# Chemoinformatic computational methods to design a new accelerator for CR vulcanization

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Thiourea-based accelerators are commonly used in the vulcanization process of synthetic elastomers and in particular of chloroprene rubbers. Their use, in fact, promotes cross-linking in the rubber, decreasing as a consequence both the process duration and temperature. One of the most popular accelerator is ethylenethiourea (ETU). However, this substance is regarded as potential source for health diseases and, according to the European REACH regulation, is going to be classified as CMR (Carcinogenic, Mutagenic, Toxic to reproduction) substance.
The SafeRubber Project (http://www.saferubber.eu) received EC funding under the FP7 framework to develop a new multifunctional accelerator which has similar vulcanization performance to ETU and, at the same time, possesses a safer toxicological profile.

The Milano Chemometrics and QSAR Research Group (http://michem.disat.unimib.it/chm/) of the University of Milano-Bicocca is involved in the SafeRubber project and is in charge for the application of chemoinformatics (*in-silico*) techniques in order to predict rheological and toxicological properties of the accelerators under analysis and mechanical properties of the final vulcanizates. Molecular modeling, in particular QSAR (*Quantitative Structure-Activity Relationships*) techniques, allow to relate properties of molecules to their molecular structure through the application of informatics simulations and mathematical models. The developed models are used to predict the same properties for new molecules, whose experimental values are unknown. Since the entire process is completely computerized, this approach allows to avoid several experimental tests for the substances under analysis, which results in economical saving and toxicological animal tests avoidance. In addition, QSAR methods are explicitly required by REACH regulation for the toxicological assessment of chemical substances, when existing experimental results are not available.

The research phase of the SafeRubber project initially led to the development of mathematical QSAR models able to relate accelerators' molecular structure (coded by computing specific molecular descriptors) to the most relevant rheological and mechanical properties of the rubber: Scorch Time, Optimum cure time, Hardness, Elongation at break and Modulus 100%. Mathematical models were developed for each property and, at present, they are undergoing a final validation. These models will enable the future prediction of rheological and mechanical properties for new molecules not yet experimentally tested, thus they will constitute an effective screening tool to search for new CR accelerators. In addition, the interpretation of the models is currently ongoing and may significantly contribute to the understanding of the mechanisms of rubber vulcanization highlighting structural features of accelerators that mainly affect the properties of the rubber itself.

Great importance was paid to the toxicological screening of the accelerators under analysis, being toxicity reduction the main objective of the research project. To this end, toxicological databases were searched for existing experimental data regarding the most relevant properties mentioned in

Annexes VII and XIII of the REACH regulation. Thereafter, QSAR models were used to predict several toxicological and eco-toxicological properties, namely bioaccumulation and biodegradability, carcinogenicity, mutagenicity, toxicity to reproduction, acute toxicity and skin sensitization. Since REACH regulation explicitly requires the application of *in-silico* computational methods to predict toxicological properties, the scientific community recently proposed several informatics tools that enable this kind of approach. In the framework of the SafeRubber project, different toxicological QSAR models were used, selected on the basis of their quality and reliability.
The OECD QSAR Toolbox (http://toolbox.oasis-lmc.org/) is probably the most complete tool regarding number of considered molecules and included QSAR models. Moreover it is one of the suggested chemoinformatics tool to assess the toxicological profile of substances within REACH.
ToxTree (http://toxtree.sourceforge.net/) is an open-source application able to estimate the toxicological potential of molecules by means of a decision tree approach, commissioned from the Joint Research Center – Computational Toxicology (Ispra) of the European Community.
Similarly, Lazar (http://lazar.in-silico.de/predict) allows to calculate toxicological properties by means of a web interface developed in the framework of the European OpenTox, project whose objective is the use of alternative methods to animal testing within REACH.
CAESAR (http://www.caesar-project.eu/) is the final result of another European research project aimed to realize toxicological QSAR models specific to REACH. CAESAR allows to predict the most relevant toxicological properties by means of QSAR models developed and validated according to the principles suggested by the Organisation for Economic Co-operation and Development (OECD).

The results provided by the considered models will be weighed and mediated (*consensus analysis*) in order to obtain more robust and reliable toxicological predictions. The scientific results of this research within the SafeRubber project will be published soon on the web portal of the project (http://www.saferubber.eu/).