a Buehler test shows the negative results for mirco-organisms or products, it is necessary to conduct the study following the Japanese guideline in principle.

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes
Explanation / remarks:
The label must demonstrate that it has sensitization by specific hazard phrases depending on the positive ratio of the study.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: No
Product: No
Explanation / remarks:
Only the data of skin sensitisation study for products is required. Even if a maximization test shows the negative results for micro-organisms or products, it is necessary to conduct the study following the Japanese guideline in principle.

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes
Explanation / remarks:
The label must demonstrate that it has sensitization by specific hazard phrases depending on the positive ratio of the study.

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: No
Product: No
Explanation / remarks:
Only the data of skin sensitisation study for products is required. Even if a LLNA test shows the negative results for micro-organisms or products, it is necessary to conduct the study following the Japanese guideline in principle.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes
Explanation / remarks:

The label must demonstrate that it has sensitization by specific hazard phrases depending on the obtained Stimulation Index (SI) value of the study.

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

No

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes
Explanation / remarks:
The data of skin sensitisation study for products containing micro-organisms is required without exception. The study should be done based on the Japanese guidelines in principle.
If the product shows positive results in any sensitisation study, the label must demonstrate that it has sensitization by specific hazard phrases depending on the result of the study.

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

If the product shows positive results in any sensitisation study, it is necessary to wear gloves, masks, working clothes with long sleeves and pants.
Basically, protective equipment is not required for re-entry workers.

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

No, it does not. Protective equipment is required for non-professional users as well.

Netherlands

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

"Micro-organisms may have the potential to provoke sensitising reactions."

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

Depending on formulation type and application.
In general: gloves, coverall. If significant inhalation exposure is expected, RPE is needed (e.g. mixing & loading powders, high pressure spraying)

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

None

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: No
Product: No

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks:
We label with the safety precautionary sentence: "Contains "strain name of the microorgansism"; may have the potential to provoke sensitising reactions."

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: No

Product: No
Explanation / remarks:
We label generically as described above

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: No
Product: No

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes
Explanation / remarks:
We always use the safety precautionary sentence: "Contains "strain name of the microorganism"; may have the potential to provoke sensitising reactions."

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Not with R43/H317/H334. The standard safety precautionary sentence: "Contains "strain name of the microorganism"; may have the potential to provoke sensitising reactions." applies.

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Depending on formulation type and application. In general for operator: gloves, coverall. If significant inhalation exposure is expected, RPE is needed (e.g. mixing & loading powders, high pressure spraying); No PPE/RPE for re-entry worker.

10. Non-professional use
Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

No

New Zealand

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

We would evaluate a dossier that does not include a skin sensitisation study; However we would normally request that the applicant provides some justification/rationale for not conducting a study.

We have generally referred to the US EPA data requirements for microbial pesticides, where a skin sensitisation study is not required but a report should be provided on hypersensitivity incidents during the production or testing of the technical grade of the active ingredient, the manufacturing-use product or the end-use product. However in some cases we have approved a microbial pesticide even without this information.

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

Labelling may depend on whether any of the other components of the product are considered to be sensitisers.

If sensitising components are present at concentrations ≥ 0.1% (as specified under regulations underpinning the New Zealand Hazardous Substances and New Organisms [HSNO] Act) we would normally classify the product as a sensitiser and this would trigger labelling requirements.

If none of the components are considered sensitisers and there is no data on the micro-organism we would not currently require the product to be labelled.

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

A requirement for personal protective equipment (PPE) is triggered by almost all hazard classifications of a substance (the exceptions being for a mild skin irritant or an eye irritant). We would generally recommend that PPE is worn when a pesticide is used even if a risk assessment did not indicate a need for protective equipment to be worn, as it is considered good practice.

Under the HSNO Act the specific PPE that should be worn by an operator is generally left to the discretion of the person in charge of the hazardous substance unless we identify a need to require a specific type of equipment (e.g. a particular glove type).

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Gloves and a long sleeve shirt may be required depending on the outcome of our risk assessment. A re-entry interval may potentially be required.

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: Yes
Product: Yes
Explanation / remarks:
We have previously used study data when provided, although we may request that justification is provided as to the appropriateness of the study.

We are aware that there are questions over the validity of skin sensitisation studies for micro-organisms. We are currently reviewing our data requirements for microbial pesticides, taking into account the requirements of overseas regulators, and our position may change in future.

