LIFE Project Acronym and Number

ANTARES

LIFE08 ENV/IT/000435

Deliverable Report

Deliverable Name and Number

Deliverable 7

Evaluation on the model availability for at least 20 endpoints (preliminary report)

Deliverable Date

31/12/2010

Deliverable Data

Associated action	Action 4: list of (Q)SAR models for the ecotoxicological, toxicological and environmental endpoints for REACH, and their rewiev
Beneficiary Responsible	KnowledgeMiner Software Frank Lemke
Monitoring	IRFMN

Introduction

The purpose of the action 4 is to identify the (Q)SAR models for the ecotoxicological, toxicological and environmental endpoints for REACH.

Preliminarily a set of criteria has been identified, as reported into the deliverable 2, and consequently chosen ten main endpoints to analyze to pass the action 5.

The ten endpoints have been chosen to cover equally the four group: Physical chemical, environmental, ecotoxicological and toxicological, in particular the skin sensitization, oral acute toxicity, carcinogenicity and mutagenicity for the toxicological group; BCF and maybe persistence for the environmental group; Acute fish toxicity and acute daphnids toxicity for the ecotoxicological group; LogP and Solubility for the Physical chemical group.

To select these endpoints the availability of implemented software to have the predictions has been considered.

About the software, the free ones are preferred and for the commercial ones have been considered them only for those endpoints where their use is frequently observed. Finally literature sources have been considered as last resource.

The scores will be then assigned according to criteria indentified in deliverable 2.

Endpoint analysis

From ANNEX 1, endpoint for REACH and possible QSAR:

Physical chemical properties:

This section gives a brief description about the endpoints analyzed.

About the endpoints belonging to the physical chemical properties a very few articles have been found and no QMRF are available.

7.2 MELTING/FREEZING POINT

Software (and developer):

- ✓ MPBPVP (Syracuse Research Corporation) - Commercial:
  This program calculates melting point by two methods, that of Joback and Reid (Joback KG, Reid RC. 1987. Estimation of pure-component properties from group contributions. *Chem Eng Commun* 57:233–243.) and that of Gold and Ogle (Gold PI, Ogle GJ. 1969. Estimating thermophysical properties of liquids. Part 4—Boiling, freezing and triple-point temperatures. *Chem Eng* 76:119–122.);
- ✓ ChemOffice (CambridgeSoft) - Commercial:
  This program uses the method of Joback and Reid (Joback KG, Reid RC. 1987. Estimation of pure-component properties from group contributions. *Chem Eng Commun* 57:233–243.);
- ✓ ProPred (Technical University of Denmark) – Commercial;

Articles:

- ✓ Quantitative structure-property relationships for prediction of boiling point, vapor pressure, and melting point. Dearden J.C. Environmental Toxicology and Chemistry, 2003, Vol. 22, 1696-1709.
- ✓ New contribution method for estimating properties of pure compounds. Costantinou L. *et al.* Thermodynamics, 1994, Vol. 40, No. 10.

QMRF:

No QMRF found.

7.3 BOILING POINT

Software (and developer):

- ✓ SPARC (University of Georgia) - http://ibmlc2.chem.uga.edu/sparc ;
- ✓ Advanced Chemistry Development (ACD) program - www.acdlabs.com ;
- ✓ Molecular Modeling Pro - www.chemsw.com ;
- ✓ ProPred.(Technical University of Denmark) - www.capec.kt.dtu.dk ;
- ✓ ChemOffice.(CambridgeSoft) - www.cambridgesoft.com;
- ✓ Melting Point, Boiling Point, Vapor Pressure (MPBPVP), version 1.4 (Syracuse Research Corporation, SRC) – Commercial.

