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Sharing of Government Biocides Reviews: Standard Operating Procedure and Harmonised Study Review Forms of the "6 pack" Acute Studies

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Series on Biocides

No. 14

Sharing of Government Biocides Reviews: Standard Operating Procedure and Harmonised Study Review Forms of the "6 pack" Acute Studies

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
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Foreword

This document provides the first outputs of the Review Sharing initiative which the Working Group on Biocides (WGB) has undertaken over the last few years. Review sharing was proposed to more efficiently leverage constrained specialist resources and permit those specialists (generally toxicologists) to pursue more value-added activities such as risk or exposure assessment.

An expert group of the WGB over the course of several meetings defined a process and created the necessary documents to realize the objectives of the project. The expert group reviewed available national checklists and processes to draft and refine Harmonized Standard Review Forms for the studies in scope and develop a Standard Operating Procedure for applicants and government reviewers to follow.

The studies included in this document are the acute studies commonly known as the “6 Pack”.

This publication has been made available thanks to the financial contribution of the South Korean government.

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Sharing of Government Biocides Reviews: Standard Operating Procedure and Harmonised Study Review Forms of the "6 pack" Acute Studies

Definition

Review sharing should not be confused with work sharing or joint reviews where a dossier is concurrently reviewed by several cooperating authorities. Further, review sharing does not suggest mandatory acceptance of classification, risk assessment, recommended risk mitigation measures or registration decisions by individual governments. Review sharing is instead the voluntary reference of reviews conducted by one government by other governments to obviate the need for multiple detailed reviews of common and straightforward studies. The studies included in the proposal are the acute studies commonly known as the “6 Pack” which includes:

- Acute Oral LD50
- Acute Dermal LD50
- Acute Inhalation LC50
- Ocular Irritation
- Dermal Irritation
- Skin Sensitization

Expected benefits

OECD Test Guidelines are in place for these studies and they are a commonly required element of dossiers for both active substances and formulated products. With the volume of product submissions received by government authorities, streamlining the review of these studies could have a significant positive impact in increased a capacity for other activities, one of which could be peer review or selective audit of shared reviews. The savings are expected to be considerable: should one product data set be submitted for registration to 30 OECD governments the “6 pack” would drive 180 independent reviews, review sharing could obviate the need for 174 of those reviews.

Process

The process envisioned for review sharing is fairly straightforward;

1. The data is generated per an OECD Guideline (or a local test guideline that is a verbatim adoption)
2. The study summary is prepared per the Harmonized Standard Review Form (HSRF)
3. The receiving government ensures the report is fit for review, reviews the study against agreed criteria in the HSRF, and issues their decision
4. The government provides the approved HSRF to the company. The company shares the HSRT with other governments.
5. Other governments may decide to rely on the HSRF rather than review the study.

The initial government reviewer would ensure that the laboratory adhered to the relevant OECD Test Guideline, followed Good Laboratory Practices (GLPs) and would comment on the report author's conclusions (agreeing or questioning). The reviewer would also comment on whether any deviations from the Test Guideline or GLP could have affected the outcome of the study.

On application to further governments, the initial review would be included by the applicant as a dossier element along with the original study and summary thus allowing any further reviews to be based on the study or reference to the initial review.

Box 1. Relationship between the Harmonised Study Review Forms and the OECD Harmonised Templates

The existing OECD Harmonised Templates (OHTs) are standard data formats for reporting information used for the risk assessment of chemicals, mainly studies done on chemicals to determine their properties or effects on human health and the environment, but also for storing data on use and exposure. They are aimed at developers of database systems, as they prescribe the formats by which information can be entered into and maintained in a database. By using these templates, governments and industry are easily able to electronically exchange test study summary information through these databases. The templates can be used to report summary test results for any type of chemical (e.g., pesticides, biocides, industrial chemicals). For more information on the OHTs, see http://www.oecd.org/ehs/templates/ .

Nevertheless, the OHTs do not contain any dedicated fields for documenting the outcome of the review of the studies by authorities. This is the subject of the present document, with a focus on acute studies for biocides.

As not all countries request summaries of studies in accordance with OHTs as part of the application dossier, the proposed Harmonised Study Review Forms (HSRFs) described in this document will contain both summary information of the submitted studies as well as specific fields for documenting the outcome of the review of the studies by authorities. The relationship between the HSRFs and OHTs was carefully taken into account and the

labels and formats of data elements defined in the OHTs were reused as much as possible.

Countries that request summaries of studies in accordance with OHTs as part of the application dossier could implement an automatic export of the information contained in the OHT fields into the HSRF fields in order to reduce double work. Note that the current version of IUCLID, one of the existing electronic tool for data submission that implements the OHTs, contains a few fields for comments by the reviewer but the review fields proposed in the HSRFs would be an enhancement of those proposed in IUCLID. The OECD IUCLID User Expert Group might wish in the future to consider whether and how the technical possibilities and functions of IUCLID can be used to automatically generate the HSRF from the OHT study data collected in IUCLID and enable the exchange and updates (Document Life Cycle Management) of the HSRF.

1. Standard Operating Procedure

1.1. Issue

1. Although the processes and timelines to approve new biocide active ingredients and new biocide products differ globally, many of the data requirements and steps are quite similar. Aligning where possible and sharing information will save resources and benefit governments and industry.

1.2. Goals

- Streamline study review processes for biocides and facilitate information sharing across regulatory authorities.
- Leverage the expert reviews for standard individual laboratory studies to free up limited government resources to pursue more value-added activities.
- Support independent risk assessments and approval decisions by regulatory authorities.

1.3. Benefits

2. Sharing study reviews will result in more efficient government approval of safe, efficacious biocides and resource savings for governments and industry. The savings offered by review sharing are expected to be considerable. If one new product was submitted for approval to 30 OECD governments, 180 independent reviews would be necessary for the acute studies. Review sharing could avoid the need for 174 of those reviews.

