

## **Annex V**

### **Performance Characteristics for Use of LLNA EC3 Values to Predict Human Skin Sensitization Potency Categories**

#### **Annex V-1**

Performance Characteristics for the Use of LLNA EC3 to Classify 63 Sensitizers into Strong Sensitizer ( $DSA_{05} \leq 500 \mu\text{g}/\text{cm}^2$ ) and Other Sensitizer ( $DSA_{05} > 500 \mu\text{g}/\text{cm}^2$ ) Categories ..... C-323

#### **Annex V-2**

Performance Characteristics for the Use of LLNA EC3 to Classify 136 Substances into Strong Sensitizer ( $DSA_{05} \leq 500 \mu\text{g}/\text{cm}^2$ ), Other Sensitizer ( $DSA_{05} > 500 \mu\text{g}/\text{cm}^2$ ), and Nonsensitizer Categories ..... C-329

This page intentionally left blank

## **Annex V-1**

### **Performance Characteristics for the Use of LLNA EC3 to Classify 63 Sensitizers into Strong Sensitizer ( $DSA_{05} \leq 500 \mu\text{g}/\text{cm}^2$ ) and Other Sensitizer ( $DSA_{05} > 500 \mu\text{g}/\text{cm}^2$ ) Categories**

The 63 sensitizers in the LLNA and human skin sensitization tests include 25 strong and 38 other human sensitizers based on the criteria of the Globally Harmonized System of Classification and Labelling of Chemicals (UN 2009).

This page intentionally left blank

EC3 Cutoff (%)	Substances Correctly Classified as Strong Sensitizers <sup>1</sup>	Other Sensitizers Overclassified as Strong <sup>1</sup>	Underclassified Strong Sensitizers <sup>1</sup>	Substances Correctly Classified as Other Sensitizers <sup>1</sup>	Correct Classification Rate	Overclassification Rate	Underclassification Rate
0.02	1	0	24	38	62%	0%	96%
0.04	2	0	23	38	63%	0%	92%
0.06	3	0	22	38	65%	0%	88%
0.09	3	1	22	37	63%	3%	88%
0.12	4	1	21	37	65%	3%	84%
0.14	5	1	20	37	67%	3%	80%
0.28	5	2	20	36	65%	5%	80%
0.44	6	2	19	36	67%	5%	76%
0.49	7	2	18	36	68%	5%	72%
0.53	8	2	17	36	70%	5%	68%
0.62	9	2	16	36	71%	5%	64%
0.71	10	2	15	36	73%	5%	60%
0.81	11	2	14	36	75%	5%	56%
0.94	12	2	13	36	76%	5%	52%
1.19	13	2	12	36	78%	5%	48%
1.37	13	3	12	35	76%	8%	48%
1.69	14	3	11	35	78%	8%	44%
<b>2.00</b>	<b>14</b>	<b>3</b>	<b>11</b>	<b>35</b>	<b>78%</b>	<b>8%</b>	<b>44%</b>
2.20	14	4	11	34	76%	11%	44%
2.45	15	4	10	34	78%	11%	40%
2.54	16	5	9	33	78%	13%	36%
2.66	16	6	9	32	76%	16%	36%

The 63 sensitizers in the LLNA and human skin sensitization tests include 25 strong and 38 other human sensitizers based on the criteria of the Globally Harmonized System of Classification and Labelling of Chemicals (UN 2009).

**Boldface** data show the results for the optimal EC3 value of 3.79% and the GHS cutoff EC3 value of 2%.

<sup>1</sup> Values are numbers of substances.

