RISKCYCLE (#226552)

Deliverable 3.3. – Review of models for predicting the concentration of chemicals in air, water and soil to human exposure, including mathematical and functional specification of the multimedia software

Deliverable of WP3

D.3.3: Review of models for predicting the concentration of chemicals in air, water and soil to human exposure, including mathematical and functional specification of the multimedia software

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1. Introduction

Our technological society makes extensive and intensive use of chemicals (most of them organics) and this number is continuously growing. Thus, for instance the European Inventory of Commercial Chemical Substances (EINECS) reports up today 100,204 commercially available substances [1] and similar figures hold for the U.S.A [2-3].

Hence, depending on their properties, mode and extent (volume) of use, this large amount of different chemicals can potentially reach the environment, having unpredictable environmental and health effects in long term. This has become a matter of major concern and constitutes the reason to release new regulations related to the safety of chemicals. Thus, for instance, the existing European Union regulation REACH (EC 1907/2006) [4] foresees to regulate chemicals used in commerce and consumer products, including a list of c.a. 30,000 compounds. About 10,000 have been already registered. From these, 2,782 are produced in large quantities (> 1,000 tons/year) [3].

On the other hand, a simultaneous and huge progress on the analytical methods and techniques has taken place, mostly associated to the development of multiresidue analytical methods based on chromatographic techniques (GC and LC) coupled to mass spectrometry (MS), capable to identify and quantify compounds at environmental trace levels of ng or pg/l. Such progress has substantially enlarged the possibilities of environmental monitoring and control. However, since not all measurable compounds are worth to be measured some kind of prioritisation or ranking is required in order to allocate analytical control efforts towards some target compounds, otherwise the task would be unbearable. The underlying rationale in the majority of the prioritisation lists of chemicals is based on the notion of risk assessment. Risk is broadly defined as the combination (i.e., product) of a probability of occurrence of some event by its hazard effects:

RISK = OCCURRENCE x EFFECTS

Correspondingly, the risk assessment process may be defined as the set of procedures aiming to identify hazards and to quantify the associated risk (in our

case, related to chemicals) concerning human health and/or ecosystems impairment (see Figure 1).
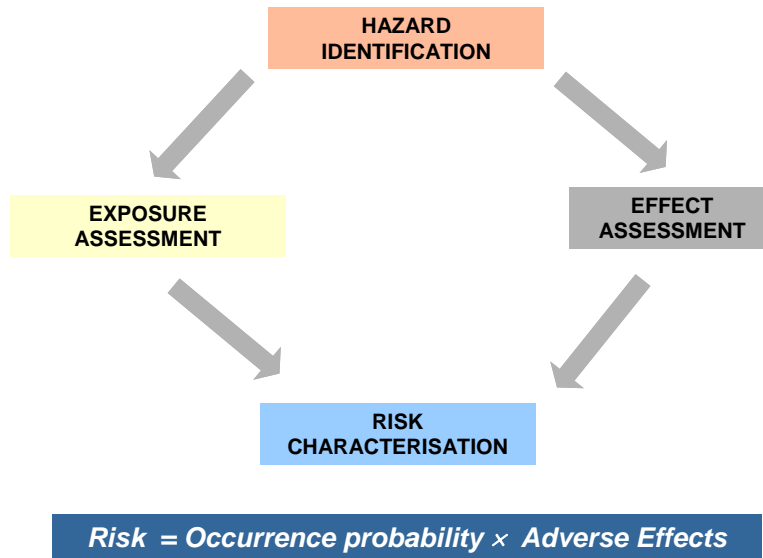
Figure 1. The risk assessment process

In the case of the environmental risk posed by chemicals, 'hazard effects' are related to the intrinsic properties of each compound [5] whereas 'occurrence' is associated to its environmental exposure, usually expressed in terms of environmental concentration.

