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Annex 8: Denmark's supplementary analyses of DASS specificity by inclusion of additional "potential LLNA-negatives"

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After the enlargement of the DASS consolidated reference set with additional LLNA-negatives in April 2020, the number of LLNA negatives had grown from 11 to 33. According to DASS SD Annex 5 (see reference 4 in Annex 5) around 20% of 11,096 REACH-registered mono-constituent organic substances are predicted to be sensitizers in the Danish (Q)SAR Database (as of 2021) by use of a majority vote between three QSAR models, i.e. the remaining 80% are predicted to be negative or are out of the QSAR model domains. Similar percentage of skin sensitizers amongst REACH registered substances has been estimated by Luchtenfeld et al 2016. We were concerned that the 33 LLNA negatives in the DASS reference set would not be a sufficiently large collection to be representative for the many thousands of substances on regulatory inventories expected not to be skin sensitizers.
Furthermore, the relatively low number of LLNA-negative reference substances in the DASS reference set (33 substances) gave concerns that the robustness of the DA specificity measures would be low.
Hence, it was decided to make supplementary analyses to investigate the specificity of the DA approaches with a more relaxed definition of the LLNA-negatives.
We defined the following criteria for identifying additional substances which were likely LLNA-negatives ("potential LLNA-negatives"):

TG 429 procedures seem to have been followed with only minor deviations except that:

- *Max. test concentration ≥ 25% and < 50% without justification AND*
- *Requirement in relation to linear correlation between measured SI values:*
  - *When $R^2 \geq 0.7$ the extrapolated SI at 100% test concentration should be less than 3*
  - *When $R^2 < 0.7$ all measured SI values should be below 2.5*

From the proposed additional LLNA negatives, 13 DK potential LLNA-negatives, which also had DA high confidence predictions in addition to the 33 LLNA-negatives in the DASS reference set, were identified from the brutto list assessed by the DASS Expert Group. The additional substances were:

Curated.name	CASRN	EC	DA.2o3_Op1_1_DPRA_VSBR_MR	DA.2o3_Op1_2_DPRA_VSBR_MR	DA.2of3.CallConf	DA.2of3.Confidence	DA.ITSv1.6.CallConf	DA.ITSv1.6.Confidence	DA.ITSv2.6.CallConf	DA.ITSv2.6.Confidence	LLNA.CallDK
2-Acetylcyclohexanone	874-23-7	212-858-5	1	1	1	High	1	High	1	High	0
Benzaldehyde	100-52-7	202-860-4	1	1	1	High	1	High	inconcl.	Low	0
1-Bromobutane	109-65-9	203-691-9	1	1	1	High	1	High	1	High	0
Chlorobenzene	108-90-7	203-628-5	0	0	0	High	0	High	1	High	0
Dihydromyrcenol	18479-58-8	242-362-4	0	0	0	High	1	High	inconcl.	Low	0
Ethyl benzoylacetate	94-02-0	202-295-3	inconcl.	inconcl.	inconcl.	Low	0	High	0	High	0
Isobornyl acetate	125-12-2	204-727-6	0	0	0	High	1	High	1	High	0
2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol	63500-71-0	613-238-0	inconcl.	inconcl.	inconcl.	Low	0	High	0	High	0
Methyl dihydrojasmonate	24851-98-7	246-495-9	0	0	0	High	Inconcl.	Low	inconcl.	Low	0
1-(3-Methyl-2-benzofuranyl)ethanone	23911-56-0	429-100-6	1	1	1	High	1	High	1	High	0
6-Methylcoumarin	92-48-8	202-158-8	0	0	0	High	0	High	0	High	0
Propylparaben	94-13-3	202-307-7	1	1	1	High	1	High	1	High	0
Sulfanilic acid	121-57-3	204-482-5	0	0	0	High	0	High	0	High	0

NB Information on borderline results for 2o3 were not available for all the DK potential negatives

This gave the following results for the set of DK potential negatives alone and integrated with the DASS reference set:

	DK potential negatives			DASS reference set			DK set + DASS set		
DA	TN	FP	Specificity	TN	FP	Specificity	TN	FP	Specificity
2o3	6	5	45	22	4	85	28	9	76
ITSv1.6	5	7	42	21	9	70	26	16	62
ITSv2.6	4	6	40	20	10	67	24	16	60

These results indicated that the specificity of the DASS predictions for the DK potential LLNA-negatives were much lower than the specificity of the DASS predictions for the DASS reference set LLNA-negatives.
I.e. the results of this supplementary specificity analysis showed that such relaxed criteria for LLNA negatives would result in marked lower specificity values for the three DASS approaches. An explanation of the lower specificities measured based on the DK potential LLNA-negatives could be that some of these in fact are weak skin sensitisers not caught in LLNA due to low maximum concentration.
The supplementary analysis was performed after the EG agreement was obtained regarding the criteria for identification of the LLNA-negative reference substance. However, the results of the supplementary specificity analyses support that EG-agreed and applied strict criteria for identifying LLNA-negative reference substances is reasonable, although the number of such substances was relatively low, i.e. approximately 4 times lower than the number of LLNA-positive reference substances (33 LLNA-negatives vs. 134 LLNA-positives) implying a higher uncertainty for the measured specificity values than that for the measured sensitivity values.

Luechtefeld, T. et al. Analysis of publically available skin sensitization data from REACH

registrations 2008-2014. ALTEX 33, 135–148 (2016).