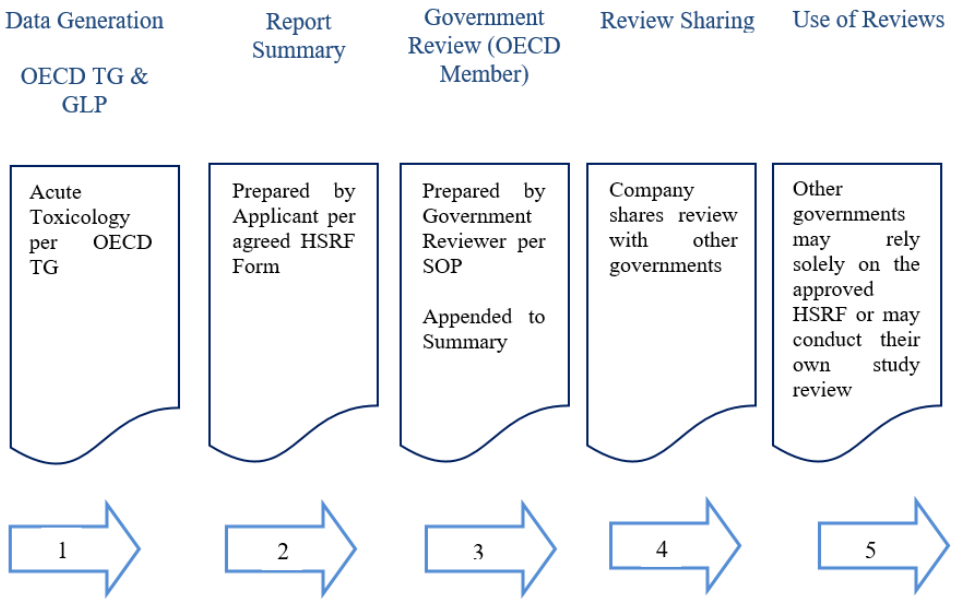
1.4. Scope

3. Acute *in vivo* toxicity studies for biocide products and active substances (commonly referred to as "6-pack studies"), which are primarily used for hazard classification and labeling.

- Acute Oral Toxicity LD50
- Acute Dermal Toxicity LD50
- Acute Inhalation Toxicity LC50
- Ocular Irritation
- Dermal Irritation
- Skin Sensitization

1.5. Process

Figure 1: Overview of the review sharing procedure for acute *in vivo* "6-pack"toxicity studies



1.5.1. Conduct of Studies

4. This procedure applies to studies conducted according to the respective OECD test guidelines (or local guideline that is a verbatim adoption) (Figure 1, step 1).

1.5.2. Applicant Submission of Acute Toxicology Data

5. Applicants will include in their application dossier a Harmonized Study Review Form (HSRF) for each study subject to this process. The Applicant should complete the sections of the HSRF summarizing the study information (Figure 1, step 2).

6. Applicants should also include a list of countries to which they intend to submit the data set.

1.5.3. Review of Acute Toxicology Data

7. The government reviewer should add reviewer decisions and revise applicant proposed information in the HSRF as necessary. The government should return the completed and approved HSRF to the applicant following their typical procedures. Or, the applicant should request return of the completed HSRFs if necessary in accordance with local practice (Figure 1, step 3).

Versions

8. A government commenting on a received HSRF (corrections, edits, general comments) should append their input to the original HSRF. The appended HSRF should be provided to the applicant as described in ***1.5.3***.

Formulation Changes

9. The test formulation is identified in both the study report and the accompanying HSRF. Local government policies would determine sufficiency of an HSRF developed for a different formulation.

1.5.4. Sharing of Reviews and Use by Other Government Authorities

Applicant

10. Provide a copy of the HSRF approved by the first government in each subsequent application to other governments (Figure 1, step 4).

Government

11. Governments receiving these documents may choose to save resources and rely solely on the HSRF approved by the first government. Governments may also choose to do their own review of the study. The outcome of additional reviews could be compared to the initial review and comments shared with the applicant and reviewing authority as deemed appropriate. Each government will make independent regulatory decisions.

2. Harmonized Standard Review Forms

Table 2.1. Harmonised study review form (HSRF) for acute oral toxicity procedures (OECD TG 420, 423, 425)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report? (yes/no, if no why?)	

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD (specify which guideline was used)	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
30			**Test Material**	
31	X		Product name (Product Code; Batch No.)	
32	X		Physical Appearance	
33	X		Composition of formulation[1]	(see Annex A)
34	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
35	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
36	X		pH of formulation	
37	X		Source of test material[2]	
38		X	Is text associated with SRPs in rows 31 to 37 consistent with report?	(yes/no, if no why?)
39		X	Is AI approved for use in new product under review?[3]	(yes/no)

[1] See Annex A for formulation composition or the location of such information in the dossier.

[2] For example, "Test material obtained from a pressurized aerosol can".

[3] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
40			**Reference Product**[4] (if applicable)	
41	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)
42		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)
43		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
			METHODS	
44			**Animals**	
45	X		Species	
46	X		Strain	
47	X		Gender	
48	X		Age	
49	X		Body weight upon receipt	
50	X		Number of animals/sex/group	
51	X		Housing and feeding conditions	
52	X		Acclimatization period	
53	X		Source (name & address)	
54		X	Is text associated with SRPs in rows 45 to 53 consistent with report?	(yes/no, if no why?)

[4] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is refered to as "bridging". See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program.

Row No.	Completed by Applicant	Completed by Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
55			**Test Material**	
56	X		Dose(s) tested (mg/kg/bw)	
57	X		Dose volume (ml test material/kg/bw)	
58	X		Vehicle/Dilution	
59	X		Route of administration	
60		X	Is text associated with SRPs in rows 56 to 59 consistent with report?	(yes/no, if no why?)
61			**Toxicological Measurements**[5]	
62	X		Body weight at pre-dose	
63	X		Post exposure observation period	
64	X		Body weight at 7 & 14 days post-dose	
65	X		Mortality/clinical signs first several hours post-dose	
66	X		Mortality/clinical signs at least once daily for 14 days	
67	X		Necropsy and histological findings at end of study	
68		X	Is text associated with SRPs in rows 62 to 67 consistent with report?	(yes/no, if no why?)