Articles:

- ✓ Quantitative structure-property relationships for prediction of boiling point, vapor pressure, and melting point. Dearden J.C. Environmental Toxicology and Chemistry, 2003, Vol. 22, 1696-1709.
- ✓ Hall LH, Story CT. 1996. Boiling point and critical temperature of a heterogeneous data set: QSAR with atom type electrotopological state indices using artificial neural networks. *J Chem Inf Comput Sci* 36:1004–1014.
- ✓ Basak SC, Gute BD, Grunwald GD. 1996. A comparative study of topological and geometrical parameters in estimating normal boiling point and octanol/water partition coefficient. *J Chem Inf Comput Sci* 36:1054–1060.
- ✓ Stein SE, Brown RL. 1994. Estimation of normal boiling points from group contributions. *J Chem Inf Comput Sci* 34:581–587.

QMRF:

No QMRF found.

7.5 VAPOUR PRESSURE

Software (and developer):

- ✓ SPARC (University of Georgia) - http://ibmlc2.chem.uga.edu/sparc ;
- ✓ Advanced Chemistry Development (ACD) program - www.acdlabs.com ;
- ✓ Molecular Modeling Pro - www.chemsw.com;
- ✓ MPBPVP (Syracuse Research Corporation) – Commercial.

Articles:

- ✓ Quantitative structure-property relationships for prediction of boiling point, vapor pressure, and melting point. Dearden J.C. Environmental Toxicology and Chemistry, 2003, Vol. 22, 1696-1709.
- ✓ Katritzky AR, Wang Y, Sild S, Tamm T, Karelson M. 1998. QSPR studies on vapor pressure, aqueous solubility, and the prediction of water–air partition coefficients. *J Chem Inf Comput Sci* 38:720–725.
- ✓ Liang CK, Gallagher DA. 1998. QSPR prediction of vapor pressure from solely theoretically-derived descriptors. *J Chem Inf Comput Sci* 38:321–324.
- ✓ Basak SC, Gute BD, Grunwald GD. 1997. Use of topostructural, topochemical, and geometric parameters in the prediction of vapor pressure: A hierarchical QSAR approach. *J Chem Inf Comput Sci* 37:651–655.
- ✓ Basak SC, Mills D. 2001. Quantitative structure–property relationships (QSPRs) for the estimation of vapor pressure: A hierarchical approach using mathematical structural descriptors. *J Chem Inf Comput Sci* 41:692–701.
- ✓ Chastrette M, Crétin D. 1995. Structure–property relationships — Determination of the vapor pressure of hydrocarbons and oxygenated compounds using multifunctional autocorrelation method (MAM). *SAR/QSAR Environ Res* 3:131–149.

7.7 WATER SOLUBILITY

Software (and developer):

- ✓ SArchitect ™ Designer program, available from Strand Life Sciences (http:// www.strandls.com/sarchitect; version 2.5.0).

Articles:

- ✓ QSAR-based solubility model for drug-like compounds, Gozalbes R *et al.* Biorganic & medicinal Chemistry 18 (2010) 7078-7084.

QMRF:

No QMRF found.

7.9 FLASH POINT

Software (and developer):

- ✓ CODESSA PRO software A.R. Katritzky, V.S. Lobanov, M. Karelson, CODESSA Reference Manual Version 2.0, Gainesville, 1996.

Articles:

- ✓ QSPR modeling of flash points: An update, Katritzy A. R. *et al.* Journal of molecular graphica and modeling 26 (2007) 529-536.

QMRF:

No QMRF found.

7.10 FLAMMABILITY

Software (and developer):

- ✓ Genetic Algorithm based multivariate linear regression (GA-MLR).

Articles:

- ✓ A QSPR model for estimation of lower flammability limit temperature of pure compounds based on molecular structure, Gharagheizi F. Journal of Hazardous Materials 169 (2009) 217-220.

QMRF:

No QMRF found.

Toxicological group:

In case of the endpoints belonging to the toxicological group a lot of articles and QMRF are available.

8.3 SKIN SENSITIZATION

Software (and developer):

- ✓ Caesar project models (Mario Negri Institute) – Freely available;
- ✓ Derek (Lhasa Ltd) – Commercial;
- ✓ Oasis-TIMES (Laboratory of Mathematical Chemistry, Bourgas University) – Commercial;
- ✓ Topkat (Accelrys) – Commercial.

