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

ENV/JM/TG/RD(2015)6
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Test Guidelines Programme

COMPILATION OF COMMENTS RECEIVED ON THE DRAFT REVISED TEST GUIDELINES ON SKIN IRRITATION/CORROSION

27th Meeting of the Working Group of National Co-ordinators of the Test Guidelines Programme (WNT)

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Comments were received from Germany, the United States, the European Commission and ICAPO.

ACTION REQUIRED ***The WNT is invited to take note of the responses to comments and approve the draft updated Test Guidelines in documents ENV/JM/TG(2015)11 to ENV/JM/TG(2015)15, amended as appropriate.***

TG 404

No.	Country/ affiliation	Comment	Response
		Paragraph 1	
1	EC	Suggest to consider the following editorial changes (in red): *"This updated version of Guideline 404 (originally adopted in 1981, revised in 1992, 2002 and 2014) includes reference to the Guidance Document on Integrated Approaches to Testing and Assessment (IATA) for Skin Irritation/Corrosion (1), proposing a modular approach for skin irritation and skin corrosion* ***testing****.* ~~***This***~~ ***The*** *IATA* ***describes*** ~~***provides guidance***~~ ~~***over***~~ *several modules* ***which group various information sources and analysis tools*** ***and provices guidance*** *on (i) how to integrate and use existing test****ing*** *and non-test****ing*** *data for the assessment of the skin irritation and skin corrosion potentials of chemicals (1) and (ii) proposes an approach when further testing is needed (1).*	Changes proposed have been inserted in the text.
		Paragraph 24	
2	United States	Consider revision. "Description of *in vitro* tests performed, including details of procedures, results ~~Obtained~~ obtained."	Done.

TG 430

No.	Country/ affiliation	Comment	Response
		Paragraph 2	
3	EC	Suggest to rephrase the sentence as follows: In addition to the present TG 430 (originally adopted in 2004)(4), ~~**several**~~ other *in vitro* test methods for testing ~~**of corrosivity**~~ **the skin corrosion potential of chemicals** have been validated and adopted as OECD Test Guidelines 431 (53) and 435 (64), that are also able to **support** ~~**identify**~~ sub-categori**sationes** ~~**when required**~~.	Ok to insert the changes proposed in the first two lines. However, the term "to support sub-categorisation" is unclear. Either sub-categories are identified by the TG or they are not. "Support" means that there are other ways to sub-categorise and the way proposed in the TG can be used as

			a supplement.
		Paragraph 9	
4	Germany	"… However, due to the fact that mixtures cover a wide spectrum of categories and composition, and that only limited information is currently available ~~in the public domain~~ on the testing of mixtures, in cases where evidence can be demonstrated on the non-applicability of the Test Guideline to a specific category of mixtures (e.g. following a strategy as proposed by Eskes et al., 2012) (19), the Test Guideline should not be used for that specific category of mixtures. …" Regarding the testing of mixtures, the sentences "Before use of the test guideline on a mixture for generating data for an intended regulatory purpose, it should be considered whether, and if so why, it may provide adequate results for that purpose. Such considerations are not needed, when there is a regulatory requirement for testing of the mixture." should be integrated as agreed by WNT 26. Please add before the passage cited above. Previous in-house data have shown that pesticide formulations tested in RhE Skin Irritation Tests showed very equivocal results (described in "Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations", Eskes et al., 2012). As a reason it was described that "pesticides have very particular formulations, which are designed to be toxic, and may present physico-chemical properties (e.g., sticky) that require specific spreading aide and could lead to prolonged exposures due to difficulties in rinsing." Therefore, we suggest providing more data to prove that mixtures as for example agrochemicals fall into the applicability domain of the test.	The text agreed at WNT-26 about mixtures testing has been added. The paragraph 9, augmented with the sentences agreed at WNT-26, is carefully worded to raise caution about the applicability to mixtures and the limited validation data on mixtures testing.

TG 431

No.	Country/ affiliation	Comment	Response
		General comment	
5	Germany	The detailed description regarding analysis of test chemicals interfering with MTT detection (colorants and direct MTT reducers in TG 431 is appreciated.	Noted.

