THE IMPORTANCE OF HAVING A SOLID PC DATA PACKAGE TO SUPPORT HUMAN HEALTH/ENVIRONMENTAL RISK ASSESSMENT AND READ ACROSS UNDER REACH

F. Tencalla, J. Muller, S. Mishra, and T. Petry

ToxMinds
THINKING AHEAD IN TOXICOLOGY

Introduction

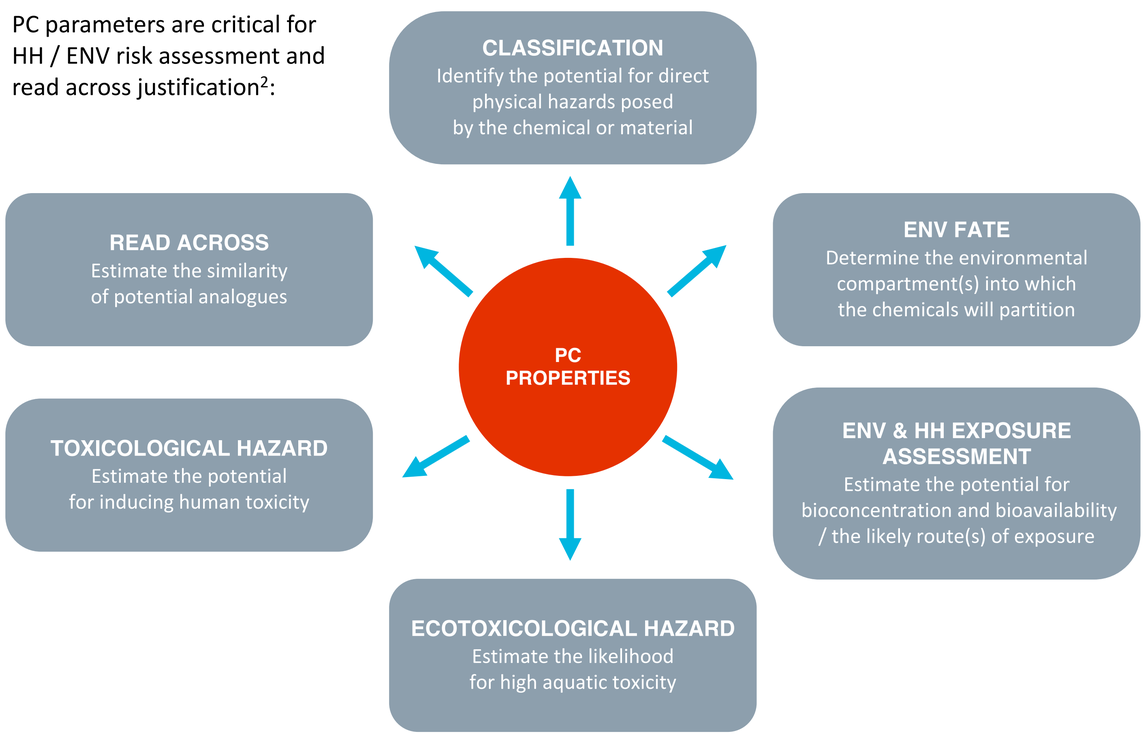
Developing a solid and consistent data package for physico-chemical (PC) properties, especially when dealing with substances linked together by read across, is a crucial but sometimes underestimated part of every REACH[1] registration. PC parameters are critical endpoints used for hazard, exposure and risk assessment. They are also a cornerstone of the read across approaches applied when data gaps are present.

Whereas compiling a robust, guideline-compliant, PC data package may be straightforward in some cases, there are many pitfalls when dealing with certain types of chemistries, for example very low water solubility substances or complex reaction mixtures (Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials, known as 'UVCBs' under REACH).

This poster illustrates some of the challenges encountered in developing suitable PC data for difficult substances and the impact this may have for human health (HH) and environmental (ENV) risk assessment, and/or the justification of read across.

Why focus on developing a solid PC properties data package?

