Refinements in TIMES for skin sensitisation: Does volatility play a role?

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G Poryazova[a*], C Kuseva[a], G Ellis[b], R Hunziker[c], P Kern[d], L Low[e], G Patlewicz[f**], S Ringeissen[g], G Veith[h], O Mekenyan[a]
[a]Laboratory of Mathematical Chemistry, Prof "As Zlatarov", Bourgas, Bulgaria, [b]Givaudan Swiss SA, Vernier, Switzerland, [c]Dow Europe GmbH, Toxicology and Environmental Research and Consulting, Horgen, Switzerland, [d]Procter Gamble Eurocor, Strombeek-Bever, Belgium, [e]ExxonMobil, Biomedical Sciences, Inc., Division of Toxicology and Environmental Sciences, Annandale NJ, USA, [f]DuPont Haskell Global Centers for Health & Environmental Sciences, Newark DE, USA, [g]L'Oreal R&I, Aulnay-sous-Bois, France, [h]International QSAR Foundation (IQF), Two Harbors, MN, USA
Presenting author* geri_d@btu.bg Corresponding author** patlewig@hotmail.com

ABSTRACT

The TImes MEtabolism Simulator platform for predicting Skin Sensitisation (TIMES-SS) is a hybrid expert system that was developed at Bourgas University using funding and data from a consortium comprising experts from industry and regulatory agencies and coordinated by IQF. In 2010, a new industry consortium was established to refine the model in light of new data and chemical insights.
One of the specific aims was to evaluate the applicability domain of the underlying experimental data. The current version of TIMES-SS relies upon data principally from both mice and guinea pigs derived from the local lymph node assay (LLNA) and guinea pig maximisation assay (GPMT) protocols. In the event of multiple results, the LLNA outcome has been taken as the default preferred outcome for TIMES-SS. In light of revisions to the LLNA Test Guidance 429, certain classes of chemicals such as some surfactants are now known to elicit false positives in the LLNA. This prompted a review of the underlying training set to identify cases where multiple LLNA and GPMT existed and evaluate and rationalise any inconsistencies observed. In the majority of cases evaluated, the GPMT and LLNA data were found to be in good agreement, the conflict amounting to a slight change in potency categorisation. Where there were more substantial inconsistencies, three scenarios were proposed as possible explanations; species specific metabolism, skin irritation and volatility.
This study investigated the effect of chemical volatility on the LLNA. A set of 31 chemicals with LLNA EC3 data, time for 50% evaporation of the chemical and information from other studies (such as GPMT; HRIPT; *in vitro* peptide reactivity) was compiled. The observed time [min] for 50% evaporation of the chemical was found to be well correlated by the estimated log vapour pressure [Pa]. The trend between vapour pressure and sensitisation potency was then explored. In fact, a pragmatic cut off for volatility could be established whereby chemicals with high vapour pressures (VP>100 Pa) appeared to be underpredicted by the LLNA relative to other supporting information whereas chemicals with low vapour pressures (VP<100 Pa) elicited LLNA outcomes consistent with other assays. There were several outliers to this general trend (notably highly reactive chemicals) although these are still under investigation. Based on the trends observed to date, vapour pressure appears to be a useful alert to help justify false positives in TIMES-SS's predictions of the LLNA. This flag is being implemented in TIMES-SS as a new refinement.

DATASET UNDER STUDY

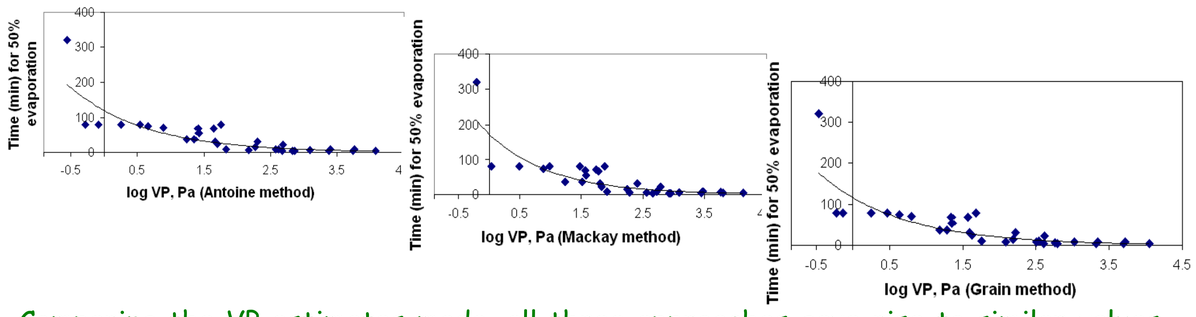
A set of 33 chemicals were made available by Givaudan. These 33 substances had the following information available:

- EC3 values from the LLNA,
- results from other assays including GPMT. HRIPT or *in vitro* assays and
- time (min) taken to result in 50% evaporation