		Paragraph 2	
6	EC	Proposed modifications in red): *"Furthermore ~~a~~ several validated in vitro test method~~s~~ ~~has~~have been adopted as OECD TG 439 (5), to be used for testing skin irritation potential."*	Ok, changes made.
		Paragraph 8	
7	Germany	"…However, due to the fact that mixtures cover a wide spectrum of categories and composition, and that only limited information is currently available ~~in the public domain~~ on the testing of mixtures, in cases where evidence can be demonstrated on the non-applicability of the Test Guideline to a specific category of mixtures (e.g. following a strategy as proposed in (25)), the Test Guideline should not be used for that specific category of mixtures" With regard to the applicability for mixtures, WNT 26 agreed to use the following sentences as general considerations: "Before use of the test guideline on a mixture for generating data for an intended regulatory purpose, it should be considered whether, and if so why, it may provide adequate results for that purpose. Such considerations are not needed, when there is a regulatory requirement for testing of the mixture." We suggest adding this sentence before the sentence cited above. From a regulatory point of view false negative results are especially problematic as products for the end-consumer would be authorised without the necessary PPEs, e.g. gloves, protection suit, etc.. Previous in-house data have shown that pesticide formulations tested in RhE Skin Irritation Tests showed very equivocal results (described in "Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations", Eskes et al., 2012). As a reason it was described that "pesticides have very particular formulations, which are designed to be toxic, and may present physico-chemical properties (e.g., sticky) that require specific spreading aide and could lead to prolonged exposures due to difficulties in rinsing." Therefore, we suggest providing more data to prove that mixtures as for example agrochemicals fall into the applicability domain of the test.	Change made. Text added as suggested. The text proposed in the TG is cautious about applicability of the method for mixtures testing. It assumes that it is applicable based on limited data available, unless demonstrated otherwise.
		Paragraph 9	
8	EC	Suggest modifying the end of paragraph 9 to (proposed modifications in red):	

		"… for corrections. The type of adapted controls that may be required will vary depending on the type of interference produced by the test chemical and the procedure used to measure MTT formazan (see paragraphs 25-31)." *The same applies to TG 439.*	Ok, text proposed was added.
		Paragraph 13	
9	EC	Suggest modifying the end of paragraph 13 to (proposed modifications in red): *"… (e.g. from the ~~list of reference chemicals (23)~~chemicals used in the validation of the VRMs (8)(10) and in post-validation studies (Desprez et al., 2015)) provided that the same selection criteria as described in Table 1 ~~is~~ are applied."* *The same applies to TG 439.*	Directing the reader to three different sources is not an improvement. The full reference Desprez et al, 2015 is not provided. Further, the the list of reference chemicals is cited as 'eg' only.
		Paragraph 18	
10	EC	Suggest modifying the end of paragraph 18 to (proposed modifications in red): *"… or ET_{50} (Table 3). The barrier function of each batch of the RhE model used should be demonstrated by the RhE model developer/vendor upon supply of the tissues to the end user (see paragraph 21)."* *The same applies to TG 439.*	Ok, text proposed was added.
		Paragraph 19	
11	EC	Suggest modifying the end of paragraph 19 to (proposed modifications in red): "… of human epidermis. Histological examination of each batch of the RhE model used demonstrating appropriate morphology of the tissues should be provided by the RhE model developer/vendor upon supply of the tissues to the end user (see paragraph 21)." *The same applies to TG 439.*	Ok, text proposed was added.
		Paragraph 25	
12	EC	First line in page 9 (paragraph 25): *"… interference if the test absorbs,…"*	Ok, correction made.

		should read *"... interference if the test chemical absorbs,..."*	
13	EC	Paragraphs 25-28 should be aligned with paragraphs 35-38 of the draft RhCE TG, in particular in clarifying that NSC controls are not required when using HPLC/UPLC, while NSMTT controls are always required independently of the procedure used to measure tissue viability. *The same applies to TG 439.*	The paragraphs have been amended for more clarity, as requested.
		Paragraph 28	
14	Germany	In Paragraph 26 of TG 431, it is stated that killed tissues absorb and bind the test chemical in a similar way than viable tissues. In Paragraph 28 of TG 431, however, it is said that the test chemical may not necessarily bind in the same amount and with the same strength to living and killed tissues. The correction for MTT reducers is based on the assumption that binding to killed and living cells is comparable. Therefore it is suggested to delete the above mentioned sentence in Paragraph 28 of TG 431.	Sentence has been removed.
15	EC	Paragraph 28, line 13 (proposed modification in red): *"... this additional control, the test chemical is applied on at least two killed tissue replicates per exposure time, which undergo..."*	Text has been added.
		Paragraph 38	
16	EC	Suggest modifying the second bullet point in "Test Conditions", paragraph 38 to (proposed modifications in red): *"~~Calibration information for measuring device (e.g. spectrophotometer),~~Wavelength and band pass (if applicable) used for ~~measuring cell viability~~quantifying MTT formazan, and ~~OD~~ linearity range of measuring device;"* *Probably the same applies to TG 439.*	Text was slightly amended as requested. But leaving the 'Calibration information…)' because it is part of GLP to have the spectrophotometer calibrated, and for the HPLC/UPLC this rebounces with the new annex 4. We should ensure the apparatus is properly calibrated… in addition to having information on wavelength and linearity