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes (classification with the NZ equivalent)
Explanation / remarks:
The regulations underpinning the HSNO Act provide specific criteria for classification as a contact sensitiser based on study data. A positive result in a sensitisation test would generally trigger classification unless we had good information to question the validity of the test.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: Yes
Product: Yes
Explanation / remarks:
We have previously used study data when provided, although we may request that justification is provided as to the appropriateness of the study.

We are aware that there are questions over the validity of skin sensitisation studies for micro-organisms. We are currently reviewing our data requirements for microbial pesticides, taking into account the requirements of overseas regulators, and our position may change in future.

5. Positive Maximisation test (micro-organism)

If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes (to the NZ equivalent)
Explanation / remarks:
The regulations underpinning the HSNO Act provide specific criteria for classification as a contact sensitiser based on study data. A positive result in a sensitisation test would generally trigger classification unless we had good information to question the validity of the test.

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: Yes / No
Product: Yes / No
Explanation / remarks:
We may have more reservations regarding the suitability of the LLNA for microorganisms, and we may require an applicant to provide a justification as to the applicability of the study.

We are aware that there are questions over the validity of skin sensitisation studies for micro-organisms. We are currently reviewing our data requirements for microbial pesticides, taking into account the requirements of overseas regulators, and our position may change in future.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes / No
Explanation / remarks:
The regulations underpinning the HSNO Act provide specific criteria for classification as a contact sensitiser based on study data. A positive result in a sensitisation test would generally trigger classification unless we had good information to question the validity of the test.

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

No
Explanation / remarks:
This is the current state of play in New Zealand however this position could potentially change in future as we review overseas practice.

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes

Explanation / remarks:

If there was no sensitising study with the product we would generally make a decision on whether to classify the product in accordance with mixture rules. Currently in New Zealand if a substance contains ≥ 0.1% of a sensitising component then classification as a sensitiser is triggered. So if the micro-organism active ingredient was present ≥ 0.1% we would classify the product as a sensitiser.

9. Protective Equipment

9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

As noted above a requirement for PPE would be triggered by the classification as a sensitiser. Under the current New Zealand framework the specific PPE to be worn is generally left to the discretion of the person in charge of the substance.

10. Non-professional use

Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

While the HSNO Act does not have a specific clause that the need for protective equipment prevents use by non-professionals, we may have concerns over whether a non-professional user would be likely to use the necessary PPE. This could potentially lead to us recommending that a substance is not approved; However this would be on a case by case basis.

Sweden

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

Yes

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

Contains XXX, may cause a sensitising reaction.

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

Gloves and respiratory protection.

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Gloves.

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: No
Product: No
Explanation / remarks:
Micro-organism: The test is not validated for micro-organisms.
Product: The test should be performed with a single compound where the concentration can be maximised and controlled. A formulated product is too diluted. Furthermore, a substance could accumulate in the skin and cause a sensitising reaction after repeated exposure which would not be detected in the test.

3. Positive Buehler test (micro-organism)
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No
Explanation / remarks:
We would accept the positive result and consider the organism as sensitising.
The CLP regulation is not applicable to micro-organisms as it states that it is only intended for chemical substances.

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: No

Product: No

Explanation / remarks:

Micro-organism: This test uses intradermal injection which would make it more reliable than the Buehler and LLNA tests as it ensures dermal bioavailability. However, it is not validated for micro-organisms.

Product: The test should be performed with a single compound where the concentration can be maximised and controlled. A formulated product is too diluted. Furthermore, a substance could accumulate in the skin and cause a sensitising reaction after repeated exposure which would not be detected in the test.

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No

Explanation / remarks:

We would accept the positive result and consider the organism as sensitising.

The CLP regulation is not applicable to micro-organisms as it states that it is only intended for chemical substances.

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: No

Product: No

Explanation / remarks:

Micro-organism: The test is not validated for micro-organisms.

Product: The test should be performed with a single compound where the concentration can be maximised and controlled. A formulated product is too diluted. Furthermore, a substance could accumulate in the skin and cause a sensitising reaction after repeated exposure which would not be detected in the test.

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

No

Explanation / remarks:

We would accept the positive result and consider the organism as sensitising.

The CLP regulation is not applicable to micro-organisms as it states that it is only intended for chemical substances.