Different risk assessment approaches have been developed in order to identify and rank compounds of environmental concern for both regulatory and monitoring purposes. Whereas most of all the existing schemes share the basic underlying risk assessment paradigm, they differ on how both factors, i.e., occurrence and effects, are defined and hence quantified.

2. Assessing environmental concentrations of chemicals: Measuring *vs.* Modelling

There are two basic approaches for establishing environmental concentrations, namely, measurement or modelling, the derived respective concentrations usually referred as MEC (Measured Environmental Concentrations) or the so called PEC (Predicted Environmental Concentrations). The most obvious and classical is

through analytical chemistry obtaining MEC's. However, the development of environmental modelling provides an interesting alternative.

Essentially, the main drawback of measuring is that it is focussed on certain pre-selected analytes so that there is low chance of finding new targets. Other aspects of concern are their limited possibilities regarding time and space coverage, which can miss certain events. Sampling issues become thus important since analytical campaigns are usually expensive and time consuming.

Conversely, the main advantage of measurement is that it provides reliable results that are quite independent of the laboratories (at least, it is true for those that have an adequate Quality Assurance/Quality Control System). As far as modelling is concerned, it is fast and relatively affordable and has very good time and space coverage possibilities, being on the other hand its main weakness a strong dependence on the model chosen and the inherent uncertainty because of the lack of reliable data: physical-chemical properties, sources and fate.

Both options, measuring and modelling, have been discussed in detail by Johnson et al. [6] and their respective pros and cons are summarized in Table 1. However, since they are complementary, the wisest recommendation would be making use of both alternatives in order to exploit their respective advantages. Unfortunately, such desirable complementary approach is rarely seen together (see as instances, [7-8]).

Table 1: Comparative overview of strengths and weaknesses of analytical measurement vs. modelling in environmental studies (Adapted from reference [6]).

Analytical measurement	**Pros**	-Results obtained reflect well reality. -Repeatability and reproducibility of results (at least between good qualified labs)". -Measurements are independent of information/data sources. -Multipurpose analytical methods can cover many compounds on a single run. -Even the best model will ultimately need to be experimentally checked. -Discovery of new emerging contaminants is possible.
	Cons	-Determination of compounds at very low quantities may be difficult. -Time and space coverage require expensive monitoring campaigns. -Sampling campaigns may miss crucial episodes. -Analytical measurements give a snapshot, rather a continuous picture. -Expensive analytical equipment and method development. - Target monitoring may miss pollutants: "you only find what you are looking for"
Predicting (Modelling)	**Pros**	-Very good coverage capabilities of time and space. - Computation equipment is affordable. - Possibility of application to hypothetical scenarios: "What if?" - Useful for extrapolations to future (predictions on space and time, even for products not yet in the market). - Simultaneous modelling of many compounds. -Once the model is set up are fast and cheap to use.
	Cons	- Different models may render very different results. - Models are strongly dependent on parameter and data input. - Diffuse sources of pollution may be very difficult to model.

3. Use of exposure models in the risk assessment of chemicals

Current state of the art on spatially explicit multimedia fate models have been recently reviewed by Pistocchi et al. [9]. These authors distinguish three basic approaches:

(i)   Multiple box models.

(ii)   Numerical solutions to the advection-dispersion transport models.

(iii)   Meta-models. Geographic information system (GIS)-based modelling.

A full description and discussion of all the above models is beyond the scope of the present document (more information can be find in [9] and in other references cited therein). However, irrespectively of the type of model we are dealing with, they share some common requirements regarding to the input data. First of all, the basic environmental fate of a chemical compound is governed by its physical and chemical properties, such as partition constants, solubilities or kinetic constants characterizing the different dynamic phenomena like reactions (biodegradation, hydrolysis, photodegradation, etc.), adsorption, volatilization etc., as well as flow velocities, wind, temperature etc. On the other hand, the second major input information required is related to the physical factors associated to the receiving environment (i.e., temperature, humidity, wind speed etc.). Finally, a third group of factors is related the emission of the contaminant. Here, the amount of product released (consumption), the mode of use (closed cycle, spreading or chemical additives) and emission characteristics (point or diffuse) are very important. These aspects have been reviewed in a previous deliverable (Deliverable 3.2.: "*Overview*

of environmental factor influence over additive exposure and release into the environment")