[5] Briefly described measurements noted in rows 62 to 67 and study dates on which they were taken.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		

69			**RESULTS**	
70	X		Estimated LD_{50}	
71	X		Table with Number Deaths/Number Tested for males, females and combined also reflecting the clinical signs, duration of signs and time of death[6]	
72	X		Method to determine LD_{50}	
73		X	OECD Statistical Software run by reviewing competent authority [Applies to OECD TG 425 only] [7]	(reviewer attaches print-out of statistical evaluation in Annex D)
74	X		Clinical Observations	
75	X		Body weight gain/loss	
76	X		Gross necropsy	
77		X	Is text associated with SRPs in rows 70 to 76 consistent with report?	(yes/no, if no why?)
78				
79			**CONCLUSIONS**	
80		X	Overall conclusions and comments	
81		X	Does the reviewer agree with the reported LD_{50}?	(yes/no)
82		X	If no, reviewer's rationale is stated.	
83		X	Hazard Classification	
84		X	GHS	
85		X	Local	
86		X	Local Label [optional]	
87	X		Report[8]	

[6] See Annex C

[7] Print-out of OECD Statistical Software (AOT425StatPgm) placed in Annex D by the reviewing competent authority

[8] Full report is mentioned in Annex E.

Table 2.2. Harmonised Study Review Form (HSRF) for Acute Dermal Toxicity (OECD TG 402)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report?	(yes/no, if no why?)
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)
30			**Test Material**	
31	X		Product Name (Product Code; Batch No.)	
32	X		Physical Appearance	
33	X		Composition of formulation[9]	(see Annex A)
34	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
35	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
36	X		pH of formulation	
37	X		Source of test material [10]	
38		X	Is text associated with SRPs in rows 31 to 37 consistent with report?	(yes/no, if no why?)
39		X	Is AI approved for use in new product under review? [11]	(yes/no)
Row No.	**Completed by: Applicant**	**Completed by: Reviewer**	**Study Review Parameter (SRP)**	**Text Entered by Applicant or Reviewer**
40			**Reference Product**[12] (if applicable)	
41	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)
42		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)

43		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
44			**METHODS**	
45			**Animals**	
46	X		Species	
47	X		Strain	
48	X		Gender	
49	X		Age	
50	X		Body weight upon receipt	
51	X		Housing and feeding conditions	
52	X		Acclimatization period	
53	X		Number of animals/sex/group	
54	X		Source (name & address)	
55		X	Is text associated with SRPs in rows 46 to 54 consistent with report?	(yes/no, if no why?)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		

[9] See Annex A for formulation composition or the location of such information in the dossier.

[10] For example, “Test material obtained from a pressurized aerosol can”.

[11] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

[12] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is referred to as “bridging”. See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program

			METHODS (continued)	
56			**Test Material**	
57	X		Dose(s) tested (mg/kg/bw)	
58	X		Dose volume (ml test material/kg/bw)	
59	X		Vehicle/Dilution	
60	X		Area Covered	
61	X		Occlusion	
62	X		Duration of exposure	
63	X		Removal of test substance	
64		X	Is text associated with SRPs in rows 57 to 63 consistent with report?	(yes/no, if no why?)
65			**Toxicological Measurements**[13]	
66	X		Body weight at pre-dose	
67	X		Post observation period	
68	X		Body weight at 7 & 14 days post-dose	
69	X		Mortality/clinical signs first several hours post-dose	
70	X		Mortality/clinical signs at least once daily for 14 days	
71	X		Necropsy and histopathological findings at end of study	
72		X	Is text associated with SRPs in rows 66 to 71 consistent with report?	(yes/no, if no why?)

[13] Briefly described measurements noted in rows 66 to 71 and study dates on which they were taken.

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
73			**RESULTS**	
74	X		Estimated LD_{50}	
75	X		Table with Number Deaths/Number Tested for males, females and combined also reflecting the clinical signs, duration of signs and time of death[14]	
76			Method to determine LD_{50}	
77	X		Clinical Observations	
78	X		Body weight gain/loss	
79	X		Gross necropsy	
80		X	Is text associated with SRPs in rows 75 to 79 consistent with report?	(yes/no, if no why?)
81			**CONCLUSIONS**	
82		X	Overall conclusions and comments	
83		X	Does the reviewer agree with the reported LD_{50}?	(yes/no)
84		X	If no, reviewer's rationale is stated.	
85		X	Hazard Classification	
86		X	GHS	
87		X	Local	
88		X	Local Label [optional]	
89	X		Report[15]	

[14] See Annex F

[15] Full report is mentioned in Annex G

Table 2.3. Harmonised Study Review (HSRF) for Acute Inhalation Toxicity Study (OECD TG 403)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report?	(yes/no, if no why?)
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)
30			**Test Material**	
31	X		Product Name (Product Code; Batch No.)	
32	X		Physical Appearance	
33	X		Composition of formulation[16]	(see Annex A)
34	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
35	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
36	X		pH of formulation	
37	X		Source of test material [17]	
38		X	Is text associated with SRPs in rows 31 to 37 consistent with report?	(yes/no, if no why?)
39		X	Is AI approved for use in new product under review? [18]	(yes/no)
Row No.	**Completed by: Applicant**	**Completed by: Reviewer**	**Study Review Parameter (SRP)**	**Text Entered by Applicant or Reviewer**
			Test Material (continued)	
40			**Reference Product**[19] (if applicable)	
41	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)

42		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)
43		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
44			**METHODS**	
45			**Animals**	
46	X		Species	
47	X		Strain	
48	X		Gender	
49	X		Age	
50	X		Body weight upon receipt	
51	X		Number of animals/sex/group	
52	X		Housing and feeding conditions	
53	X		Acclimatization period	
54	X		Source (name & address)	
55		X	Is text associated with SRPs in rows 46 to 54 consistent with report?	(yes/no, if no why?)

[16] See Annex A for formulation composition or the location of such information in the dossier.