Articles:

- ✓ Global QSAR models of skin sensitisers for regulatory purposes, Chaudhry Q. *et al.* Chemistry Central Journal 2010, 4 (Suppl 1): S5.
- ✓ An evaluation of selected global (Q)SARs/expert systems for the prediction of skin sensitization potential, Patlewicz G. *et al.* SAR and QSAR in Environmental Research, Vol18, Nos.5-6, July-September 2007, 515-541.
- ✓ Determinants of skin sensitization potential, Roberts D.W. *et al.* Journal of applied toxicology 2008; 28: 377-387.
- ✓ Global (Q)SARs for skin sensitization-assessment against OECD principles, Roberts D.W. *et al.* SAR and QSAR in Environmental Research, Vol.18, Nos. 3-4, May-June 2007, 343-365.
- ✓ Identification of mechanisms of toxic action for skin sensitization using a SMARTS pattern based approach, Enoch S:J. *et al.* SAR and QSAR in Environmental Research, Vol.19, Nos. 5-6, September 2008, 555-578.

QMRF:

QMRF	*TITLE*	*Software*	*Algorithm*	*Author*
Q2-15-8-108	QSAR for skin sensitisation via Schiff base formation	N/A	multilinear regression QSAR	David W Roberts
Q13-34-34-257	Derek for Windows - Skin sensitisation	BioByte Corp	Expert system	Lhasa Limited
Q17-10-1-241	Nonlinear QSAR: artificial neural network for classification of skin sensitisation potential	QSARModel 3.3.8	Neural network	Molcode model development team

8.9.1 CARCINOGENICITY STUDY

Software (and developer):

- ✓ PASS (Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow) - Freely available.
- ✓ OncoLogic (US EPA) – Freely available;
- ✓ Lazar (In Silico Toxicology; Freiburg University) – Freely available;
- ✓ Caesar project models (Mario Negri Institute) – Freely available;
- ✓ ADMET Predictor (Simulations Plus Inc.) – Commercial;
- ✓ BioEpisteme – Commercial;
- ✓ Derek (Lhasa Ltd) – Commercial;
- ✓ Hazard Expert (CompDrug) – Commercial;
- ✓ Leadscope (Leadscope) – Commercial;
- ✓ MCASE / MC4PC (MultiCASE) – Commercial;
- ✓ MDL QSAR (MDL) – Commercial – Commercial;
- ✓ Pallas Suite including ToxAlert, Cytotoxicity (CompuDrug) – Commercial;
- ✓ TOPKAT (Accelrys) – Commercial;
- ✓ Toxtree (JRC) – Commercial;
- ✓ Molcode Toolbox (Molcode Ltd) – Commercial;

Articles:

- ✓ Quantitative Structure-activity Relationship (QSAR) for Pesticide Regulatory Purposes, E. Benfenati, Elsevier 2007.
- ✓ Predicting Toxicity through Computers: a changing world, E. Benfenati, Chemistry Central Journal, December 2007.
- ✓ H.S. Rosenkranz, A.R. Cunningham, Y.P. Zhang, H.G. Claycamp, O.T. Macina, N.B. Sussman, S.G. Grant, G. Klopman, Development, characterization and application of predictive toxicology models, SAR QSAR Environ. Res. 10 (1999) 277–298.
- ✓ QSAR modeling of carcinogenicity by balance of correlations, Toropov A.A. *et al.* Mol Divers (2009) 13:367-373.

