



1 **STATEMENT ON**

2 **THE USE OF EXISTING LOW VOLUME EYE TEST (LVET) DATA FOR WEIGHT**  
3 **OF EVIDENCE DECISIONS ON CLASSIFICATION AND LABELLING OF**  
4 **CLEANING PRODUCTS AND THEIR MAIN INGREDIENTS**

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6 At its 31<sup>st</sup> meeting, held on 7 and 8 July 2009, the non-Commission members of the ECVAM  
7 Scientific Advisory Committee (ESAC) unanimously endorsed the following statement:

8 **1. The ESAC strongly recommends that the Low Volume Eye Test (LVET) method, a**  
9 **modification of the standard Draize eye test, is NOT conducted in the future to generate**  
10 **new testing data concerning the intrinsic properties of xenobiotic substances (chemicals,**  
11 **cosmetic ingredients etc.).**

12 **2. ESAC nevertheless acknowledges that existing<sup>1</sup> LVET data of the limited use domain**  
13 **of household detergents and cleaning products as well as their main ingredient class (i.e.**  
14 **surfactants as used in these products) may be used for purposes of classification and**  
15 **labelling decisions.**

16 **3. Moreover, existing LVET data of this limited use domain may be used as**  
17 **supplementary data in the context of a subset of future validation studies.**

18 **4. Finally, the ESAC recommends that no additional testing is done to further develop or**  
19 **validate the LVET test method.**

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22 The ESAC recommends that consideration be given on a case by case basis to the limited use  
23 of existing Low Volume Eye Test (LVET) data as supplementary in vivo data within Weight  
24 of Evidence (WoE) evaluations of alternative testing methods and strategies, and for decision  
25 making on the necessity to conduct additional standard in vivo test method(s) for eye irritation  
26 for purposes of classification and labelling for the above specified limited use domain.

27 This recommendation is based on conclusions reached following the assessment of a dossier  
28 submitted to ECVAM concerning data and test results relating to detergents, cleaning  
29 products and, to a lesser extent, their main ingredients (surfactants).

30 In making these recommendations, ESAC acknowledges:

31 (1) the considerable amount of existing LVET data for the domain of household detergents  
32 and cleaning products;

33 (2) that the LVET makes use of direct corneal exposure to mimic specific human exposure  
34 scenarios that can be reasonably expected (e.g. accidental ocular exposure during household  
35 use) and for the specific use domain of household detergents and cleaning products as well as  
36 their main ingredients (i.e. surfactants) as used in these products.

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<sup>1</sup> Existing data in this context refers to data that were generated *prior* to the date of this statement.



37 (3) that LVET data, being based on exposure scenarios likely to be relevant in humans, may  
38 predict effects in humans with improved accuracy when compared to the Conventional  
39 Calculation Method (CCM) traditionally used for C&L decisions on products of this use  
40 domain;

41 (4) the provisions of the Regulation on the Classification, Labelling and Packaging of  
42 Substances and Mixtures ('CLP' Regulation 1272/2008/EC; Ref. 1), which foresees an WoE  
43 assessment based on existing data to determine whether or not testing with accepted standard  
44 tests (i.e. those described in the Test Method Regulation 440/2008/EC; Ref. 2) is necessary or  
45 may be dispensed with.

46 The ESAC furthermore recognises that several databases for alternative methods for eye  
47 irritation test methods may be of an acceptable size only if existing LVET testing data can be  
48 considered as an additional and secondary source of supporting information. Some differences  
49 in classification based on LVET data are to be expected with respect to reference data for the  
50 established eye irritation test (i.e. Draize eye data), and the tendency of them to give lower  
51 hazard categories than the classical Draize eye test (Ref. 3) must be kept in mind.  
52 Nevertheless these data may still be useful on a case by case basis, and only with respect to  
53 testing data for household detergents, cleaning products and surfactants used in such products.  
54 Subject to these considerations existing LVET data may on occasion contribute to a  
55 knowledge base against which alternative methods may be validated for this specific use  
56 domain.