EC3 Cutoff (%)	Substances Correctly Classified as Strong Sensitizers <sup>1</sup>	Other Sensitizers Overclassified as Strong <sup>1</sup>	Underclassified Strong Sensitizers <sup>1</sup>	Substances Correctly Classified as Other Sensitizers <sup>1</sup>	Correct Classification Rate	Overclassification Rate	Underclassification Rate
3.00	16	7	9	31	75%	18%	36%
3.29	17	7	8	31	76%	18%	32%
3.40	18	7	7	31	78%	18%	28%
3.54	19	7	6	31	79%	18%	24%
3.64	19	8	6	30	78%	21%	24%
3.74	20	9	5	29	78%	24%	20%
<b>3.79</b>	<b>21</b>	<b>9</b>	<b>4</b>	<b>29</b>	<b>79%</b>	<b>24%</b>	<b>16%</b>
4.00	21	9	4	29	79%	24%	16%
4.03	21	10	4	28	78%	26%	16%
4.28	21	11	4	27	76%	29%	16%
4.52	21	12	4	26	75%	32%	16%
4.87	21	13	4	25	73%	34%	16%
4.99	21	14	4	24	71%	37%	16%
5.29	22	14	3	24	73%	37%	12%
5.70	22	15	3	23	71%	39%	12%
5.86	22	16	3	22	70%	42%	12%
6.00	22	16	3	22	70%	42%	12%
6.10	22	17	3	21	68%	45%	12%
6.55	22	18	3	20	67%	47%	12%
7.30	22	19	3	19	65%	50%	12%
7.79	23	19	2	19	67%	50%	8%
7.87	23	20	2	18	65%	53%	8%
8.00	23	20	2	18	65%	53%	8%
8.36	23	21	2	17	63%	55%	8%

**Boldface** data show the results for the optimal EC3 value of 3.79% and the GHS cutoff EC3 value of 2%.

<sup>1</sup> Values are numbers of substances.

EC3 Cutoff (%)	Substances Correctly Classified as Strong Sensitizers <sup>1</sup>	Other Sensitizers Overclassified as Strong <sup>1</sup>	Underclassified Strong Sensitizers <sup>1</sup>	Substances Correctly Classified as Other Sensitizers <sup>1</sup>	Correct Classification Rate	Overclassification Rate	Underclassification Rate
9.04	23	22	2	16	62%	58%	8%
9.38	24	22	1	16	63%	58%	4%
9.76	24	23	1	15	62%	61%	4%
10.00	24	23	1	15	62%	61%	4%
10.51	24	24	1	14	60%	63%	4%
14.16	24	25	1	13	59%	66%	4%
17.51	24	26	1	12	57%	68%	4%
17.78	24	27	1	11	56%	71%	4%
18.96	24	28	1	10	54%	74%	4%
21.54	24	29	1	9	52%	76%	4%
23.53	24	30	1	8	51%	79%	4%
24.90	24	31	1	7	49%	82%	4%
25.90	24	32	1	6	48%	84%	4%
27.79	24	33	1	5	46%	87%	4%
30.24	24	34	1	4	44%	89%	4%
31.70	25	34	0	4	46%	89%	0%
32.51	25	35	0	3	44%	92%	0%
38.01	25	36	0	2	43%	95%	0%
57.70	25	37	0	1	41%	97%	0%

**Boldface** data show the results for the optimal EC3 value of 3.79% and the GHS cutoff EC3 value of 2%.

Abbreviations: DSA<sub>05</sub> = induction dose per skin area, in µg/cm<sup>2</sup>, in a human repeat-insult patch test or human maximization test that produces a positive response in 5% of the tested population; EC3 = estimated concentration of a substance expected to produce a stimulation index of 3, which is the threshold value for a substance to be considered a sensitizer in the LLNA; GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN 2009); LLNA = murine local lymph node assay.

<sup>1</sup> Values are numbers of substances.

This page intentionally left blank

## **Annex V-2**

**Performance Characteristics for the Use of LLNA EC3 to Classify 136 Substances into  
Strong Sensitizer ( $DSA_{05} \leq 500 \mu\text{g}/\text{cm}^2$ ), Other Sensitizer ( $DSA_{05} > 500 \mu\text{g}/\text{cm}^2$ ),  
and Nonsensitizer Categories**