- ✓ Predictivity and Reliability of QSAR models: the case of mutagens and carcinogens, Benigni R. *et al.* Toxicology Mechanims and Methods, 18:137-147, 2008.
- ✓ The Benigni / Bossa rulebase for mutagenicity and carcinogenicity –a module of Toxtree Romualdo Benigni, Cecilia Bossa, Nina Jeliazkova, Tatiana Netzeva and Andrew Worth, JRC Scientific and Techincal Reports.
- ✓ New public QSAR model for carcinogenicity, Fjodorova N. *et al.* Chemistry Central Journal 2010, 4 (Suppl 1):S3.
- ✓ Lazy structure-activity relationships (lazar) for the prediction of rodent carcinogenicity and Salmonella mutagenicity Christoph Helma Molecular Diversity (2006) 10: 147–158

QMRF:

QMRF	*TITLE*	*Software*	*Algorithm*	*Author*
Q8-10-14-153	QSAR for female rat carcinogenicity (TD50) of nitro compounds	QSARModel 3.5.0	Multilinear regression QSAR	Molcode model development team
Q11-25-20-154	TOPKAT NTP Rodent Carcinogenicity Model (Female Mouse)	DS TOPKAT v2.1	Linear discriminant analysis model	Deqiang Zhang
Q13-34-21-252	Derek for Windows - Carcinogenicity	Derek for Windows version 12	Expert system	Lhasa Limited
Q17-10-1-225	Nonlinear QSAR: aritficial neural network for mouse carcinogenicity	QSARModel 3.3.8	Neural network	Molcode model development team
Q19-35-35-291	Toxtree QSAR 8: carcinogenicity of aromatic amines	Toxtree	QSAR	Romualdo Benigni
Q26-35-35-295	Toxtree: Benigni-Bossa rulebase for genotoxic and non-genotoxic carcinogenicity	Toxtree	Expert System	Romualdo Benigni

Ecotoxicological group:

About the endpoints belonging to this group a very few articles and no QMRF have been found.

9.1.6. LONG-TERM TOXICITY TESTING ON FISH

9.1.6.1. FISH EARLY-LIFE STAGE (FELS) TOXICITY TEST

9.1.6.2. FISH SHORT-TERM TOXICITY TEST ON EMBRYO AND SAC-FRY STAGES

9.1.6.3. FISH, JUVENILE GROWTH TEST

Software (and developer):

- ✓ ECOSAR http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

9.2.2.1. HYDROLYSIS AS A FUNCTION OF pH

Software (and developer):

- ✓ SPARC: http://ibmlc2.chem.uga.edu/sparc/
- ✓ HYDROWIN: www.epa.gov/oppt/exposure/pubs/episuitedl.htm

Articles:

- ✓ Harris JC. 1990. Rate of hydrolysis. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds, Handbook of Chemical Property Estimation Methods, 3rd ed. American Chemical Society, Washington, DC, pp. 7-1-7-48.
- ✓ Johnson H, Kenley RA, Rynard C, Golub MA. 1985. Qsar for cholinesterase inhibition by organophosphorus esters and CNDO/2 calculations for organophosphorus ester hydrolysis. Quant Struct -Act Relat 4:172-180.
- ✓ Wolfe NL, Steen WC, Burns LA. 1980. Phthalate-ester hydrolysis - linear free-energy relationships. Chemosphere 9:403-408.
- ✓ Wolfe NL, Zepp RG, Paris DF. 1978. Use of structure-reactivity relationships to estimate hydrolytic persistence of carbamate pesticides. Wat Res 12:561-563.

✓ Peijnenburg WJGM, Debeer KGM, Denhollander HA, Stegeman MHL, Verboom H. 1993. Kinetics, products, mechanisms and QSARs for the hydrolytic transformation of aromatic nitriles in anaerobic sediment slurries. Environ Toxicol Chem 12:1149-1161.