			range….
17	EC	Suggest modifying the first bullet point in "Test Procedure", Paragraph 38 to include only "Details of the test procedure used;" and delete all remaining text, including the two sub-bullet points. *Please check if also applicable to TG 439.*	The sub-bullets and text have been removed as requested, but suggest adding '(including washing procedure) – see proposed TG 431. It is an important step in the protocol, so suggest to maintain it…
18	EC	Suggest inclusion of "Demonstration of proficiency in performing the test method before routine use by testing of the proficiency chemicals;" as a last bullet point under "Test Conditions" in paragraph 38. *Please check if also applicable to TG 439.*	The text has been added where requested.
19	EC	Suggest modifying the end of the first bullet point in "Results", paragraph 38 to (proposed modifications in red): "…, mean percent tissue viability, difference between tissue replicates, and SDs and/or ~~ranges and~~ CVs if applicable;"	The new text has been added where requested.
20	EC	Suggest modifying the end of the second bullet point in "Results", paragraph 38 to (proposed modifications in red): "…, %NSC_{killed}, difference between tissue replicates, SDs and/or CVs if applicable, and final correct percent tissue viability;"	The new text has been added where requested.

TG 435

No.	**Country/ affiliation**	**Comment**	**Response**
		Paragraph 3	
21	Germany	Please include information on the outcome of the cited validation studies regarding accuracy, sensitivity and specificity of the test method.	The sensitivity, specificity and number of chemicals tested (similar to TG 430) have been added to parag. 3
22	EC	Paragraph 3 should make clear that this TG covers only one single test method, that is only available through commerce, i.e. cannot readily be sourced or constructed otherwise:	

		We propose to include the following sentence after the second sentence of Para 3: *"Currently, only one in vitro test method is covered by this Test Guideline, the Corrositex® method and consequently there is currently only one single commercial source for the test method covered by this TG"* NC position: This needs further discussion in the context of the discussion of proprietary methods and OECD TGs and how to deal with them	The proposed text was added as it is an accurate reflection of reality.
		Paragraph 7	
23	Germany	Regarding the testing of mixtures, the sentences "Before use of the test guideline on a mixture for generating data for an intended regulatory purpose, it should be considered whether, and if so why, it may provide adequate results for that purpose. Such considerations are not needed, when there is a regulatory requirement for testing of the mixture." should be integrated as agreed by WNT 26. Moreover, the following sentences "However, due to the fact that mixtures cover a wide spectrum of categories and composition, and that only limited information is currently available on the testing of mixtures, in cases where evidence can be demonstrated on the non-applicability of the Test Guideline to a specific category of mixtures (e.g. following a strategy as proposed in Eskes et al. 2012, Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations. Regul.Toxicol.Pharmacol. 62, 393-403), the Test Guideline should not be used for that specific category of mixtures." should be added afterwards (similar to the Draft TG 430 and 431). Eskes et al. 2012 should be included in the reference list. Previous in-house data have shown that pesticide formulations tested in RhE Skin Irritation Tests showed very equivocal results (described in "Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations", Eskes et al., 2012). As a reason it was described that "pesticides have very particular formulations, which are designed to be toxic, and may present physico-chemical properties (e.g., sticky) that require specific spreading aide and could lead to prolonged exposures due to difficulties in rinsing." Therefore, we suggest providing more data to prove that mixtures as for example agrochemicals fall into the applicability domain of the test.	The Corrositex validation dataset includes a number of mixtures (both simple mixtures and product formulations), so that such statement may not be justifiable here.
		Paragraph 11	
24	EC	Suggest modifying the end of paragraph 11 to (proposed modifications in red):	I would leave it as