[17] For example, “Test material obtained from a pressurized aerosol can”.

[18] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

[19] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is referred to as “bridging”. See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
			METHODS (continued)	
56			**Key Exposure Parameters**	
57	X		Whole body or nose only?	
58	X		Exposure to gas/vapour/aerosol or mixture	
59	X		Type of preparation of particles	
60	X		Vehicle/dilution	
61	X		Chamber volume (L)	
62	X		Total air flow (L/min)	
63	X		Temperature (°C)	
64	X		Relative humidity (%)	
65	X		Atomization process (if required)	
66	X		Time to equilibrium (min)	
67	X		Exposure duration	
68	X		Mass Median Aerodynamic Diameter ± GSD[20]	
69	X		Mean actual exposure concentration (mg/L)	
70	X		Mean nominal concentration (mg/L)	
71	X		Were exposure concentrations measured by gravimetric or chemical analysis?	
72		X	Is text associated with SRPs in rows 57 to 71 consistent with report?	(yes/no, if no why?)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer

[20] GSD = Geometric Standard Deviation

73			**Toxicological Measurements**[21]	
74	X		Body weight prior to exposure on day 0	
75	X		Post exposure observation period	
76	X		Body weight at 1, 3, 7 & 14 days post-exposure	
77	X		Mortality/clinical signs during and up to 1 hr after exposure on day 0	
78	X		Mortality/clinical signs at least once daily for 14 days after exposure	
79	X		Gross necropsy (and histology) on moribund animals and all animals that survive to end of study	
80		X	Is text associated with SRPs in rows 74 to 79 consistent with report?	(yes/no, if no why?)
81			**RESULTS**	
82	X		Estimated LC_{50}	
83	X		Table with Number Deaths/Number Tested for males, females and combined also reflecting the clinical signs, duration of signs and time of death[22]	
84	X		Method to determine LC_{50}	
85	X		Clinical observations	
86	X		Body weight gain/loss	
87	X		Gross necropsy	
88		X	Is text associated with SRPs in rows 82 to 87 consistent with report?	(yes/no, if no why?)

[21] Briefly described measurements noted in rows 74 to 79 and study dates on which they were taken

[22] See Annex H

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)		Text Entered by Applicant or Reviewer
89			**CONCLUSIONS**		
90		X	Overall conclusions/comments		
91		X	Does the reviewer agree with the reported LC_{50}?	(yes/no)	
92		X	If no, reviewer's rationale is stated.		
93		X	Hazard Classification		
94		X		GHS	
95		X		Local	
96		X	Local Label [optional]		
97	X		Report[23]		

[23] Full report is mentioned in Annex I

Table 2.4. Harmonised Study Review Form (HSRF) for Acute Eye Irritation/Corrosion (In Vivo) Study (OECD TG 405)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report?	(yes/no, if no why?)
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)
30	X		Justification for *in vivo* testing taking into considerations noted in OECD TG 405 (2015) under "Initial Considerations"	
31			**Test Material**	
32	X		Product Name (Product Code; Batch No.)	
33	X		Physical Appearance	
34	X		Composition of formulation[24]	(see Annex A)
35	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
36	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
37	X		pH of formulation	
38	X		Source of test material [25]	
39		X	Is text associated with SRPs in rows 32 to 38 consistent with report?	(yes/no, if no why?)
40		X	Is AI approved for use in new product under review? [26]	(yes/no)
Row No.	**Completed by**		**Study Review Parameter (SRP)**	**Text Entered by Applicant or Reviewer**
	Applicant	Reviewer		
41			**Reference Product**[27] (if applicable)	
42	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)

43		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)
44		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
45			**METHODS**	
46			**Animals**	
47	X		Species	
48	X		Strain	
49	X		Gender	
50	X		Age	
51	X		Body weight upon receipt	
52	X		Number of animals/sex/group	
53	X		Housing and feeding conditions	
54	X		Acclimatization period	
55	X		Source (name & address)	
56		X	Is text associated with SRPs in rows 47 to 55 consistent with report?	(yes/no, if no why?)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		

[24] See Annex A for formulation composition or the location of such information in the dossier.

[25] For example, “Test material obtained from a pressurized aerosol can”.

[26] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

[27] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is referred to as “bridging”. See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program

57			**Administration of Test Material**	
58	X		Pre-dose ocular anesthesia regimen	
59	X		Vehicle (identification, conc., volume)	
60	X		Test material volume	
61	X		Concentration tested	
62	X		Duration of administration (aerosol spray time, if applicable)[28]	
63	X		Untreated eye as control	
64	X		Exposure duration	
65	X		Time point of removal and conditions of washing	
66	X		Ocular sites observed (cornea, iris, conjunctiva)	
67	X		Observation times relative to dosing	
68	X		Description of evaluation method	
69	X		Description of method used to score irritation (e.g. hand slit-lamp, biomicroscope, fluorescein)	
70		X	Is text associated with SRPs in rows 58 to 69 consistent with report?	(yes/no, if no why?)
71			**METHODS (continued)**	
72	X		**Toxicological Measurements**[29]	
73	X		Body weight prior to dose on day 0	
75	X		Post exposure observation period	
76	X		Body weight at end of study	
77	X		Mortality/clinical signs at least once daily during testing period	
78		X	Is text associated with SRPs in rows 73 to 77 consistent with report?	(yes/no, if no why?)

[28] Applicable if test material was administered as an aerosol.

[29] Briefly describe measurements noted in rows 73 to 77 and study dates on which they were taken.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
79			**RESULTS**	
80	X		Maximum Mean Total Score (MMTS)	
81	X		Table with ocular irritation scores for cornea, iris and conjunctiva per observation period for each animal tested[30]	
82	X		Brief summary of clinical observations	
83	X		Brief summary of body weight gain/loss	
84		X	Is text associated with SRPs in rows 80 to 83 consistent with report?	(yes/no, if no why?)
85			**CONCLUSIONS**	
86		X	Overall conclusions and comments	
87		X	Reviewer agrees with the reported MMTS[31]	(yes/no)
88		X	Overall conclusions and comments	
89		X	If no, reviewer's rationale is stated.	
90		X	Hazard Classification	
91		X	GHS	
92		X	Local	
93		X	Local Label [optional]	
94	X		Report[32]	

[30] See Annex J.