Environmental group:

BIOCONCENTRATION FACTOR

Software (and developer):

- ✓ CAESAR, CORAL http://www.caesar-project.eu - Freely available
- ✓ BCFWIN http://www.epa.gov/oppt/exposure/docs/episuitedl.htm - Freely available
- ✓ T.E.S.T. http://www.epa.gov/nrmrl/std/cppb/qsar/index.html#TEST - Freely available
- ✓ OECD QSAR Application toolbox http://www.oecd.org/env/existingchemicals/qsar - Freely available
- ✓ DRAGON http://www.talete.mi.it/ - Freely available
- ✓ TAOBAC model http://www.trentu.ca/academic/aminss/envmodel/models/TAOv101.html - Freely available
- ✓ Fish model http://www.trentu.ca/academic/aminss/envmodel/models/Fish2.html - Freely available
- ✓ CQSAR http://www.biobyte.com/bb/prod/cqsarad.html - Freely available
- ✓ Foodweb Model http://www.trentu.ca/envmodel/ - Freely available
- ✓ ACD/LogDSuite http://www.acdlabs.com/products/pc_admet/physchem/physchemsuite/ - Commercial
- ✓ ASTER expert system http://www.epa.gov (not publicly available) - Commercial
- ✓ OASIS CATABOL http://oasis-lmc.org/?section=software&swid=1 - Commercial
- ✓ MultiCASE http://multicase.com/ - Commercial
- ✓ WINTOX – Commercial

Articles:

- ✓ Lassiter, R.R. (1975). Modeling Dynamics of Biological and Chemical components on Aquatic Ecosystems, U.S. Environmental protection Agency report No. EPA-660/3-75-012, Washington, D.C.
- ✓ Veith, G.D., Kosian, P. (1983). Estimating bioconcentration potential from octanol/water partition coefficients. In: Mackay, D., Paterson, S., Eisenreich, S.J., Simons, M.S. (eds). Physical behavior of PCBs in the Great Lakes, Ann Arbor Sciences Publishers, Ann Arbor, P. 269-282.
- ✓ Mackay, D. (1982). Correlation of bioconcentration factors. Environmental Science & Technology, 16, 274-278.
- ✓ Schüürmann, G., Klein, W. (1988). Advancesin bioconcentration prediction. Chemosphere, 17, 1551-1574.
- ✓ Lu, X.X., Tao, S., Cao, J., Dawson, R.W. (1999). Prediction of fish bioconcentration factors of nonpolar organic pollutants based on molecular connectivity indices. Chemosphere, 39, 987-999.
- ✓ Escuder-Gilabert, L., Martin-Biosca, Y., Sagrado, S., Villanueva-Camañas, R.M., Medina-Hernandez, M.j. (2001). Biopartitioning micellar chromatography to predict ecotoxicity. Analytica Chimica Acta, 448, 173-185.
- ✓ Neely, W.B., Branson, D.R., Blau, G.E. (1974). Partition coefficients to measure bioconcentration potential of organic chemicals in fish. Environmental Science Technology, 8, 1113-1115.
- ✓ Zok, S., Görge, G., Kalsch, W., Nagel, R. (1991). Bioconcentration, metabolism, and toxicity of substituted anilines in the zebrafish (Brachydaniorerio). Science of the Total Environment, 109/110, 411-421.
- ✓ Bintein, S., Devillers, J., Karcher, W. (1993). Nonlinear dependence of fish bioconcentration on n-Octanol/water partition coefficients. SAR and QSAR in Environmental Research, 1, 29-39.
- ✓ Dimitrov, S.D., Mekenyan, O.G., Walker, J.D. (2002). Non-linear modeling of bioconcentration using partition coefficients for narcotic chemicals. SAR and QSAR in Environmental Research, 13 (1), 177-188.
- ✓ Könemann, H., van Leeuwen, C. (1980). Toxicokinetics in fish: accumulation and elimination of six chlorobenzenes in guppies. Chemosphere, 9, 3-19.