8. Product labelling

8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes

Explanation / remarks:

We would label it with "Contains XXX, may cause a sensitising reaction".

PPE would be recommended as described above.

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

No

Explanation / remarks:

Since the conclusion on the product is based on data on the active micro-organism, the product should be labelled with "Contains XXX, may cause a sensitising reaction". Classification and labelling according to CLP would be relevant if the product contained a sensitising chemical substance.

9. Protective Equipment

9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

Operators: Gloves and protective equipment.
Re-entry workers: Gloves.

10. Non-professional use

Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?

In general yes. There might be exceptions however. We would primarily try to authorise products where exposure is minimised, e.g. closed systems

ANNEX 3: SURVEY QUESTIONNAIRE

Questionnaire on Regulatory and Testing Issues for the Sensitisation Potential of Micro-organisms

July 2014

Background

Plant Protection and biocidal products are available on the market that are based on or derived from micro-organisms. Micro-organisms have the potential to provoke sensitisation reactions by inhalation as well as through dermal exposure. However, it has been argued that the available skin sensitisation studies (Buehler, Guinea Pig Maximisation Test (GPMT), Local Lymph Node Assay (LLNA)) might not be useful or validated for the testing of micro-organisms. This has led to certain requirements in some OECD Member countries, e.g. in the EU it was agreed to use the following warning phrase on the label of packaging containing micro-organisms or products containing or based on micro-organisms:

'Micro-organisms may have the potential to provoke sensitising reactions'.

Instructions for completing the Questionnaire

The purpose of this questionnaire is to collect OECD Member country opinions and requirements on this subject so that commonalities or differences can be identified and options to help Member countries with this issue developed.

To make the results of the questionnaire as informative as possible, we specifically ask EU Member States to present their own opinion, and not the EU agreed position.

If you have any questions regarding the questionnaire, please contact the secretariat.

Please return this questionnaire to the secretariat (email to dan.merckel@oecd.org, cc Anna.Chahtahtinsky@oecd.org) by Friday the 26 September 2014.

1. No studies available
1a. Do you accept the dossier if no skin sensitisation study is provided for the micro-organism?

1b. If you do not have any sensitisation tests with the micro-organism and you agree that no sensitisation tests with the micro-organism are needed, how would you label the product containing these micro-organisms?

1c. What kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

1d. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

2. Negative Buehler test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Buehler test?

Micro-organism: Yes / no
Product: Yes / no
(please delete as applicable)

3. **Positive Buehler test (micro-organism)**
If a micro-organism shows positive results in a Buehler test, would you classify and/or label the micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes / no
(please delete as applicable)

4. Negative Maximisation test (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a Maximisation test?

Micro-organism: Yes / no
Product: Yes / no
(please delete as applicable)

5. Positive Maximisation test (micro-organism)
If a micro-organism shows positive results in a Maximisation test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes / no
(please delete as applicable)

6. Negative LLNA (micro-organism, product)
For micro-organisms or products containing micro-organisms, do you accept the negative results in a LLNA test?

Micro-organism: Yes / no
Product: Yes / no
(please delete as applicable)

7. Positive LLNA (micro-organism)
If a micro-organism shows positive results in a LLNA test, would you classify and/or label the micro-organism with R43 / H317 / H334?

Yes / no
(please delete as applicable)

8. Product labelling
8a. In your country, are there specific requirements for labelling products containing micro-organisms in terms of their potential hazard for skin/respiratory sensitisation and/or need for risk management (e.g. personal protective equipment)?

Yes / no
(please delete as applicable)
Explanation / remarks (i.e. what kind of labelling is used, examples)

8b. If a micro-organism (active ingredient) shows positive results in a sensitisation test, and there is no sensitisation study with the product, would you label the product containing this micro-organism with R43 / H317 / H334 or any other (chemical) hazard phrase?

Yes / no
(please delete as applicable)

9. Protective Equipment
9a. If you accept the positive results of any of the above mentioned sensitisation studies on the micro-organisms or the products, what kind of protective equipment would be needed (gloves, coverall, respiratory protection) for the operator during mixing and loading and during application?

9b. What kind of protective equipment – if at all - would in this case be needed (gloves, coverall, respiratory protection) for re-entry workers?

10. Non-professional use

Does the need for protective equipment for a product containing micro-organisms exclude the use by non-professionals in your country?