DTU Library

Should these potential CMR substances have been registered under REACH?

Wedebye, Eva Bay; Nikolov, Nikolai Georgiev; Dybdahl, Marianne; Abildgaard Rosenberg, Sine; Niemelä, Jay Russell

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Should these potential CMR substances have been registered under REACH?

Eva B. Wedebye, Nikolai G. Nikolov, Marianne Dybdahl, Sine A. Rosenberg, Jay R. Niemelä

Abstract (Q)SAR models were applied to screen around 68,000 REACH pre-registered substances for CMR properties (carcinogenic, mutagenic or toxic to reproduction). Predictions from 14 relevant models were combined to reach overall calls for C, M and R. Combining predictions may reduce "noise" and increase accuracy in the overall call. The Nordic substance register database (SPIN) was used to identify not registered substances where human exposure is likely to be significant. The Danish EPA may use the results for future priority setting for e.g. proposals for (harmonized) CMR-classification or targeted experimental confirmatory testing and potential inclusion on the EU CORAP list.

Background REACH pre-registration substances (PRS) classified for C, M or R in category 1 or 2 should have been registered by December 2010. However, it is well-known that for low tonnage and even for the high tonnage EU industrial substances the majority have few or no experimental CMR test data /1/. As a result, CMR substances presently used in the EU may with high probability not have been REACH registered under REACH, and registered substances may not have been classified for CMR effects.

Aim The aim was by (Q)SAR to predict potential CMR properties and on this basis make overall CMR calls for the following substances:

> • Registered substances that are not self-classified by industry as C and/or M and/or R
> • Not registered PRS possibly due to unrecognized CMR properties / lack of test data.

Start lists The initial lists were the ECHA list of registered substances as of 15th June 2012 with 5,306 publishable registered substances /2/ and the ECHA PRS with 143,835 substances /3/.

Step 1 The applied (Q)SAR models can predict discrete organic substances based on structural information (e.g. SMILES). No formal structure set exists for the PRS so a list made by the EU JRC was used /4/. This list contains structure information for 80,413 substances of which 70,983 could be used in the applied (Q)SAR software.
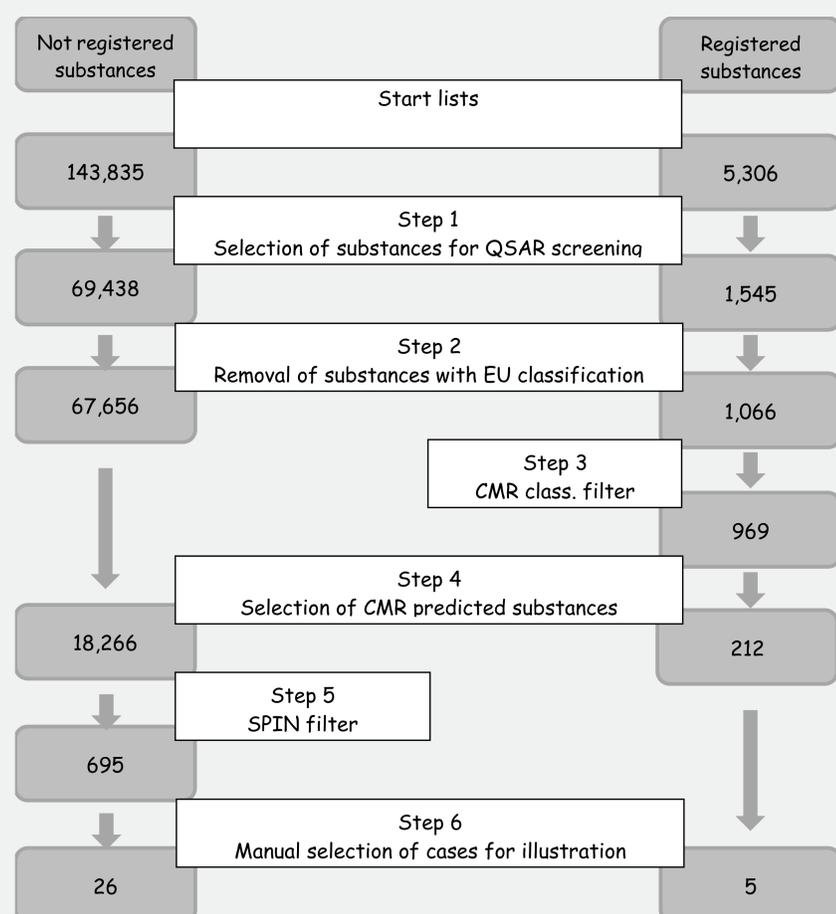
Step 2 Substances with EU harmonized classifications were removed by CAS number comparison, where possible also for group entries.