- ✓ Hawker, D.W., Connell, D.W. (1986). Bioconcentration of lipophilic compounds by some aquatic organisms. Ecotoxicology and Environmental Safety, 11, 184-197.
- ✓ Geyer, H.J., Scheunert, I., Brüggemann, R., Steingerg, C., Korte, F., Kettrup, A. (1991). QSAR for organic chemical bioconcentration in Daphnia, algae, and mussels. Science of the Total Environment, 109/110, 387-394.
- ✓ Geyer, H.J., Politzki, G., Freitag, D. (1984). Prediction of ecotoxicological behaviour of chemicals: relationship between n-octanol/water partition coefficient and bioaccumulation of organic chemicals by algae Chlorella. Chemosphere, 13, 269-284.
- ✓ Ellgenhausen, H., Guth, J.A., Esser, H.O. (1980). Factors determining the bioaccumulation potential of pesticides in the individual compartments of aquatic food chains. Ecotoxicology and Environmental Safety, 4, 134-157.
- ✓ Geyer, H.J., Sheehan, D., Kotzias, D., Freitag, D., Korte, F. (1982). Prediction of ecotoxicological behaviour of chemicals: relationship between physicochemical properties and bioaccumulation of organic chemicals in the mussel. Chemosphere, 11, 1121-1134.
- ✓ Hansch, C., Kim, D., Leo, A. S., Novellino, E., Silipo, C., Vittoria, A. (1989). Toward a quantitative comparative toxicology of organic compounds. CRC Critical Reviews in Toxicology, 19, 185-226.
- ✓ Kubinyi, H. (1976). Quantitative structure-activity relationships. IV. Non-linear dependence of biological activity on hydrophobic character: a new model. Arzneimittel-Forschung-Drug Research, 26, 1991-1997.
- ✓ Veith, G.D., DeFoe, D.L., Bergstedt, B.V. (1979). Measuring and estimating the bioconcentration factor of chemicals on fish. Journal of Fisheries Research Board of Canada, 36, 1040-1048.
- ✓ European Commission. 2003. Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances, and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.
- ✓ Banerjee, S., Baughman, G.L. (1991). Bioconcentration Factors and Lipid Solubility. Environmental Science Technology, 25, 536-539.
- ✓ Isnard, P., Lambert, S. (1988). Estimating Bioconcentration factors from octanol- xater partition coefficient and aqueous solubility. Chemosphere, 17, 21-34.

✓ Connell DW and Hawker DW (1988). Use of polynomial expressions to describe the bioconcentration of hydrophobic chemicals by fish. Ecotoxicology and Environmental Safety, 16, 242-257.

QMRF:

QMRF	*TITLE*	*Software*	*Algorithm*	*Author*
Q2-17-16-140	QSAR for bioconcentration factor in fish	DRAGON	multilinear regression QSAR	Ester Papa
Q8-10-14-207	QSAR for the bioconcentration factor of non-ionic organic compounds	QSARModel 3.5.0	multilinear regression QSAR	Molcode model development team
Q8-10-14-175	QSAR for bioconcentration (flow through fish test) of pesticides	QSARModel 3.5.0	multilinear regression QSAR	Molcode model development team
Q8-10-24-173	QSAR for bioconcentration (flow-through fish test) of polychlorinated biphenyls	QSARModel 3.3.5	multilinear regression QSAR	Molcode model development team

PERSISTENCE

Articles:

- ✓ QSARs for identifying and prioritizing substances with persistence and bioconcentration potential, Walker J.D. *et al.* SAR and QSAR in Environmental Research, 2002 Vol. 13 (7-8), pp. 713-725.
- ✓ Toxic Ratio as an Indicator of the intrinsic toxicity in the assessment of Persistence, Bioaccumulative, and toxic chemicals, Maeder V. *et al.* Environ. Sci. Technol. 2004, 38, 3659-3666.

QMRF:

QMRF	*TITLE*	*Software*	*Algorithm*	*Author*
Q8-10-30-265	QSAR model for persistence: abiotic degradation in water	QSARModel 4.0.4	Multilinear regression QSAR	Molcode model development team
Q8-10-30-266	QSAR for persistence: abiotic degradation in air	QSARModel 4.0.4	Multilinear regression QSAR	Molcode model development team