This page intentionally left blank

EC3 Cutoff (%)	Substances Correctly Classified as Strong Sensitizers <sup>1</sup>	Other Sensitizers Overclassified as Strong <sup>1</sup>	Underclassified Strong Sensitizers <sup>1</sup>	Substances Correctly Classified as Other <sup>1</sup>	Other Substances Underclassified as Nonsensitizers <sup>1</sup>	Nonsensitizers Overclassified as Sensitizers <sup>1</sup>	Correctly Classified Nonsensitizers <sup>1</sup>	Correct Classification Rate <sup>2</sup>	Over-classification Rate <sup>3</sup>	Under-classification Rate <sup>4</sup>
0.02	1	0	26	38	11	35	25	47%	32%	49%
0.04	2	0	25	38	11	35	25	48%	32%	47%
0.06	3	0	24	38	11	35	25	49%	32%	46%
0.09	3	1	24	37	11	35	25	48%	33%	46%
0.12	4	1	23	37	11	35	25	49%	33%	45%
0.14	5	1	22	37	11	35	25	49%	33%	43%
0.28	5	2	22	36	11	35	25	49%	34%	43%
0.44	6	2	21	36	11	35	25	49%	34%	42%
0.49	7	2	20	36	11	35	25	50%	34%	41%
0.53	8	2	19	36	11	35	25	51%	34%	39%
0.62	9	2	18	36	11	35	25	51%	34%	38%
0.71	10	2	17	36	11	35	25	52%	34%	37%
0.81	11	2	16	36	11	35	25	53%	34%	36%
0.94	12	2	15	36	11	35	25	54%	34%	34%
1.19	13	2	14	36	11	35	25	54%	34%	33%
1.37	13	3	14	35	11	35	25	54%	35%	33%
1.69	14	3	13	35	11	35	25	54%	35%	32%
<b>2.00</b>	<b>14</b>	<b>3</b>	<b>13</b>	<b>35</b>	<b>11</b>	<b>35</b>	<b>25</b>	<b>54%</b>	<b>35%</b>	<b>32%</b>
2.20	14	4	13	34	11	35	25	54%	36%	32%
2.45	15	4	12	34	11	35	25	54%	36%	30%
2.54	16	5	11	33	11	35	25	54%	37%	29%
2.66	16	6	11	32	11	35	25	54%	38%	29%

**Boldface** data show the results for the GHS EC3 cutoff of 2%.

<sup>1</sup> Values are numbers of substances.

<sup>2</sup> Correctly classified human strong sensitizers, human other sensitizers, and human nonsensitizers.

<sup>3</sup> Includes human other sensitizers and nonsensitizers that are overclassified by the LLNA (n = 109).

<sup>4</sup> Includes human strong sensitizers and other sensitizers that are underclassified by the LLNA (n = 76).

<b>EC3 Cutoff (%)</b>	<b>Substances Correctly Classified as Strong Sensitizers<sup>1</sup></b>	<b>Other Sensitizers Overclassified as Strong<sup>1</sup></b>	<b>Underclassified Strong Sensitizers<sup>1</sup></b>	<b>Substances Correctly Classified as Other<sup>1</sup></b>	<b>Other Substances Underclassified as Nonsensitizers<sup>1</sup></b>	<b>Nonsensitizers Overclassified as Sensitizers<sup>1</sup></b>	<b>Correctly Classified Nonsensitizers<sup>1</sup></b>	<b>Correct Classification Rate<sup>2</sup></b>	<b>Over-classification Rate<sup>3</sup></b>	<b>Under-classification Rate<sup>4</sup></b>
3.00	16	7	11	31	11	35	25	53%	39%	29%
3.29	17	7	10	31	11	35	25	54%	39%	28%
3.40	18	7	9	31	11	35	25	54%	39%	26%
3.54	19	7	8	31	11	35	25	55%	39%	25%
3.64	19	8	8	30	11	35	25	54%	39%	25%
3.74	20	9	7	29	11	35	25	54%	40%	24%
3.79	21	9	6	29	11	35	25	55%	40%	22%
4.00	21	9	6	29	11	35	25	55%	40%	22%
4.03	21	10	6	28	11	35	25	54%	41%	22%
4.28	21	11	6	27	11	35	25	54%	42%	22%
4.52	21	12	6	26	11	35	25	53%	43%	22%
4.87	21	13	6	25	11	35	25	52%	44%	22%
4.99	21	14	6	24	11	35	25	51%	45%	22%
5.29	22	14	5	24	11	35	25	52%	45%	21%
5.70	22	15	5	23	11	35	25	51%	46%	21%
5.86	22	16	5	22	11	35	25	51%	47%	21%
6.00	22	16	5	22	11	35	25	51%	47%	21%
6.10	22	17	5	21	11	35	25	50%	48%	21%
6.55	22	18	5	20	11	35	25	49%	49%	21%
7.30	22	19	5	19	11	35	25	49%	50%	21%
7.79	23	19	4	19	11	35	25	49%	50%	20%
7.87	23	20	4	18	11	35	25	49%	50%	20%