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58 Joachim Kreysa

59 Head of Unit

60 In-Vitro Methods Unit

61 European Centre for the Validation of Alternative Methods

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63 Ispra, 9. July 2009



64 **Explanatory background to this ESAC recommendation:**

65 This recommendation is based on a submission of LVET data to ECVAM concerning  
66 household detergents and cleaning products as well as their main ingredient class, i.e.  
67 surfactants. The LVET data were correlated to effects in man observed in response to  
68 accidental splashes and as documented in poison control centres and clinics. To a lesser extent  
69 also clinical exposure data from human volunteers on substances of the mild irritant range  
70 were used. The submission was evaluated by ECVAM in 2006 and, after requested  
71 amendments had been performed, underwent independent ESAC peer review from April 2007  
72 to June 2009.

73 The LVET is a minor modification of the classical Draize eye irritation test (Ref. 4): the  
74 LVET differs from the Draize test only with regard to two aspects both relating to exposure:  
75 (1) The LVET uses only a tenth of the volume of liquids (=10µL) or weight of solids (=10mg)  
76 in comparison to the Draize (0.1 mL of liquids and 100mg of solids); (2) both liquids and  
77 solids are applied directly on the cornea in the LVET, without subsequent forced closure of  
78 eyelids, in contrast to the Draize test where the test material is instilled in the conjunctival sac  
79 of the rabbit eye. All other parameters such as e.g. exposure time and visual scoring of effects  
80 on the cornea, conjunctiva and iris are unchanged with regard to the Draize eye test. The  
81 rationale for using a reduced amount of test substances (as described in the submission) and  
82 for applying it directly to the cornea is to mimic household exposure scenarios such as  
83 accidental splashes with detergents and cleaning products in man and to consequently  
84 approximate the effects in man. The ESAC PRP held that while such exposure scenarios may  
85 be reasonable specifically for household detergents and cleaning products they do not take  
86 into consideration other possible routes of exposure such as, for instance, the accidental  
87 exposure to pesticides using pressure pumps during field work. Thus, while the LVET  
88 exposure settings may be appropriate for household exposure to cleaning products and,  
89 possibly, personal hygiene products (i.e. cosmetics), they do at present not appear appropriate  
90 for a wide range of substances and associated exposure scenarios – at least until further data  
91 supporting such use becomes available.

92 The LVET has been and is used mainly by industry to benchmark finished products  
93 (formulations = mixtures= preparations), a blend of individual chemical substances  
94 purposefully mixed in measured and defined proportions for specific uses and applications  
95 (e.g. cleaning products, shampoos etc.). In practice, LVET data were used to contribute to  
96 classification and labelling decisions. Up to January 2009, when the new CLP regulation  
97 came into force (see below), classification and labelling of substances was performed  
98 according to the Dangerous Substance Directive (Directive 67/548/EEC; Ref. 5) and that of  
99 mixtures according to the Dangerous Preparations Directive (Directive 1999/45/EC; Ref. 6).  
100 In December 2008 the EU adopted the Regulation on the Classification, Labelling and  
101 Packaging of Substances and Mixtures (so-called CLP regulation 1272/2008/EC; Ref. 1) that  
102 aligns existing EU legislation to the United Nations Globally Harmonised System (GHS). The  
103 CLP Regulation will, after a transitional period, replace the current rules on classification,  
104 labelling and packaging of substances (Directive 67/548/EEC; Ref. 5) and mixtures (Directive  
105 1999/45/EC; Ref. 6). The date from which classification and labelling must be consistent with  
106 the new rules will be 1 December 2010 for substances and 1 June 2015 for mixtures. Notably,  
107 the CLP regulation amends the REACH regulation (concerning the Registration, Evaluation,



108 Authorisation and Restriction of Chemicals, 'REACH'; 1907/2006/EC, Ref. 7) with respect to  
109 classification and labelling.

110 Both, the CLP regulation and REACH foresee the possibility of WoE assessments to decide  
111 on the necessity of standard tests to be performed (i.e. tests laid down in the Test Method  
112 Regulation 440/2008/EC; Ref. 2): the CLP regulation in the context of classification and  
113 labelling decisions of substances and mixtures (formerly referred to as 'preparations' or  
114 'formulations'; these may include finished products for consumer use) and REACH in the  
115 context of chemical safety assessments.