		"... (e.g. from the ~~list of reference chemicals (10)~~chemicals used in the validation of the VRM (7)) provided that the same selection criteria as described in Table 1 ~~is~~are applied."	currently states, especially since ref. 10 in vivo data is reported to have been peer-reviewed, whereas ref. 7 as suggested by ECVAM is based on a submitted validation and the quality of in vivo data is less clear.
		Table 2	
25	EC	The range of break-through times obtained with Corrositex® for each of the Proficiency Substances, e.g. from the validation study, should be included in Table 2.	We agreed in Nov. this was not a critical requisite. First because not certain to retrieve it (still waiting for info from ICCVAM) second for harmonization with the other TGs on skin (TG 430 and 431)
		Paragraphs 12-21	
26	EC	The procedure described in paragraphs 12-21 should be specific for Corrositex® as this is the only method currently covered by TG 435, rather than being generic as stated in paragraph 12. NC position: This needs further discussion in the context of the discussion of proprietary methods and OECD TGs and how to deal with them	The beginning of paragraph 12 was slightly modified accordingly.
		Paragraphs 12-21	
27	EC	The components of the test method need to be obtained commercially from the producer of Corrositex® until similar methods are developed, validated and included in TG 435. Therefore, the statement in paragraph 12 that "The membrane barrier and the compatibility/indicator and categorisation solutions can be constructed, prepared or obtained commercially, e.g., Corrositex®" is misleading and should be modified to "The membrane barrier and the compatibility/indicator and categorisation solutions can be	Noted. However, we cannot be as prescriptive as requested by the commenter, the commercial availability of the components could be broader than what it currently is. It is better to

		obtained commercially from the producer of Corrositex®". NC position: This needs further discussion in the context of the discussion of proprietary methods and OECD TGs and how to deal with them	leave it open.
28	EC	The Corrositex® acceptance criteria, e.g. accepted penetration response time range for the positive control, should be clearly described in paragraph 26	Agree. Text has been added accordingly.
29	EC	The Corrositex® prediction model (cut-off times) should be included in paragraph 27.	Agree.
30	EC	Suggest inclusion of "Demonstration of proficiency in performing the test method before routine use by testing of the proficiency chemicals;" as a last bullet point under "Test Conditions" in paragraph 29.	

TG 439

No.	Country/ affiliation	Comment	Response
		General comment	
31	Germany	The detailed description regarding analysis of test chemicals interfering with MTT detection (colorants and direct MTT reducers in TG 439 is appreciated.	Noted.
		Paragraph 3	
32	EC	Undo deletion *"... based on those developed by EC ECVAM..."* and preserve the references (8) and (9). This is useful background and it would be only consequential to maintain this reference here, since reference is still made to the development of the PS in Annex 2.	The text deleted has been restored.
		Paragraph 4	
33	Germany	Please include information on the outcome of the cited validation studies regarding accuracy, sensitivity and specificity of the test method.	The overall predictive capacity demonstrated in the validation studies and expected from similar test method has been inserted at the end of the sentence. For specific predictive capacity of each method, the user is referred to the validation studies.

