October 2021

DASS Guideline 497 Webinar

Answered questions in writing during the webinar:

Question: Is it no longer possible to fulfill this endpoint only with QSAR? Do we always have to do at least one in vitro study?

Answer: For REACH, QSAR is still a possibility to be used as an adaptation according to Annex XI, section 1.2, if specific conditions are met. E.g. the DASS ITS v2 contains the automated workflow for skin sensitisation which is different from using toolbox in a standard way.

Question: What if a substance is only sensitizing after metabolization? How is this handled with the defined approach?
Answer: There were a number of pre/pro-haptens in the reference chemical database and the DAs performed well (better than the LLNA) against this chemical set. Simulated metabolism is also considered in the in silico tools.

Question: Could you tell me the examples of the scientific justification for those chemicals which are accepted negative even though the highest concentration used was not at least 50%?
Answer: For example when the highest soluble concentration was tested or when higher concentrations would lead to excessive irritation and/or systemic toxicity

Question: Does this in vitro method for skin sensitization already validated?
Answer: The Defined Approaches in GL 497 are based on validated in vitro methods (DPRA, Keratinosens and hCLAT in TG 442C, 442D and 442E respectively).

Question: Will the individual test guidelines for TG 442 c, d, and e be updated to include the borderline range decision trees?
Answer: This is something that will be taken up by the expert group on skin sensitization, but to me it makes sense.

Question: What does a non-sensitzier outside the applicability domain mean for my substance/product?
Answer: When a test chemical is outside the applicability domain of a method/combination of methods, it is not recommended to use it.

Question: In the event that you end up with an inconclusive result is the use of methods that do not yet have OECD TGs such as the GARD assay or the SENS-IS to provide additional data for a WoE acceptable?
Answer: This would depend on the regulatory authority/region, but this would certainly consistute WoE

Question: Has there been or will there be consideration to also incude KE2 assays into the ITS for potency?
Answer: This would be considered a new DA, but could be evaluated using the assessment framework from GL 497.

Question: It was said that, for some chemistries, DA is better than LLNA. Which chemistries? And how should regulators use existing LLNA data for those chemistries? Throw it out?
Answer: In fact, it is the high log P substances where the LLNA tends to over-predict the skin sensitization potential as compared to human data. How regulators would handle existing data is dependent on the regulatory authority.

Question: Do the steps in the AOP have to happen in sequence? Does step 1- protein binding, has to occur before step two can occur and does step 2 has to occur before step 3 can take place? If so

how does one interpret data when tests for step 1 or 2 is negative but the HCLAT is positive? It suggest concerns with the assays or that chemicals can skip steps in the pathway to initiate sensitization.
Answer: In the Defined Approaches the steps of the AOP don't need to be addressed in sequence. In case of discordant results this is already taken into consideration by the Data interpretation procedure of the defined approaches which are meant to overcome the limitations of the individual tests.

Question: Is FDA accepting DAs-based data for skin sensitiziation for medical devices? If no, why not? Thank you.
Answer: CDRH currently does not accept the DASS for medical devices as we have not yet been provided with qualification data to support that such an approach can be used on complex mixtures of weak/moderate sensitizers extracted from medical devices. There are also often challenges with optimization of in vitro test systems to accommodate use with a broad range of medical devices with varied chemical and physical properties in a standardized fashion.

Question: Regarding the "future work" on quantitiative risk assessment, what is the anticipated timing? will this be available in the near future?
Answer: The proposal to add this project to the OECD workplan is being drafted now, for submission in mid-November for the next review cycle. If the WNT approves inclusion of the project, then we hope to perform the feasability study on including a DA for QRA into GL 497 within the next 2 years. Regardless, the NICEATM/Unilever collaboration is moving forward to apply the SARA model to case study compounds and to work on making the model publicly available.

Question: Can you provide the link for the SARA model?
Answer: "https://doi.org/10.1016/j.comtox.2018.10.004 Part of the NICEATM/Unilever collaboration will be to make the SARA model publicly available via the ICE dashboard: https://ice.ntp.niehs.nih.gov/"

Question: To Nicole Kleinstreuer: you mentioned the work of ANN by Shiseido and the cooperation with Unilever and their SARA - is there a plan to further work on the Bayesian Network DIP (BN-ITS-3) for hazard and potency identification of skin sensitizers (P&G) (case study IX of guidance on testing 256)?
Answer: The BN-ITS-3 DA could of course be evaluated using the assessment framework from GL 497. NICEATM has not been approached by P&G to collaborate on such a project but they may be working on it themselves.