[31] MMTS = Mean Maximal Total Score

[32] Full report is mentioned in Annex K.

Table 2.5. Harmonised Study Review Form (HSRF) for Acute Dermal Irritation/Corrosion (In Vivo) Study (OECD TG 404)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report?	(yes/no, if no why?)
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)
30	X		Justification for *in vivo* testing taking into considerations noted in OECD TG 404 (2015) under "Initial Considerations"	
31			**Test Material**	
32	X		Product Name (Product Code; Batch No.)	
33	X		Physical Appearance	
34	X		Composition of formulation[33]	(see Annex A)
35	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
36	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
37	X		pH of formulation	
38	X		Source of test material [34]	
39		X	Is text associated with SRPs in rows 32 to 38 consistent with report?	(yes/no, if no why?)
40		X	Is AI approved for use in new product under review? [35]	(yes/no)
Row No.	**Completed by**		**Study Review Parameter (SRP)**	**Text Entered by Applicant or Reviewer**
	Applicant	Reviewer		
41			**Reference Product**[36] (if applicable)	
42	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)

43		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)
44		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
S				
45			**METHODS**	
46			**Animals**	
47	X		Species	
48	X		Strain	
49	X		Gender	
50	X		Age	
51	X		Body weight upon receipt	
52	X		Number of animals/sex/group	
53	X		Housing and feeding conditions	
54	X		Acclimatization period	
55	X		Source (name & address)	
56		X	Is text associated with SRPs in rows 47 to 55 consistent with report?	(yes/no, if no why?)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		

[33] See Annex A for formulation composition or the location of such information in the dossier.

[34] For example, “Test material obtained from a pressurized aerosol can”.

[35] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

[36] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is referred to as “bridging”. See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program

57			**Administration of Test Material**	
58	X		Fur clipping procedure	
59	X		Application area	
60	X		Topical application procedure (e.g., dermal occlusion, Elizabethan collars, application site cleansing)	
61	X		Time point of removal	
62	X		Duration	
63	X		Vehicle, including amount	
64	X		Test dose (mL or g)	
65	X		Description of evaluation method	
66		X	Is text associated with SRPs in rows 58 to 65 consistent with report?	(yes/no, if no why?)
67			**METHODS (continued)**	
68	X		Toxicological Measurements[37]	
69	X		Body weight prior to dose on day 0	
70	X		Post exposure observation period	
71	X		Body weight at end of study	
72	X		Mortality/clinical signs (local and systemic) at least once daily during testing period	
73	X		Gross necropsy (and histology) on moribund animals and all animals that survive to end of study, if necessary	
74		X	Is text associated with SRPs in rows 68 to 73 consistent with report?	(yes/no, if no why?)

[37] Briefly describe measurements noted in rows 69 to 73 and study dates on which they were taken.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
75			**RESULTS**	
76	X		Primary Dermal Irritation Index (PDII)	
77	X		Table with mean erythema, mean edema and primary dermal irritation (PDI) scores per observation period[38]	
78	X		Brief summary of clinical observations	
79	X		Brief summary of body weight gain/loss	
80		X	Is text associated with SRPs in rows 76 to 79 consistent with report?	(yes/no, if no why?)
81			**CONCLUSIONS**	
82		X	Overall conclusions and comments	
83		X	Reviewer agrees with the reported PDII	(yes/no)
84		X	If no, reviewer's rationale is stated.	
85				
86		X	Hazard Classification	
87		X	GHS	
88		X	Local	
89		X	Local Label [optional]	
90	X		Report[39]	

[38] See Annex L.

[39] Full report is mentioned in Annex M.

Table 2.6. Harmonised Study Review Form (HSRF) for Dermal Sensitization: Buehler Procedure (OECD TG 406)

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
1			**ADMINSTRATIVE**	
2		X	Competent Authority	
3		X	Reviewer	
4		X	HSRF No.	
5	X		Sponsor/Address	
6	X		Product Name	
7	X		Sponsor's Product Code	
8	X		Study Title	
9	X		Laboratory Study No.	
10	X		Testing Laboratory/Address	
11	X		Study Director	
12	X		Start and end dates of in-life phase of study	
13	X		Report Date	
14		X	Is text associated with SRPs in rows 5 to 13 consistent with report?	(yes/no, if no why?)
15			**Relevant Study Guidelines**	
16	X		Local	
17	X		OECD	
18		X	**Summary of the Review Findings**	
19			**Acceptability of Study**	
20		X	Is study acceptable for review in accord with relevant local guideline?	(yes/no, if no why?)
21		X	Is study acceptable for review in accord with relevant OECD guideline?	(yes/no, if no why?)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
22	X		**Deviations from guideline**	
23		X	Do you agree that a complete list of deviations is presented in row 22 as noted from your review of the report?	(yes/no, if no why?)
24		X	Do deviations preclude review?	(yes/no, if yes why?)
25			**ADMINSTRATIVE (continued)**	
26			**Compliance / Data Confidentiality**	
27		X	Is a signed GLP Statement provided?	(yes/no)
28		X	Is a signed QA Statement provided?	(yes/no)
29		X	Is a signed Data Confidentiality Statement provided?	(yes/no)
30			**TEST MATERIAL**	
31	X		Product Name (Product Code; Batch No.)	
32	X		Physical Appearance	
33	X		Composition of formulation[40]	(see Annex A)
34	X		AI(s) (% w/w) in test material as stated in pre- & post-study certificates of analysis	Pre-dose: Post-dose:
35	X		Is AI stable in test material during testing period as concluded from certificates of analysis?	(yes/no)
36	X		pH of formulation	
37	X		Source of test material [41]	
38		X	Is text associated with SRPs in rows 31 to 37 consistent with report?	(yes/no, if no why?)
39		X	Is AI approved for use in new product under review? [42]	(yes/no)

Row No.	Completed by: Applicant	Completed by: Reviewer	Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer

[40] See Annex A for formulation composition or the location of such information in the dossier.