PC parameters are critical for HH / ENV risk assessment and read across justification[2]:



Standard methods for selected PC parameters

Water solubility, partition coefficient and vapour pressure are determining parameters for which standard test guidelines are available[2]:

	HH and ENV parameters influenced	Standard test guidelines	Measurement methods
Water solubility	• Human exposure and uptake • Environmental exposure and behaviour	OECD 105	• Column elution • Shake flask
Partition coefficient (log Pow)	• Uptake in humans and other organisms • Environmental behaviour • Potential for bioaccumulation	OECD 107 OECD 123 OECD 117	• Shake flask • Slow-stirring • HPLC
Vapour pressure	• Human exposure • Environmental exposure and behaviour	OECD 104	• Dynamic • Static • Isoteniscope • Effusion – vapour pressure balance • Effusion – Knudsen cell • Effusion – isothermal thermogravimetry • Gas saturation • Spinning rotor

COMMONLY ENCOUNTERED CHALLENGES:

- Standard test methods are not appropriate for all types of chemistries
- Minor differences in experimental methodology can give rise to significant variations in PC values
- Development of specific analytical methodology to determine test substance concentrations can represent an important barrier to obtaining meaningful results

Case study 1: Obtaining suitable water solubility data

BACKGROUND

- Data poor complex UVCB consisting of 3 subgroups of constituents
- Water solubility testing required as part of the REACH data package and to assess the read across feasibility to a potential data-rich analogue

WATER SOLUBILITY TESTING - PROCESS

- Experienced Contract Research Organisation (CRO) selected for the work
- OECD 105 was first choice method
- Analytical detection method development guided by previous work at another testing facility

WATER SOLUBILITY TESTING - OUTCOME

- Analytical method development proved to be a hurdle for the conduct of OECD 105 testing: only selected constituents from 2 of the 3 subgroups could be detected despite numerous attempts
- Switch to less sensitive methods: total organic carbon (TOC) and critical micelle concentration (CMC)

IMPACT

- Due to analytical difficulties, less reliable water solubility value obtained which challenge the development of the read across justification

Case study 2: Selection of key value for risk assessment

BACKGROUND

- Complex UVCB consisting of more than 10 constituents. Two main constituents represent >90%.
- Water solubility value needed for risk assessment

WATER SOLUBILITY VALUE - PROCESS

- Due to analytical limitations, water solubility could be determined with OECD 105 only for one major constituent
- Testing was complemented with (Q)SAR modelling for individual constituents, yielding a wide range of predicted values
- The highest values were for constituents present at low concentrations (<5%)
- Water solubility testing - outcome
- Key water solubility value for risk assessment was selected based on the more complete modelled dataset
- As a reasonable worst-case approach: a weighted average (Q)SAR value was determined based on constituents representing >80-90% of the composition, excluding constituents present at <5%

IMPACT

- Reasonable worst-case approach used for risk assessment taking into account partial testing results and (Q)SAR modelling

Case study 3: Data interpretation in the context of read across

BACKGROUND

- Large category of UVCBs substances divided into three subgroups based on chemical structure
- Water solubility data available for all substances but different test methods used
- Reliable and consistently determined water solubility data needed to support read across between the three subgroups

WATER SOLUBILITY TESTING - PROCESS

- Experienced Contract Research Organisation (CRO) selected for the work
- OECD 105 was first choice method

WATER SOLUBILITY TESTING - OUTCOME

- Test results could be obtained for most members of two subgroups but testing was not possible for the third subgroup due to very strong emulsion issues
- Alternative approaches attempted, all yielding similar difficulties

IMPACT

- Risk assessment approach revised due to unexpected behaviour of substances in water solubility testing. One subgroup handled separately whereas read across remained supportable for the other two subgroups

References

1 Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No. 793/93 and Commission Regulation (EC) No. 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

2 ECHA (2016) Practical guide for SME managers and REACH coordinators. How to fulfil your information requirements at tonnages 1-10 and 10-100 tonnes per year. Practical guide for SME managers and REACH coordinators - Publications Office of the EU (europa.eu).