34	EC	Paragraph 4 and paragraph 18 Delete "four" in the first and second sentence. It is very likely that in the foreseeable future more (me-too) methods will qualify for inclusion into this TG since the OECD has PS available that allow conducting validation studies in relation to this TG. This deletion will facilitate further updates. This suggestion has been made repeatedly before, e.g. when suggesting the creation of what is now Annex 2. The sentences will read as follows: *"Prevalidation [no hyphen necessary], optimisation and validation studies have been completed for **~~four~~** commercially available in vitro test methods based on the RhE test system. These **~~four~~** test methods are included in this TG and are listed in Annex 2."* **This comment holds for the entire document**. We suggest deleting any reference to the current status quo in terms of current number of test methods covered by this TG and simply referring to the "test methods adhering to this TG". This will make updating this TG easier. Regular updates can be expected as many more me-too methods will be validated by industry and then, consequentially, need to be included in the Annex	The intention of the WNT was to be specific and clear about the coverage of the TG at a given point in time. Otherwise, anyone can claim that their method adhere to the TG, without review by authorities. Mentioning numbers does not in any way impede the update of a TG. Also, discussion at WNT is warranted on the intention with TGs that contain several me-too methods. Is this intention to continue adding to the list of methods in the annex, or to make a selection of the best methods available?
35	EC	Reference is being made to three test methods that have been used to define the performance standards. In contrast, Annex 2 clearly indicates that only EpiSkin and EpiDerm have been used to define the PS. The fact that data / reference chemicals were used from method 3 (SkinEthic) when updating the PS– as correctly stated in the footnote in Annex 2 – does not justify the statement that the PS are **based** on three methods. Moreover, the paragraph subsumes all three as validated reference methods. This would be inappropriate since method three (SkinEthic) was validated *in reference* to the PS. Propose: Either: *"As noted in Annex 2, **two ~~three~~** of these methods have been used to develop the present TG and the Performance Standards referred to as Validated Reference Method (VRM)."* *"As noted in Annex 2, **two ~~three~~** of these methods have been used to develop the present TG and the Performance Standards referred to as Validated Reference Method (VRM). Data*	"Three" has been corrected to "two". The additional sentence is superfluous in a Test Guideline which is intended for users.

		from one method validated against the original version of these PS have been used to update the PS in 2009."	
		Paragraph 8	
36	Germany	Regarding the testing of mixtures, the sentences "Before use of the test guideline on a mixture for generating data for an intended regulatory purpose, it should be considered whether, and if so why, it may provide adequate results for that purpose. Such considerations are not needed, when there is a regulatory requirement for testing of the mixture." should be integrated as agreed by WNT 26. Moreover, the following sentence "However, due to the fact that mixtures cover a wide spectrum of categories and composition, and that only limited information is currently available on the testing of mixtures, in cases where evidence can be demonstrated on the non-applicability of the Test Guideline to a specific category of mixtures (e.g. following a strategy as proposed in Eskes et al. 2012, Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations. Regul.Toxicol.Pharmacol. 62, 393-403), the Test Guideline should not be used for that specific category of mixtures." should be added afterwards (similar to the Draft TG 430 and 431). Eskes et al. 2012 should be included in the reference list. Previous in-house data have shown that pesticide formulations tested in RhE Skin Irritation Tests showed very equivocal results (described in "Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations", Eskes et al., 2012). As a reason it was described that "pesticides have very particular formulations, which are designed to be toxic, and may present physico-chemical properties (e.g., sticky) that require specific spreading aide and could lead to prolonged exposures due to difficulties in rinsing." Therefore, we suggest providing more data to prove that mixtures as for example agrochemicals fall into the applicability domain of the test.	Noted. A new paragraph 9 was added, using text proposed by Germany, that provides cautious statement about mixtures testing using TG 439.
37	EC	The first sentence, due to the deletion of the word 'testing' is misleading: *"This Test Guideline addresses the in vitro skin irritation"* There is no such thing as 'in vitro skin irritation'. Skin irritation is per definition an event of	Text in the 1st sentence was aligned with other TGs.

		skin. However, the term 'in vitro skin irritation testing' as was written beforehand makes sense: the TG addresses the testing of skin irritation through in vitro methods. Therefore, **either** undelete the word "testing" at the end of the sentence: *"This Test Guideline addresses* ***~~the~~*** *in vitro skin irritation* ***testing****"* **or** write: *"This Test Guideline addresses the testing of chemicals in view of their skin irritation potential and allows identifying irritant substances and those not requiring classification for skin irritation in agreement with the UN GHS."*	
38	ICAPO	The guideline currently states: "This Test Guideline addresses the in vitro skin irritation." In line with other TGs it should say: "This Test Guideline addresses in vitro skin irritation." i.e. delete 'the'	Text in the 1st sentence was aligned with other TGs.
		Paragraph 14	
39	EC	In line with comment made on para 4 (listing four test methods), delete "four" and simply write: *"Prior to routine use of any of the* ***~~four~~*** *validated test methods that adhere to this Test Guideline…"*	See above response to comment No.34.
40	EC	The second sentence is difficult to understand due to the insertion "or where justifiable". Suggest to split this sentence in two as shown below (insertion / deletions in bold): In situations where, **for instance,** a listed substance is unavailable ***~~or where justifiable~~***, another substance for which adequate *in vivo* and *in vitro* reference data are available may be used (e.g. from the list of reference chemicals (8)). **However, such deviations should be justified** and ***~~provided~~*** ***~~that~~*** **the** same selection criteria as described in Table 1 ***~~is~~*** **should be** applied.	The sentence has been split as requested.
		Paragraph 18	
41	EC	Suggest to delete "magnitude", and use the term 'quantifying':	