The main weaknesses of most models rely on the great uncertainties embodied in many of those parameters. For this reason they are usually subjected to appropriate sensitivity analysis. Often, results obtained from modelling require further fine tuning of model parameters, which is only possible through empirical adjustment after experimental measurement. These models predict the distribution of a chemical between several environmental compartments and the final output of models will be the spatially distributed Predicted Environmental Concentration (PEC).

Exposure models are therefore valuable tools for indirect exposure assessment offering high versatility for quantifying risk associated to chemical exposure. Some of their already proved advantages are the following [10]:

– They allow predicting potential exposures for future or hypothetical releases/scenarios.

– They allow combining different types of contaminants and emission sources.

– The degree of complexity adopted by the model can be set according to the needs of the assessment.

– They consider exposures via multiple routes and pathways.

– They reduce the need for resource-intensive monitoring programmes.

As depicted in Figure 1, a typical risk assessment process involves the estimation of both the exposure (occurrence) and the hazard associated to the compound considered. According to the nature of each compound, they can exhibit several effects against the environment, including: persistence, bioaccumulation, ecotoxicity, endocrine disruption, mutagenicity, carcinogenicity, etc.

Correspondingly, modelling may be extended to both aspects and many of the most popular modelling existing software packages so do.

In Table 2 are listed the most widespread used models, together with their most positive characteristics and limitation. Further details can be found in the original references cited and in the document issued within (WP5), entitled "*Review of models used to assess human toxicity and ecotoxicological impacts of chemicals*" (Deliverable 5.2.).

Table 2: Strong and weak points of the risk assessment models gathered on the reviewed literature. (Some information adapted from Rosenbaum et al. who made a comparison between several models and the USEtox model [11]).

MODEL	STRENGTHS	WEAKNESS	REF
Qwasi	- Equations available and easy to implement. - Considers steady and unsteady states.	- Human toxicity not considered and only considers one scale.	[12]
Ecopoints	-	- Does not distinguish between categories (human, ecosystem). - Does not realize fate and exposure analyses.	[13],[14]
ChemCAN	- Very transparent model.	- Only chemical fate model.	[15]
ECOSENSE	- Most reliable modelling of classical air pollutants amongst the observed models. - Bottom-up, i.e. spatially resolved, assessment capabilities for Europe, Russia, China/Asia, and Brazil/South America.	- Does not consider mostly of organic chemicals and use an open system boundaries. - Only inhalation exposures with respect to toxic impacts (additionally impacts on crops and building materials). - Ecosystem toxicity not assessed.	[16]
WMPT	- Key property based.	- No explicit fate results available and exposure routes not specified.	[17]
EDIP	- Key property based and normalization and weighting methods provided.	- Mainly representative for Europe. - No explicit fate results available and no severity measure for human toxicity.	[18]
Eco-indicator 99	- Environmental problems defined at the endpoint level. - Uncertainty analysis available.	- It is assumed that all emissions and land uses, and their subsequent damages occur in Europe.	[19]
CSOIL 2000	- Simplicity of the model. - Multiple human exposure ways considered.	- Ecotoxicity not considered. - Fate and toxicological effects not considered.	[20]
CalTOX	- Most encompassing in terms of exposure pathways. - Advanced modelling of soil (several layers). - Monte Carlo uncertainty estimation.	- No severity measure for human toxicity, only partly compatible with damage approach- - Ecosystem toxicity not assessed (e.g., marine environment and	[21]