40			**TEST MATERIAL (continued)**	
41			**Reference Product**[43] (if applicable)	
42	X		Side-by-side comparison of the new product's composition with that of the reference product	(see Annex B)
43		X	Is the new product substantially equivalent to reference product with respect to composition?	(yes/no, if no why?)
44		X	Do toxicology data of the reference product adequately characterize the toxicity of the new product based on compositional similarity?	(yes/no, if no why?)
45			**ANIMALS**	
46	X		Species	
47	X		Strain	
48	X		Gender	
49	X		Age	

[41] For example, "Test material obtained from a pressurized aerosol can".

[42] Applies to the jurisdiction of the reviewing competent authority (CA) and may, or may not, apply to other CAs participating in the OECD review share program.

[43] A reference product refers to a product approved for marketed use by the reviewing CA and whose toxicology data are being used by the Applicant to characterize the toxicity of the new product under review. This process is referred to as "bridging". See Annex B for formulation comparison of the new and reference products or the location of such information in the dossier. The reference product may, or may not, be approved for marketed use by other CAs participating in the OECD review share program.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
50			**TOXICOLOGICAL MEASUREMENTS**	
51	X		Body weight upon receipt	
52	X		Body weight at experimental start	
53	X		Body weight at the experimental end	
54	X		Number of animals/sex/group	
55	X		Housing and feeding conditions	
56	X		Acclimatization period	
57	X		Source (name & address)	
58	X		Results and date of reliability check with known skin sensitizers	
59		X	Is text associated with SRPs in rows 46 to 49 and rows 51 to 58 consistent with report?	(yes/no, if no why?)
60			**TOXICOLOGICAL MEASUREMENTS (cont.)**	
61			**Preliminary Irritation Screen**[44]	
62	X		Number of animals/sex/group	
63	X		Test material volume	
64	X		Concentrations tested (% undiluted by wt)	
65	X		Vehicle/dilution	
66	X		No. of concentrations tested per animal	

[44] Purpose of preliminary irritation screen is to identify the highest non-irritating concentration (HNIC) for use in induction and challenge phase.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
67			**Induction Phase**	
68	X		Number of animals/sex/group	
69	X		Test material volume	
70	X		Concentration tested (% undiluted by wt)	
71	X		Vehicle/dilution	
72	X		Was the highest concentration tested to cause mild irritation?	(yes/no, if no why?)
73	X		Number of test material applications per week	
74	X		Number of weeks test material was applied	
75	X		Duration of each application	
76	X		Were local skin reactions measured 24 and 48 hours after each application?	
77	X		Was removal of the test substance necessary?	
78	X		Duration of induction period	

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
79			**TOXICOLOGICAL MEASUREMENTS (cont.)**	
80				
81			**Challenge Phase**	
82	X		Was test material at the HNIC applied to a naïve site[45] on each animal that received test material in the induction phase?	(yes/no, if no why?)
83	X		Were test material vol./conc. identical to the concentration used in the induction phase?	(yes/no, if no why?)
84	X		Vehicle/dilution, if applicable	
85	X		Duration of challenge phase	
86	X		Number of animals used as naïve controls	
87	X		Was a positive control group tested concurrently in the study? If no, was a positive control study conducted within 6 months of the current study also submitted in the data package?	
88		X	Is text associated with SRPs in rows 82 to 87 consistent with report?	(yes/no, if no why?)
89			**RESULTS**	
90	X		Table with incidence and severity of sensitization response noted after challenge in test and naïve control animals[46]	

[45] For example, test material was applied to left side of each animal in the induction phase and to the right, naive side of the same animals in the challenge phase.

[46] See Annex N.

Row No.	Completed by		Study Review Parameter (SRP)	Text Entered by Applicant or Reviewer
	Applicant	Reviewer		
91			**CONCLUSIONS**	
92		X	Overall conclusions and comments	
93	X		Body weight gain/loss	
94	X		Clinical observations (other than irritation/sensitization, local and systemic)	
95	X		Conclusion of study director	(product is, or is not a dermal sensitizer)
96		X	Does reviewer agree with the conclusion of the study director as stated in row 95?	(yes/no)
97		X	If no, reviewer's rationale is stated.	
98		X	Hazard Classification	
99		X	GHS	
100		X	Local	
101		X	Local Label [optional]	
102	X		Report[47]	

[47] Full report is mentioned in Annex O.

Annex A. Formulation table
(referring to row 33 of Acute Oral Toxicity, Acute Dermal Toxicity, Acute Inhalation Toxicity and Dermal Sensitization, row 34 of Acute Eye Irritation and Acute Dermal Irritation)

Applicant inserts table containing all ingredients of new product formulation along with the following information: Constituents, CAS No., Concentration (% w/w) and Purpose or indicates where this information can be found in the dossier.

Annex B. (If applicable) Comparison of new product formulation with formulation of reference product (referring to row 40 of Acute Oral Toxicity, Acute Dermal Toxicity and Acute Inhalation Toxicity row 41 of Acute Eye Irritation, Acute Dermal Irritation and Dermal Sensitization)

Applicant inserts table containing all ingredients of new and reference product formulation along with the following information: Constituents, CAS No., Concentration (% w/w) and Purpose or indicates where this information can be found in the dossier.

Annex C. Example for a reporting table (referring to row 71 of Acute Oral Toxicity)

Applicant inserts the following table or indicates where this table can be found in the dossier.

Figure A C.1. Results of Acute Oral Toxicity Study in Rats Treated with <insert product code/name>

Dose (mg/kg bw)	Toxicological results*	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
xxx	x/x/x	xxx	xxx	> xxx
Female rats				
xxx	x/x/x	xxx	xxx	> xxx

Note: Number of animals which died/number of animals with clinical signs/number of animals used

Annex D. OECD Statistical Printout (referring to row 73 of Acute Oral Toxicity)

Print-out of OECD Statistical Software (AOT425StatPgm) attached by reviewer of competent authority.