2D Structures were available for 31 out of the 33 substances hence the analysis conducted was only for these 31 chemicals

SURROGATES FOR EVAPORATION DATA

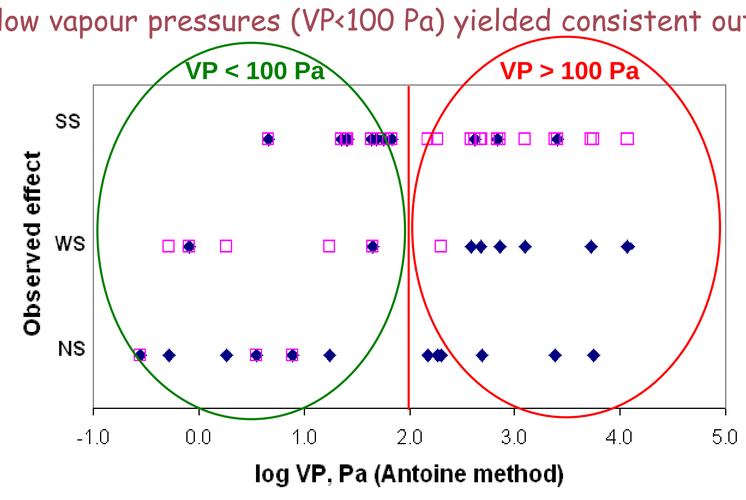
An attempt was made to find a surrogate which correlated with the evaporation data that could be linked to chemical structure.
Vapour pressure of pure substances was found to be a reasonable approximation to the evaporation information since it could mimic the evaporation loss from a solution in vehicle.
The lesser the time for evaporation, the more volatile the chemical – i.e. have higher values for VP.
Three methods are available within the EPIWIN software (US EPA) for calculating vapour pressures. These methods are the Grain, Mackay and Antoine approaches.



Comparing the VP estimates made, all three approaches gave rise to similar values. As such, the Antoine method was used as a default calculator of VP.

EFFECT OF CHEMICAL VOLATILITY TO THE OBSERVED SKIN SENSITISATION EFFECT IN LLNA AND OTHER ASSAYS

Chemicals with high vapour pressures (VP>100 Pa) had their sensitisation effect under predicted by the LLNA assay relative to other assays investigated in this study.
Chemicals with low vapour pressures (VP<100 Pa) yielded consistent outcomes for skin sensitisation.



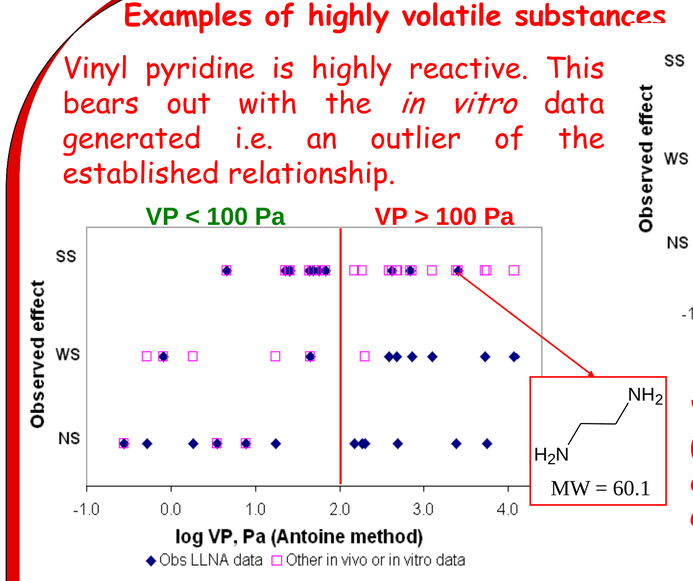
SS - strong sensitiser; WS - weak sensitiser; NS - non sensitiser