	coastal zone not included for fate modelling).		
IMPACT 2002+	- Continental average characterization factors available for different global regions - Considering indoor air exposure - Direct application of pesticides considered - HC50 approach for effect modelling	- Marine environment poorly represented so far.	[22]
EUSES	- It is valuable for both live cycle risk assessment (LCA) and risk assessment (RA). - There is a lot of media considered. - Uncertainty analysis available.	- Difficulties in the operation of certain substances	[23]
Humanex	- Simplicity of the model. - Multiple human exposure ways considered. - Capability on calculating maximum permissible concentrations (MPC) for the compounds of interest.	- Ecotoxicity not considered. - Fate and toxicological effects not considered. - Not utterly reliable when operating with non-ionic organic chemicals.	[24]
XtraFOOD	- Age and gender categories are distinguished.	- Focused on the terrestrial food chain.	[25]
RAIDAR	- Simple to apply.	- Only most sensitive endpoints into consideration.	[2]
2-FUN tool	- Capable of conducting full-chain risk assessments. - Pharmacokinetic models included. - Probabilistic and sensitivity analyses considered.	- Ecosystem toxicity not assessed.	[26]
ReCiPe	- The user can choose the detail level of the results (midpoint or endpoint). - Uncertainty analysis available.	- Different scales not considered.	[27]
USEtox	- HC50 approach for effect modelling. - Effect of intermittent rain events estimated. - Consensus model.	- Only toxicity impacts considered.	[28]

USES-LCA	- Marine environment included. - HC50 approach for effect modelling. - One-dimensional uncertainty factors available.	- Global coverage not spatially resolved.	**[29]**
GLOBOX	- Spatial differentiation (separate countries and oceans). - Metal-specific processes in freshwater and marine environments handled. - Dynamic calculations possible.	- Regions distinguished are very different in size and are characterised by a wide variation in environmental parameters. - The modelling of export and import of food for determining the intake by humans requires data and assumptions that may introduce additional uncertainty.	**[30]**
MAFRAM	- Simple to apply. - Species from different taxa considered for the ecotoxicity value computation.	- Specifically developed for agricultural chemicals. - Risk categories defined as crisp numbers.	**[31]**

4. Use of Quantitative Structure-Activity Relationships (QSAR)

Since experimental assays for determining substances effects to the environment and living forms are expensive, time-consuming and require testing on animals, risk assessors and toxicologists are using models as a tool for estimate exposure effects of chemicals. QSAR (Quantitative Structure-Activity Relationship) provides a valuable tool for predicting these effects. In QSAR models the chemical structures are quantitatively correlated with their physico-chemical properties (melting point, water solubility, etc.), environmental fate (hydrolysis, biodegradation, etc.), ecotoxicity (acute and chronic toxicity) and other activities related to human health (carcinogenicity, mutagenicity, etc.). Several programs based on QSAR are available for many endpoints. Table 3 lists the main softwares used for risk assessment procedures.

In 1989 the specification SMILES [32] (simplified molecular input line entry specification) was developed. It consists on a nomenclature for describing molecular structures. SMILES notation has been widely used as an input for modelling since it is a fast and easy way of introducing molecular structures.

QSAR models play an important role as an environmentally oriented approach for regulatory assessment, especially under the new regulations. For instance, the REACH regulation (European Commission, 2006) strongly recommends the use of QSARs. Therefore QSAR procedures represent a very useful tool for risk assessment since experimental data is not always available. In this way, results can be provided without using animal testing.

Most of the QSAR models described in the literature are applied to organic substances [33-35], however in a lesser degree, they seem to be applied to inorganic (metals and organometallic compounds) [36-38], probably due to the lack

of a suitable tool for calculating descriptors for heavy atoms [36]. Further detailed information regarding to the use of QSAR can be found in the document issued within (WP4), entitled "Report on the review of bioassays and biosensors and (Q)SAR models as candidate for the intended use" (Deliverable 4.3).