Annex E. Full report (referring to row 87 of Acute Oral Toxicity)

Applicant indicates that report can be found in the dossier

Annex F. Example for a reporting table (referring to line 75 of Acute Dermal Toxicity)

Applicant inserts the following table or indicates where this table can be found in the dossier.

Figure A F.1. Results of Acute Dermal Toxicity Study in Rats Treated with <insert product code/name>

Dose (mg/kg bw)	Toxicological results*	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
xxx	x/x/x	xxx	xxx	> xxx
Female rats				
xxx	x/x/x	xxx	xxx	> xxx

Note: Number of animals which died/number of animals with clinical signs/number of animals used.

Annex G. Full Report (referring to row 89 of Acute Dermal Toxicity)

Applicant indicates that report can be found in the dossier.

Annex H. Example for a reporting table (referring to line 83 of Acute Inhalation Toxicity)

Applicant inserts the following table or indicates where this table can be found in the dossier.

Figure A H.1. Results of Acute Inhalation Toxicity Study in Rats Treated with <insert product code/name>

Dose (mg/L air)	Toxicological results*	Duration of signs	Time of death	LC_{50} (mg/L air)** (14 days)
Male rats				
xxx	x/x/x	xxx	xxx	> xxx
Female rats				
xxx	x/x/x	xxx	xxx	> xxx

Note:
* Number of animals which died/number of animals with clinical signs/number of animals used.
** Animals were exposed to test material on day 0 for <insert duration of exposure>.

Annex I. Full Report (referring to row 97 of Acute Inhalation Toxicity)

Applicant indicates that report can be found in the dossier.

Annex J. An example of a reporting table (referring to line 81 of Acute Eye Irritation)

Applicant inserts the following tables or indicates where these tables can be found in the dossier.

Figure A J.1. Ocular Irritation Scores of Individual Animals: Eye Treated with <insert product code/name>

	Rabbit No. 1: (gender)									Rabbit No. 2: (gender)									Rabbit No. 3: (gender)								
	Hours					Days				Hours					Days				Hours					Days			
	1	24	48	72	96	7	14	21	R/I *	1	24	48	72	96	7	14	21	R/I *	1	24	48	72	96	7	14	21	R/I *
Cornea																											
Opacity																											
Area																											
Score I (AXB) x 5																											
Iris																											
Values																											
Score II AX5																											
Conjunctivae																											
Redness																											
Chemosis																											
Discharge																											
Score III (A+B+C) x 2																											
Total Score																											

Note: * Response noted as either reversible (R) or irreversible (I).

The time interval with the highest Total Score for each rabbit was used to calculate Mean Maximal Total Score (MMTS) and thereby classify the test substance (Kay & Calandra, 1962).

MMTS = [highest Total Score (rabbit#1) + highest Total Score (rabbit#2) + highest Total Score (rabbit#3)] ÷ 3

Figure A J.2. Ocular Irritation Scores of Individual Animals: Untreated Eye

	Rabbit No. 1: (gender)								Rabbit No. 2: (gender)								Rabbit No. 3: (gender)							
	Hours					Days			Hours					Days			Hours					Days		
	1	24	48	72	96	7	14	21	1	24	48	72	96	7	14	21	1	24	48	72	96	7	14	21
Cornea																								
Opacity																								
Area																								
Score I = (AXB)x5																								
Iris																								
Values																								
Score II = AX5																								
Conjunctivae																								
Redness																								
Chemosis																								
Discharge																								
Score III= (A+B+C)x2																								
Total Score																								

Note: The time interval with the highest Total Score for each rabbit was used to calculate Mean Maximal Total Score (MMTS) and thereby classify the test substance (Kay & Calandra, 1962).

MMTS = [highest Total Score (rabbit#1) + highest Total Score (rabbit#2) + highest Total Score (rabbit#3)] ÷ 3

Figure A J.3. Scale for Scoring Ocular Lesions

1. Cornea

A. Opacity-degree of density (area most dense taken for reading)

No Opacity 0

Scattered or diffuse area, details of iris clearly visible ..... 1[48]

Easily discernible translucent areas, details of iris slightly obscured ..... 2[11]

Opalescent areas, no details of iris visible, size of pupil barely discernible ..... 3[11]

Opaque, iris invisible ..... 4[11]

B. Area of cornea involved

One quarter (or less) but not zero 1

Greater than one quarter, but less than half 2

Greater than half, but less than three quarters 3

Greater than three quarters, up to whole area 4

Cornea Score: A X B X 5 Total Maximum = 80

2. Iris

A. Values

Normal 0

Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive) ..... 1[11]

No reaction to light, hemorrhage, gross destruction (any or all of these) ..... 2[11]

Iris Score: A X 5 Total Maximum = 10

[48] These scores represent a positive response

3. Conjunctivae

A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal 0
Vessels definitely injected above normal 1
More diffuse, deeper crimson red, individual vessels not easily discernible ..... 2[11]
Diffuse beefy red ..... 3[11]

B. Chemosis

No swelling 0
Any swelling above normal (includes nictitating membrane) 1
Obvious swelling with partial eversion of lids ..... 2[11]
Swelling with lids about half-closed ..... 3[11]
Swelling with lids about half-closed to completely closed ..... 4[11]

C. Discharge.

No discharge 0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) 1
Discharge with moistening of the lids and hairs just adjacent to lids 2
Discharge with moistening of the lids and hairs, and considerable area around the eye 3

Conjunctivae Score: (A + B + C) X 2 Total Maximum = 20

Total Maximum Score of 110 represents the sum of all scores obtained for the cornea (80), iris (10) and conjunctivae (20).