**Boldface** data show the results for the GHS EC3 cutoff of 2%.

<sup>1</sup> Values are numbers of substances.

<sup>2</sup> Correctly classified human strong sensitizers, human other sensitizers, and human nonsensitizers.

<sup>3</sup> Includes human other sensitizers and nonsensitizers that are overclassified by the LLNA (n = 109).

<sup>4</sup> Includes human strong sensitizers and other sensitizers that are underclassified by the LLNA (n = 76).

EC3 Cutoff (%)	Substances Correctly Classified as Strong Sensitizers <sup>1</sup>	Other Sensitizers Overclassified as Strong <sup>1</sup>	Underclassified Strong Sensitizers <sup>1</sup>	Substances Correctly Classified as Other <sup>1</sup>	Other Substances Underclassified as Nonsensitizers <sup>1</sup>	Nonsensitizers Overclassified as Sensitizers <sup>1</sup>	Correctly Classified Nonsensitizers <sup>1</sup>	Correct Classification Rate <sup>2</sup>	Over-classification Rate <sup>3</sup>	Under-classification Rate <sup>4</sup>
8.00	23	20	4	18	11	35	25	49%	50%	20%
8.36	23	21	4	17	11	35	25	48%	51%	20%
9.04	23	22	4	16	11	35	25	47%	52%	20%
9.38	24	22	3	16	11	35	25	48%	52%	18%
9.76	24	23	3	15	11	35	25	47%	53%	18%
10.00	24	23	3	15	11	35	25	47%	53%	18%
10.51	24	24	3	14	11	35	25	46%	54%	18%
14.16	24	25	3	13	11	35	25	46%	55%	18%
17.51	24	26	3	12	11	35	25	45%	56%	18%
17.78	24	27	3	11	11	35	25	44%	57%	18%
18.96	24	28	3	10	11	35	25	43%	58%	18%
21.54	24	29	3	9	11	35	25	43%	59%	18%
23.53	24	30	3	8	11	35	25	42%	60%	18%
24.90	24	31	3	7	11	35	25	41%	61%	18%
25.90	24	32	3	6	11	35	25	40%	61%	18%
27.79	24	33	3	5	11	35	25	40%	62%	18%
30.24	24	34	3	4	11	35	25	39%	63%	18%
31.70	25	34	2	4	11	35	25	40%	63%	17%
32.51	25	35	2	3	11	35	25	39%	64%	17%
38.01	25	36	2	2	11	35	25	38%	65%	17%
57.70	25	37	2	1	11	35	25	37%	66%	17%

**Boldface** data show the results for the GHS EC3 cutoff of 2%.

Abbreviations: DSA<sub>05</sub> = induction dose per skin area, in µg/cm<sup>2</sup>, in a human repeat-insult patch test or human maximization test that produces a positive response in 5% of the tested population; EC3 = estimated concentration of a substance expected to produce a stimulation index of 3, which is the threshold value for a substance to be considered a sensitizer in the LLNA; GHS = Globally Harmonized System of Classification and Labelling of Chemicals (UN 2009); LLNA = murine local lymph node assay.

<sup>1</sup> Values are numbers of substances.

<sup>2</sup> Correctly classified human strong sensitizers, human other sensitizers, and human nonsensitizers.

<sup>3</sup> Includes human other sensitizers and nonsensitizers that are overclassified by the LLNA (n = 109).

<sup>4</sup> Includes human strong sensitizers and other sensitizers that are underclassified by the LLNA (n = 76).

This page intentionally left blank