Step 3 Substances with at least one CMR R-phrase (R40, R45, R46, R49, R60, R61, R62, R63, R64 or R68) in the REACH registration dossiers were filtered out.

Step 4 (Q)SAR predictions were generated in 14 models in the MultiCASE MC4PC software. C-, M- and R-classifications were generated according to decision algorithms as done in the Danish Advisory Classification list /5/.

> **Models applied** The models are validated with established accuracies of 70-85% and generally having considerably higher specificity than sensitivity:
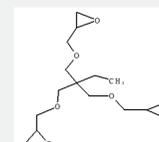> • Models for _in vitro_: • Reverse mutation test (Ames) • Chromosomal aberrations (CA) in CHO • Chromosomal aberration (CA) in CHL • Mouse lymphoma cell gene mutation test.
> • Models for _in vivo_: • Drosophila melanogaster Sex-Linked Recessive Lethal test • Comet assay in mouse • Sister chromatid exchange assay in mouse bone marrow • Rodent dominant lethal test • Mouse mammalian bone marrow erythrocyte micronucleus test • 4 FDA Cancer models for M/F Rat and Mouse plus overall cancer call • Teratogenic risk in humans.

Step 5 The Use Index for consumers in the Nordic substance register database (SPIN) was required to be greater than or equal to 3, indicating a potential for direct exposure to humans.

Step 6 To illustrate how the lists may be applied for e.g. priority setting for proposals for (harmonized) CMR-classification and/or for inclusion on the CORAP list (by targeted further confirmatory testing of CMR properties), a number of substances were further inspected manually consulting also other sources of (Q)SAR predictions and experimental information where available.

Results The results will be used by the Danish EPA in future priority setting, and the lists and a documentation report is scheduled to be published this year on their website www.mst.dk.

> **Example** CAS RN 3454-29-3 with (Q)SAR calls C, M and R based on positive predictions in models for Ames, CA CHO, CA CHL, mouse lymphoma, Drosophila m. SLRL, mouse Comet, and FDA overall cancer call based on male mouse and female mouse.
> Used in epoxy resins. No CMR relevant experimental information was identified. In SPIN, one or several uses indicate a potential exposure to consumers and a very probable exposure to workers, and 1.1 tonnes in Sweden and 1 tonne in Norway. 155 notifiers in ECHA C&L Inventory with no self-classifications for CMR.

Flowchart:

Not registered substances		Registered substances
	Start lists	
143,835		5,306
	Step 1 — Selection of substances for QSAR screening	
69,438		1,545
	Step 2 — Removal of substances with EU classification	
67,656		1,066
	Step 3 — CMR class. filter	
		969
	Step 4 — Selection of CMR predicted substances	
18,266		212
	Step 5 — SPIN filter	
695		
	Step 6 — Manual selection of cases for illustration	
26		5

References
1. Allanou, R., Hansen, Bjørn G., Bilt, Yvonne van der (1999), "Public availability of Data on EU High Production Volume Chemicals", European Commission, JRC, EUR 18996 EN.
2. http://echa.europa.eu/information-on-chemicals/registered-substances
3. http://echa.europa.eu/da/information-on-chemicals/pre-registered-substances
4. EUR 24138 EN 2010, JRC Scientific and Technical Reports, Klaus Daginnus; "Characterisation of the REACH Pre-registration Substances List by Chemical Structure and Physicochemical Properties".
5. The Danish Environmental Protection Agency (2010). Report on the Advisory list for self-classification of dangerous substances. Environmental Project No. 1322.