# Could Qsar modelling be used for some data gaps in REACH registration of polymers?

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Polymers have been used in many industrial sectors including consumer goods, construction materials, the electrical industry, packaging, food contact materials, coatings, medical equipment and agriculture. They have many functions, for example as thickeners, surfactants, emulsifiers and foam stabilisers.

The EU generally regards them as safe and therefore exempt from REACH registration or evaluation. The argument is that they are non-hazardous (with the possible exception of certain polymers used as surfactants or dispersants that may exhibit toxicity) because of their high molecular weight. They cannot accumulate in living organisms, including mammals and aquatic organisms, and so there is no concern regarding their ecotoxicity and toxicity.

However, if a member state proposes it, polymers can be subject to authorisation or restriction under REACH.

Furthermore, manufacturers and importers in the EU are currently required to register the monomers and/or other substances they have used as building blocks of a polymer (if they are present in amounts higher than 2% in the polymer molecule). This is because these molecules are considered of higher concern than the polymer molecule itself.

By contrast, there are some non-EU countries with specific regulations in force on polymers. These include South Korea (in the framework of K-REACH), China, Japan, the US, Canada and Australia.

These differences, coupled with the need to accommodate restrictions on microplastics within REACH, have seen the European Commission commit to publishing a polymers proposal by 2022. The aim will be to bring “at least some” polymers under the REACH registration requirement.

In January, Cefic laid out its vision for a ‘tailor-made’ approach to polymer regulation through amendments to REACH.

If the Commission brings polymers within the scope of REACH registration, companies will need to submit data. This will not be straightforward.

The amount of experimental data on them is limited and testing in many cases difficult. As polymers contain a variety of constituents, some of which may be unknown, it must be assumed that their physico-chemical, e-fate and (eco)toxicological properties depend on molecular weights and other parameters of those constituents. Moreover, most polymers usually contain a relatively insoluble and stable matrix that might impact the physical and biological availability of these.

It must be noted that a relatively insoluble and stable matrix definitely applies to solid polymers (plastics), but might not apply to liquid or water soluble polymers. Therefore, testing of a complete polymer might be neither suitable (as constituents not contributing to physical and/or biological effects are also tested and might even 'mask' undesired effects of other constituents), nor technically feasible. In order to overcome this, testing of the solubility and extractability behaviour is pivotal to obtain reliable data in the hazard assessment.

Subsequently, Qsar models could be used to predict or evaluate properties by comparison to the existing data available for the same or similar polymer type. They are already used for non-polymer substances.

As laid down in Annex XI of REACH, qualitative or quantitative structure-activity relationships (Qsars) can be used instead of testing if they fulfil conditions of scientific validity, compliance with an applicability domain and adequacy of result in terms of classification and risk assessment. Qsars can also be used as supporting information, or in a weight-of-evidence approach, or for prioritising testing. The main reason for developing such alternative methods is to avoid animal testing. Over the years, numerous Qsar models have been used extensively on substances including monomers that can be applied as building units for polymers.

Could Qsars specifically designed for polymers be a solution to the problem of REACH registration? Such Qsars or Qsprs (quantitative structure-property relationships) do already exist. However, generally, they are not for prediction of specific toxicity or ecotoxicity endpoints but rather physico-chemical properties. This is because commercial polymer design has always been based on these, which determine the functional characteristics of the final product. Fortunately, these properties are directly (density, surface tension), or indirectly relevant for REACH.

Over the years, Qsar models have been developed, allowing predictions to be made specifically for polymers. There are the following approaches:

- the Van Krevelen method – a group additive method, where an additive increment is assigned to each functional group in the monomer. The target property is obtained by summing the increments representing each fragment in the monomer;
- the Askadskii method – each monomer is treated as a series of harmonic oscillators. The relevant thermal movement is related to the glass transition temperature, leading to an additive model; and
- the Bicerano method – based on electrotopological indices that are defined for descriptions of molecules in terms of the connectivity of atoms and molecular shape.

These methods can be used to estimate more than a hundred physico-chemical endpoints, including mechanical thermophysical, volumetric and optical properties of polymers, copolymers, polymer blends and nanocomposites. Alternative approaches include the group interaction modelling (GIM) method or the Chickos method. While the GIM method is a group contribution method that applies the intermolecular energy of interaction between groups of atoms in adjacent polymer chains as a basis for predictions of thermo-physical properties of polymers, the Chickos method provides heat capacity estimates for the condensed phase.

We investigated four of these methods in relation to the glass transition temperature endpoint.

Calculated values were compared with experimental ones for 12 common polymers. The best correlation was achieved for the GIM method (correlation coefficient $R^2$ = 0.955), followed by the Van Krevelen method ($R^2$ = 0.951). The performance of two other methods, Askadskii and Bicerano ($R^2$ = 0.869 and 0.714 respectively), is in this case not as good especially for the latter.

Qsar models for polymers are being developed all the time and they can be improved. We observed this in relation to the heat capacity endpoint. Calculated values were compared with experimental ones for 13 solid polymers.

Here the performance of all investigated models was satisfactory, and recently developed group contribution models Crow I and Crow II outperformed the other methods (with $R^2$ = 0.997 and 0.989 respectively). Nevertheless, Chickos and Van Krevelen models also provide high correlation coefficients – $R^2$ = 0.979 and 0.981, respectively. It is to be noted that the pioneer Van Krevelen method yields good predictions for both endpoints used as examples (glass transition temperature and heat capacity), as well as in other cases not reported in this overview. Unfortunately, the applicability of this method is limited, because it is parameterised for well-known existing polymers, and generally not suitable for newly developed ones.

Due to the complexity of contemporary use and development of polymeric materials, modelling of their properties is and remains a challenge, especially in the context of computational-aided design and optimisation of new polymers with enhanced properties.

Nevertheless, a number of Qsar/Qspr studies have been recently published, dealing with refractive indices, thermal decomposition, glass transition temperature, intrinsic viscosity and fouling release activity. Of special interest from a regulatory point of view could be work on flammability modelling, since CLP does not exempt polymers. Although it is difficult to address flammability as an endpoint directly, related properties such as total heat release (THR) or heat release capacity (HRC) can be modelled. The endpoint is especially relevant to the aircraft industry, because of the requirement for flame-retardant (intended to prevent a development of ignition) properties of used materials.

In conclusion Qsar methods are available and being continuously developed for polymers, although not to the same extent as for non-polymeric substances. A big advantage of these techniques is the performance of even simple models is in many cases satisfactory and the predictions reproduce experimental values with a good approximation. For this reason, the use of Qsars for polymers is promising in the regulatory arena, for CLP, or REACH, where the substances are increasingly likely to fall under the spotlight in coming years.

*The views expressed in this article are those of the expert author and are not necessarily shared by Chemical Watch.*