To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the OECD has started the development of various outcomes such as the principles for the validation of (Q)SAR models, guidance documents as well as the QSAR Toolbox. This item is intended to make (Q)SAR methods readily accessible, transparent, and less demanding in terms of computation costs.

Table 3: QSAR software available for predicting targeted endpoints from structure-activity relationships.

QSAR software		Endpoints	Developer
ACD	*"Advanced Chemistry Development"*	- Physico chemical properties (logP, solubilities, vapour pressure, etc.). - Toxicology. - Bioaccumulation and biomagnification factors.	**[39]**
CAChe (COSMOtherm, OpenTox, etc.)	*"Computer-Aided Chemistry"*	- Physico chemical properties - Toxicology	**[40]**
CAESAR	*"Computer Assisted Evaluation of industrial chemical Substances According to Regulation"*	- Environmental fate: bioaccumulation and bioconcentration factors. - carcinogenicity and mutagenicity - Skin sensitisation.	**[41]**
CASE (MultiCASE, MCASE, CASETOX and TOXALERT)	*"Computer automated structure evaluation"*	- Acute toxicity, carcinogenicity, teratogenicity, ecotoxicity, genetic toxicity. - Biodegradation, bioaccumulation. - Enzyme inhibition. - Skin, eye irritations and allergies.	**[42-43]**
COMPACT	*"Computer-optimized molecular parametric analysis of chemical toxicity"*	- Potential toxicity and carcinogenicity.	**[44-45]**
DEMETRA		- Ecotoxicity.	**[46]**
DEREK	*"Deductive estimation of risk from existing knowledge"*	- Toxicological, including: carcinogenicity, mutagenicity and teratogenicity. - Skin sensitization, , irritancy, and respiratory sensitization	**[47]**
DRAGON		- Physico chemical properties - Toxicity.	**[48]**

		- Fate: bioaccumulation, biodegradation rates, partitioning among environmental compartments, etc.	
EPI suite (AOPWIN, BIOWIN, HYDROWIN, etc)	*"Estimation Program Interface" suite*	- Physico chemical properties. - Toxicity. - Degradation rates (photolysis, biodegradation and hydrolysis). - Fate: bioaccumulation, biodegradation, etc.	**[49]**
HazardExpert		- Toxicity, also estimates - Toxicokinetic effects: bioaccumulation and bioavailability on the basis of predicted physicochemical values.	**[50]**
OASIS	"Optimized Approach Based on Structural Indices Set"	- Physicochemical properties. - Toxic endpoints accounting for conformational flexibility of Chemicals.	**[51]**
OECD QSAR Toolbox		- (eco)toxicity - Skin sensitisation - Mutagenicity	**[52]**
OncoLogic		- Chemical reactivity. - Metabolic activation. - Mechanisms of chemical carcinogenesis [53].	**[54]**
SuCCSES	*"Substructure-Based Computerized Chemical Selection Expert System"*	- Acute and chronic toxicity - Mutagenic and carcinogenic, developmental, reproductive, or neurotoxic effects.	**[55]**
TOPKAT	"Toxicity Prediction by Komputer Assisted Technology"	- Psysico-chemical properties (logP). - Environmental fate - Acute and chronic toxicity, ecotoxicity, - Carcinogenicity, mutagenicity, and reproductive/developmental effects. - Skin and eye irritation .	**[56]**

5. Conclusions

Model development for predicting the environmental occurrence, fate and effects caused by chemicals has been a continuously growing discipline during the last years. Models have expanded their domain of application beyond research and have themselves revealed as powerful tools in management, decision support and regulation development.

Current limitations on the practical use of fate models are mostly due to lack of information on chemical emissions [9]. Therefore this is one of the R&D needs identified within the RISKCYCLE project. Its relevance is still more acute, if one takes into consideration the scenario of circulation of goods and products (and

consequently of chemicals) at earth scale through either natural or anthropogenic processes which has become the most significant characteristics of our global world.

Acknowledgements

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