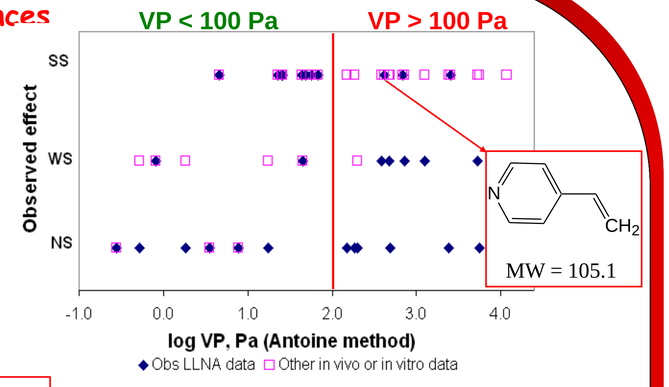
BUT there were several outliers

ANALYSIS OF OUTLIERS

Examples of highly volatile substances

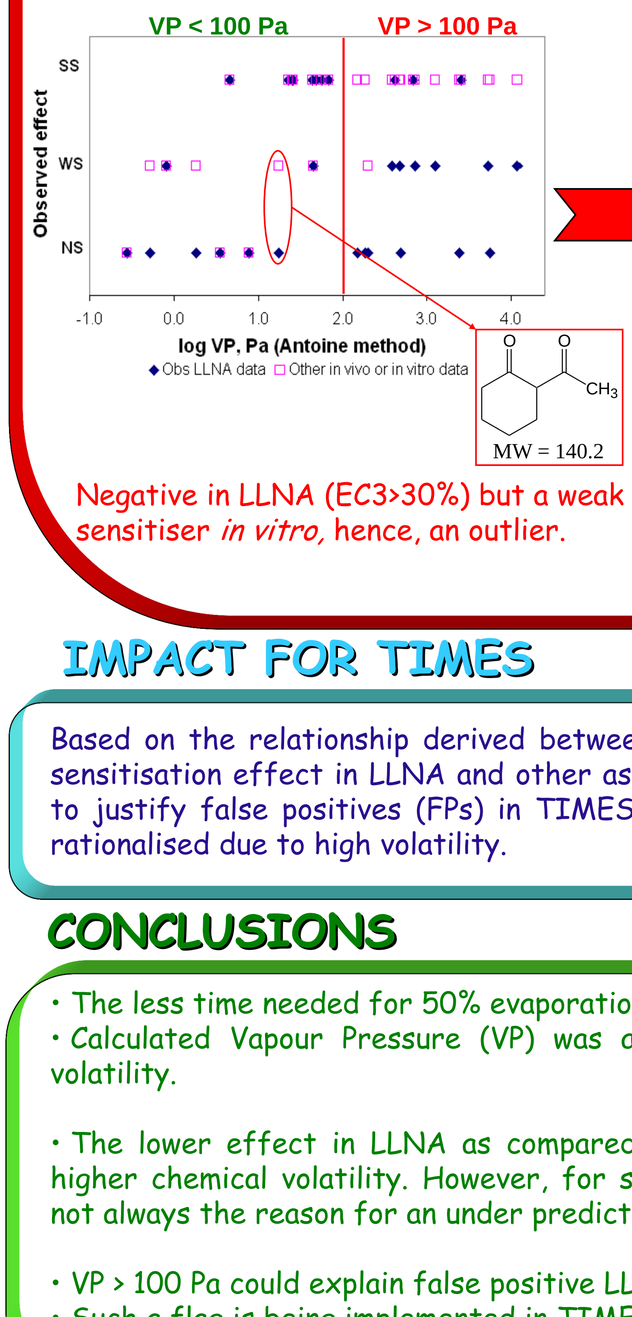
Vinyl pyridine is highly reactive. This bears out with the *in vitro* data generated i.e. an outlier of the established relationship.





Volatility does not affect LLNA result (EC3 = 2.2%). Hence, this chemical could be considered as an outlier of the established relationship.

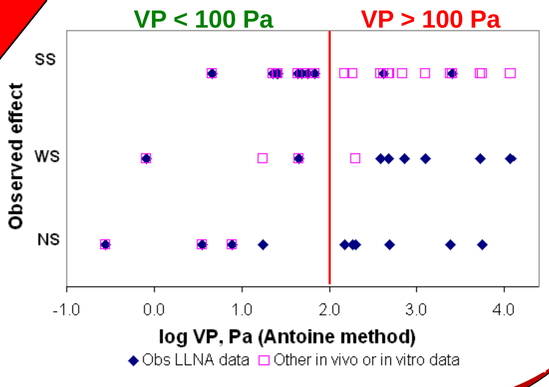
Examples of non volatile substances



Negative in LLNA (EC3>30%) but a weak sensitiser *in vitro*, hence, an outlier.

Upon removing justified outliers:

- A lower effect in LLNA compared with other assays may be due to chemical volatility
- Higher volatility is not the only reason for under prediction in the LLNA



IMPACT FOR TIMES

Based on the relationship derived between volatility of chemicals and observed skin sensitisation effect in LLNA and other assays, vapour pressure could be a useful flag to justify false positives (FPs) in TIMES predictions. 6 out of 9 FPs could be post rationalised due to high volatility.

CONCLUSIONS

- The less time needed for 50% evaporation, the more volatile the chemical.
- Calculated Vapour Pressure (VP) was a reasonable parameter to model chemical volatility.

- The lower effect in LLNA as compared to other assays could be associated with higher chemical volatility. However, for strong skin sensitisers, higher volatility was not always the reason for an under prediction in the LLNA.

- VP > 100 Pa could explain false positive LLNA predictions from the model.
- Such a flag is being implemented in TIMES-SS as a new refinement.

This poster can be downloaded from the LMC website: http://oasis-lmc.org/posters/QSAR2012