		"The assay used for quantifying ~~**determining the magnitude of**~~ cell viability is the MTT-assay…" Suggest to add that formazane is measured through OD before alerting to the OD measurement of extraction solvent alone. Use active instead of passive form. : ~~**The vital dye MTT is reduced into a blue MTT formazan precipitate by the**~~ **V**iable cells of the RhE tissue construct **can reduce the vital dye MTT into a blue formazan reaction product** which is then extracted from the tissue using isopropanol (or a similar solvent). The extracted ~~**MTT**~~ formazan may be quantified using either a standard absorbance (OD) measurement or an HPLC/UPLC-spectrophotometry procedure (30). **The optical density (OD) of the extraction solvent alone should be sufficiently small.**	Change has been made. Changes have been made as requested.
		Paragraph 24	
42	EC	Suggest to rephrase the first sentence slightly: Concurrent negative ~~**control**~~ (NC) and positive controls (PC) should be used in each run to demonstrate that viability (~~**with**~~ **using** ~~**the**~~ negative control NC), barrier function and resulting tissue sensitivity (**using** ~~**the**~~ PC) of the tissues are within a defined ~~**historical**~~ acceptance range. The suggested PC ~~**chemical substance**~~ is 5% aqueous SDS. ~~**The**~~ Suggested ~~**negative control**~~ NC**s** ~~**substances**~~ are water or phosphate buffered saline (PBS).	These changes have been made. However, the term "historical" was left in place.
		Paragraph 30	
43	Germany	In Paragraph 28 of TG 439, it is stated that killed tissues absorb and bind the test chemical in a similar way than viable tissues. In Paragraph 30 of TG 439, however, it is said that the test chemical may not necessarily bind in the same amount and with the same strength to living and killed tissues. The correction for MTT reducers is based on the assumption that binding to killed and living cells is comparable. Therefore it is suggested to delete the above mentioned sentence in Paragraph 30 of TG 439.	The sentence identified in paragraph 30 has been removed.
		Paragraph 35	
44	Germany	At the expert meeting held in Paris in November 2014 it was proposed and agree to revise the following statement under the topic Interpretation of the results and prediction model "The test chemical is considered to be irritant to skin in accordance with UN GHS Category	

		2 if the tissue viability after exposure and post-treatment incubation is less than or equal (≤) to 50%" To "The test chemical is identified as requiring classification and labelling according to UN GHS (Category 2 or Category 1) if the mean percent tissue viability after exposure and post-treatment incubation is less than or equal (≤) to 50%. Since the RhE test methods covered by this TG cannot resolve between UN GHS Categories 1 and 2, further information from other *in vitro* methods (TG 430, 431 or 435), *in silico* approaches or other relevant sources of information on the skin corrosion properties of the test chemical will be required to decide on its final classification" ECHA would propose that the following amendment is considered to be included in the updated TG. <u>NC position:</u> Please consider this, as well in view of our previous set of COM comments	
45	EC	Suggest rephrasing the description of how to interpret the cut-off values / prediction model. The current phrasing is, strictly speaking, not fully correct: the problem is that substances identified as irritants (Cat.2) could also be corrosive (Cat.1) – which cannot be resolved by this methodology (i.e. RhE for skin irritation = TG439) on its own. Further evaluation (which can involve testing using TG 431 or other sources) is required to arrive at a correct classification decision for the test substance. The IATA on skin corrosion/irritation provides detailed guidance. We therefore propose to replace the current first bullet point in paragraph 35 and write instead: *If the mean percent tissue viability after exposure and post-treatment incubation is less than or equal (≤) to 50%, the test chemical should be considered as either irritant to skin (Category 2) or corrosive to skin (Category 1). Since the RhE test methods covered by this TG cannot resolve between UN GHS Categories 1 and 2, further information from other in vitro methods (TG 430, 431 or 435), in silico approaches or other relevant sources of information are required to decide on whether to classify and label as Category 1 or Category 2.*	