116 WoE approaches are based on the integration of data from various sources and make use of  
117 synergistic effects obtained by combining data sets in cases where each single data on its own  
118 would be insufficient for decision-making but where the combination of data may allow  
119 conclusions on the absence or presence of dangerous properties of substances as regulated by  
120 the CLP regulation and the REACH regulation and finished products (i.e. "mixtures",  
121 previously referred to as "preparations"), as regulated by the CLP regulation.

122 LVET data related to above mentioned use domain may be helpful, together with other  
123 existing and available data from various sources, to decide in a WoE approach in the contexts  
124 of the two above mentioned regulations whether confirmatory standard test(s) for eye  
125 irritation are necessary or whether existing information, in its totality, is sufficient to arrive at  
126 classification and labelling conclusions without performing further testing of the  
127 substance/product in question.

128 In summary the ESAC recommendation takes into consideration:

- 129 (a) the non-negligible amount of human reference data collected in the submitted dossier;
- 130 (b) the fact that LVET data, as the classical Draize eye test, reflect these human exposure data  
131 at least for above mentioned and limited use domain (e.g. detergents/cleaning products and  
132 surfactants) (see however point c)
- 133 (c) the fact that most of the exposed patients had received anti-inflammatory treatment which  
134 complicates an appraisal to which extent observed effect in patients represented the actual  
135 hazard to be expected under observation of the precautionary principle;
- 136 (d) the appraisal that the exposure settings of the LVET may represent the exposure from  
137 accidental splashes more appropriately than the classical Draize eye test;
- 138 (e) the common practices concerning the labelling of finished products under the Dangerous  
139 Preparations Directive (Ref. 6) as well as the future practice using WoE evaluations for  
140 substance and product classification and labelling as outlined in the CLP regulation (Ref. 1);
- 141 (f) the fact that the LVET is only a very minor variation of the Draize test with no impact on  
142 i) the amount of animals required for testing and ii) with unknown effects for the test animals  
143 with regard to the extent of stress and suffering inflicted.
- 144 (g) the potential usefulness of existing LVET data as reference data for validation purposes of  
145 alternative methods to assess the ocular irritancy potential of raw materials (surfactants) and  
146 finished products of the use domain of detergents and cleaning products.
- 147 (h) the comparable reproducibility of the LVET when compared to the Draize eye test.



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## 149 REFERENCES

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180 Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC,  
181 93/105/EC and 2000/21/EC. *Official Journal of the European Union* L 396/1.



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183 The ESAC was established by the European Commission, and is composed of nominees from  
184 the EU Member States, industry, academia and animal welfare organisations, together with  
185 representatives of the relevant Commission services.

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187 This statement was endorsed by the following members of the ESAC:

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189 Ms Argelia Castaño (Spain)  
190 Ms Maija Dambrova (Latvia)  
191 Ms Alison Gray (ESTIV)  
192 Ms Katalin Horvath (Hungary)  
193 Ms Dagmar Jírová (Czech Republic)  
194 Mr Roman Kolar (Eurogroup for Animals)  
195 Ms Elisabeth Knudsen (Denmark - acting as moderator at the meeting)  
196 Mr Manfred Liebsch (Germany)  
197 Mr Gianni Dal Negro (EFPIA)  
198 Mr. Walter Pfaller (Austria)  
199 Mr Tõnu Püssa (Estonia)  
200 Mr Dariusz Sladowski (Poland)  
201 Mr Jon Richmond (UK)  
202 Ms Vera Rogiers (ECOPA)  
203 Mr Michael Ryan (Ireland)  
204 Ms Annalaura Stamatii (Italy)  
205 Mr Jan van der Valk (The Netherlands)  
206 Mr Carl Westmoreland (COLIPA)  
207 Mr Timo Ylikomi (Finland)

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209 The following Commission Services and Observer Organisations were involved in the  
210 consultation process, but not in the endorsement process itself:

211 **Commission services**

212 Mr Joachim Kreysa (DG JRC, Head of In vitro methods Unit/ECVAM, chairman)  
213 Mr Claudius Griesinger (DG JRC, ESAC secretariat)  
214 Ms Susanne Hoke (DG ENTR)  
215 Ms Susanna Louhimies (DG ENV)  
216 Mr Juan Riego Sintes (DG JRC)

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218 **The following observers were present**

219 Mr Hajime Kojima (JaCVAM)  
220 Mr William Stokes (NICEATM)  
221 Ms Marilyn Wind (ICCVAM)

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