Question: What is your recommendation for those 'challenge' chemicals (i.e., hydrophic chemicals not compatible with the cell-line based systems or high molecular weight, viscous compounds,, like polymers)?
Answer: If they are not compatible with the test system they cannot be tested in the Defined Approaches since the applicability is defined by the technical limitations of the in vitro tests.

Question: Thank you for the fantastic presentations so far!
@Nicole: reference human data is a rare commodity but animal reference standards have shortcomings - how can this be addressed?"
Answer: An increased focus on human mechanistic relevance of the DAs and information sources should be the basis for establishing scientific confidence. Also, understanding and considering the variability of the animal reference standard is important when using it as a basis for performance comparison (in the absence of human data).

Question: Will the OECD TG406 still active ?
Answer: TG 406 is still an active Test Guideline, but the introduction has been modernised this year to orient the users on other methods and approaches that have been developed and maybe considered first in view of animal welfare and other considerations

Question: Since QRA calculations are based on NESIL values and the SARA method is not publically available, how does one calculated potency
Answer: There are several models that were included in the OECD IATA case studies that also provide potency calculations, e.g. the Shiseido ANN or the BN-ITS-3.

Question: To all speakers: Could defined approaches be used to model substances/mixtures that are thought to give false positive results in LLNA? Is this approach accepted by regulatory authorities, or would LLNA results still take precedence?
Answer: For human drugs, I think the in chemico and in vitro methods could be conducted as part of an overall weight of evidence and would be interpreted along with in vivo data. I am not sure one type of data would necessarily take "precedence" over another. It would depend on the specifics.

Question: Skin sensitisation Category 1 is detailed in the CLP Regulation. Is it not possible to use this if data does not allow sub-categorisation based on potency? Would an in vivo study be needed in these cases?
Answer: The CLP indeed contains category 1, however it is up to the particular regulation whether information on potency/sub-categorisation needs to be generated. For REACH purposes, if you have old in vivo data i.e. done before May 2017 and that data does not allow potency categorisation then new data is not needed. For REACH the potency estimation became mandatory in 2017, therefore if e.g. in vivo data has been generated after that, potency needs to be covered. If the newly generated data you have does not allow potency estimation then new information needs to be covered. This could be e.g. use of read-across, additional in vitro studies or as a last resort an in vivo study. The specific details have been described in the REACH Annex VII, section 8.3.

Question: So to confirm, for a new substance being registered for REACH, can OECD 497 now be used.
Answer: Yes, if the substance is applicable to the methods listed in the OECD 497 guideline.

Question: Has IVSA been considered in the DA?
Answer: Currently the only information sources considered in the DAs are the validated methods from the KE-based TGs. There are 3D skin models that are currently undergoing validation, and in my opinion the assessment framework from GL 497 could be applied to stand-alone methods that may be equivalent to DAs as part of a submission to OECD.

Question: Comment: perhaps a difference between drugs and agrochem formulations is that many of the different formulation types can be tested in vitro - after all, they are often mixed with water and sprayed.
Answer: I don' think the validation exercises addressed these routes. Exploration of the applicability of the alternatives for these routes might be useful, however, as good nonclinical models for sensitization by these routes do not seem to exist.

Question: To Paul Brown: To which extent can results from this approach be extrapolated to substances administerd via respiratory or parental routes?
Answer: As far as I know, this has not yet been investigated.

Question: Dear Nicole, dear Silvia, one cut-off for validity of a true negative in your LLNA set was the testing of at least 50%. This high concentration threshold may be useful for making sure it is a true negative. However, some authors noted that the LLNA was not even validated for test concentrations above 25%. Is there a grey zone of LLNA benchmark information and, if so, how would you advise risk assessors to deal with it?
Answer: Risk assessors should continue evaluating the LLNA studies on the basis of GL 429 and their experience with the LLNA. The stringent criteria used for the defined approaches guideline were specifically meant to avoid using equivocal results for the assessment of the DAs.
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Question: @Nicole/Anna: When will the data on the expanded chemical space be shared?

Answer: Our hope is to be able to begin to publish/share the data by the middle of next year. It will be released in stages as we work with the agency partners that nominated the substances for testing, to analyze the data and apply the DAs and assess the performance.