Figure A J.4. Grading of Ocular Lesions[49]

Cornea	Grade
Opacity: degree of density (readings should be taken from most dense area)*	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre); details of iris clearly visible	1
Easily discernible translucent area; details of iris slightly obscured	2
Nacrous area; no details of iris visible; size of pupil barely discernible	3
Opaque cornea; iris not discernible through the opacity	4
Maximum possible: 4	
* The area of corneal opacity should be noted	
Iris	
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia; or injection; iris reactive to light (a sluggish reaction is considered to be an effect)	1
Hemorrhage, gross destruction, or no reaction to light	2
Maximum possible: 2	
Conjunctivae	
Redness (refers to palpebral and bulbar conjunctivae; excluding cornea and iris)	
Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse,crimson colour; individual vessels not easily discernible	2
Diffuse beefy red	3
Maximum possible: 3	

[49] OECD (2012), Test No. 405: Acute Eye Irritation/Corrosion, OECD Guidelines for the Testing of Chemicals

Chemosis

Swelling (refers to lids and/or nictating membranes)

Normal..... 0
Some swelling above normal..... 1
Obvious swelling, with partial eversion of lids..... 2
Swelling, with lids about half closed..... 3
Swelling, with lids more than half closed..... 4
Maximum possible: 4

Figure A J.5. Classification of Eye Irritation Scores

MMTS	Irritation Classification	Requirement For Maintenance of Classification[1]
0.0 - 0.5	non	Up to 0.5 at 1 hour with zeros at 24 hours; otherwise, increase one level
0.6 - 2.5	practically non	with zeros at 24 hours; otherwise, increase one level
2.6 - 15.0	minimally	with zeros at 48 hours; otherwise, increase one level
15.1 - 25.0	mildly	with zeros at 96 hours; otherwise, increase one level
25.1 - 50.0	moderately	with 7 day mean $\leq$ 20 and individual total scores $\leq$ 10 in at least 60% of the rabbits with no total score >30; otherwise, increase one level
50.1 - 80.0	severely	with 7 day mean $\leq$ 40 and individual total scores $\leq$ 30 in at least 60% of the rabbits with no total score > 60; otherwise, increase one level
80.1 - 100.0	extremely	with 7 day mean $\leq$ 80 and individual total scores $\leq$ 60 in at least 60% of the rabbits with no total score >100; otherwise, increase one level
100.1 - 110	maximally	with 7 day mean > 80 and individual total scores > 60 in at least 60% of the rabbits; otherwise, decrease one level

Note: [1] Kay & Calandra, 1962

Annex K. Full Report (referring to row 94 of Acute Eye Irritation)

Applicant indicates that report can be found in the dossier.

Annex L. An example of a reporting table (referring to line 77 of Acute Dermal Irritation)

Applicant inserts the following tables or indicates where these tables can be found in the dossier.

Figure A L.1. Primary Dermal Irritation Scores of Animals Treated with <insert product code/name>

		Scores after treatment (see Table below)					
Time after patch removal		1 h	24 h	48 h	72 h	14 d	Reversible (day)
Animal No. 1	Erythema						
	Edema						
Animal No. 2	Erythema						
	Edema						
Animal No. 3	Erythema						
	Edema						
Mean scores	Erythema						
	Edema						
TOTAL (PDI)							

Note: Primary Dermal Irritation score (PDI) = Mean Erythema Score + Mean Edema Score

Figure A L.2. Grading of Skin Reactions According to OECD TG 404 (2015)

Erythema and Eschar Formation
No erythema 0
Very slight erythema (barely perceptible) 1
Well defined erythema 2
Moderate to severe erythema 3
Severe erythema (beef redness) to eschar formation preventing grading of erythema 4
Maximum possible: 4

Oedema Formation
No oedema 0
Very slight oedema (barely perceptible) 1
Slight oedema (edges of area well defined by definite raising) 2
Moderate oedema (raised approximately 1 mm) 3
Severe oedema (raised more than 1 mm and extending beyond area of exposure) 4
Maximum possible: 4

Figure A L.3. Irritation Classification System

PDII Classification System

0	Non-irritating
> 0 - 2.0	Slightly irritating
2.1 - 5.0	Moderately irritating
> 5.0	Severely irritating

Note: Primary Dermal Irritation Index (PDII)
[(PDI @ 30-60 min + PDI @ 24 hrs + PDI @ 48 hr + PDI @ 72 hrs) ÷ 4]
Source: US EPA Addendum 3 on data reporting to pesticide assessment guidelines; Dermal Irritation, January 1988; https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB88161179.xhtml.

Annex M. Full Report (referring to row 90 of Acute Dermal Irritation)

Applicant indicates that report can be found in the dossier.

Annex N. An example of a reporting table (referring to line 90 of Dermal Sensitization)

Applicant inserts the following tables or indicates where these tables can be found in the dossier.

Figure A N.1. Incidence and Severity of the Sensitization Response for <insert product/code>

Observed after Challenge in Test ("induced animals") and Naïve Control Animals

	Sensitization Endpoints			
	Incidence of Positive Responses		Severity Index (SI)	
	Hours		Hours	
	24	48	24	48
Test Animals	NPR / TNA	NPR / TNA	SI	SI
Naïve Control Animals	NPR / TNA	NPR / TNA	SI	SI

Note: NPR/TNA = [Number of animals with a Positive Response] ÷ [Total Number of Animals evaluated]
Erythema scores > 0.5 are considered a positive response.
Severity index (SI) = [Sum of erythema scores greater than 0.5] ÷ [Number of animals evaluated per observation period]

Figure A N.2. Erythema Scoring System

Score	Observation
0	No reaction
0.5	Very faint erythema, usually non-confluent*
1	Faint erythema, usually confluent
2	Moderate erythema
3	Severe erythema with or without edema

Note: Very faint erythema is not considered a positive reaction

The following criteria were used to classify the test substance as a potential contact sensitizer (Robinson, et al., 1990): At the 24-hour and/or 48-hour scoring interval, 15% or more of the test animals exhibit a positive response (scores > 0.5) in the absence of similar results in the naïve control group. The positive reaction at the 24-hour interval must persist to 48 hours in at least one test animal.

Annex O. Full Report (referring to row 102 of Dermal Sensitization)

Applicant indicates that report can be found in the dossier.