CADASTER

CAse studies on the Development and Application of in-Silico Techniques for Environmental hazard and Risk assessment

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Collaborative Project

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RE	Restricted to a group specified by the consortium (including the	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Content

WP 5: QSPR-THESAURUS: Web site and standalone tools for dissemination of project results

Task 5.7 CADASTER Workshop on the development and application of QSAR models with respect to the REACH guidelines (Deliverable 5.7)

Summary

The second CADASTER workshop (http://www.cadaster.eu/workshop) was organized by the Helmholtz Zentrum Muenchen and took place in its premises from October 7th to 9th 2012. A booklet with agenda of the workshop, abstracts of all presentations, short CVs of lectors and description of the cultural program is provided as Annex 5. The workshop was aimed to provide a tutorial to all interested partners, including industry and SMEs, on how to develop new models for the assessment of REACH-end points (in particular for new scaffolds of compounds for which there are no reliable QSAR models) and how to use the software developed by the project participants. According to the previous decision of the CADASTER General Assembly (February 2012, Madrid), materials of the workshop will be published as a dedicated issue of the ATLA journal (see Annex 1 with a list of submitted manuscripts). These materials summarize the expertise of all participants by providing clear guidelines on how to use applicability domain and experimental design to select an informative set of molecules, how to develop models and to estimate their applicability domain, and how to integrate different testing strategies following a critical analysis of four case studies considered in the CADASTER grant.

The workshop was attended by 52 participants (see list of participants in Annex 2), including invited speakers from JRC - Institute for Health & Consumer Protection (Italy), EPA – Environmental Protection Agency (USA), Umwelt Bundesamt (Germany) and coordinators of the FP7 funded projects OSIRIS (Prof. G. Schüürmann) and COSMOS (Prof. M. Cronin). Dr. Barry Hardy, coordinator of the partner FP7 funded OpenTox project, had to cancel his participation due to personal reasons and sent his apologizes.

The meeting was started with a welcome reception on Sunday, October 7th, which was followed by a cultural program.

There were two main thematic areas of the workshop: 1) Data collection and QSAR Model development for REACH (October 8th) and 2) Case studies and use of QSARs in the risk assessment (October 9th). The lectures of project participants were followed by lecture of invited speakers, thus providing a better understanding to the participants of a framework for the CADASTER project studies within similar activities of other EU projects and daily work of environmental protection agencies. Lectures presented during the workshop are provided in Annex 3.

A poster session was organized during the first day of the workshop. The session included 20 posters from CADASTER partners and workshop participants (see Annex 4).

Overview of the workshop

October 7th

Dr. Igor Tetko and Prof. W. Peijnenburg opened the workshop and welcomed participants and invited lectors. In the first lecture **Prof. Peijnenburg** provided a summary of the project goals, achievements and lessons. In the absence of Dr. B. Hardy (OpenTox) **Dr. Igor Tetko** provided an overview of data modeling tools on the Internet, their differences, as well as of the place of the CADASTER QSPR-THESAURUS web site within this emerging field. **Dr. Durjava** described lessons that were learnt during the CADASTER project with respect to collection of experimental data and experimental testing. **Prof. Schüürmann (UFZ, Leipzig)** overviewed the activities within the FP7 funded OSIRIS project with respect to development of integrated testing strategy (ITS) approaches. The activities of the CADASTER project with respect to development of models according to the OECD principles using case studies for brominated flame retardants and perfluorinated compounds were presented by **Dr. E. Papa**. This lecture was followed by case studies on development of models for TAZ/BTAZ and triazoles given by **Mrs. S. Kovarich**, who is finishing her PhD within the CADASTER project at the University of Insubria.

After a short break for lunch, **Prof. M. Cronin (Liverpool John Moores University, UK)** provided an overview of methods for the grouping of chemicals. These methods are important to make predictions by read-across and have received considerable interest for use in REACH and are increasingly being used, and accepted, for regulatory assessment. **Dr. U. Sahlin** described the theoretical basis of the uncertainty in QSAR predictions and importance of its use in risk assessment and/or in contexts of other decision-making processes. The lecture of **Dr. Sushko** overviewed methods for applicability domain assessment of QSAR models and their importance for the evaluation of uncertainty of quantitative and qualitative predictions. The majority of the presented approaches are available at the QSPR THESAURUS web site. The on-line demonstration by **Dr. Tetko and Mr. Brandmaier** was provided to demonstrate the practical use of the tools developed within the CADASTER project. Dr. Tetko concentrated on data upload, model development, application and interpretation. Mr. Brandmaier exemplified the use of experimental design approaches, which were developed and implemented on the CADASTER QSPR THESAURUS web site and are part of his PhD thesis.

The theoretical and on-line training was followed by the poster session. There were more than 20 posters presenting work of CADASTER partners as well as of workshop participants. The second day of the workshop was finished with a Workshop dinner.

October 8th

The invited lecture from **Dr. A. Richard (USA, Environmental Protection Agency)** overviewed ToxCast and Tox21 projects which probe high-throughput screening (HTS) technologies for toxicity prediction and modeling. The subsequent lecture of **Mrs. L. Golstein** was devoted to case studies for estimation of Maximum Permissible Emission (MPE) using example of triazoles. The influence of parameter uncertainties on the decision making process were exemplified. This work within the CADASTER project is a part of the PhD thesis of the lector. As an invited lecture, **Dr. M. Brandt (Umweltbundesamt, Germany)** described practical the use of QSAR methodology in the German Environmental Protection Agency. **Dr. T. Aldenberg** described how the uncertainty of QSAR predictions can be incorporated to improve the estimation of the Species Sensitivity Distributions (SSDs). **Dr. E. Rorije** examplified the use of read across estimates for the risk assessment using fragrances, which is one class of compounds studied in CADASTER project.

The morning session lectures were followed by a lunch in the HMGU cafeteria.

Dr. A. Worth (European Commission's Joint Research Centre, Ispra) described the use of Threshold of Toxicological Concern (TTC) approach, which provides a framework for integrating a range of computational methods in chemical risk assessment, including (Q)SARs, chemical categories and read-across, as well as physiologically-based biokinetic modeling. In her second lecture, **Dr. U. Sahlin** presented an impact of uncertainty of models on prioritization of chemical compounds for risk assessment. **Dr. A Schipper** presented her study of an impact of chemicals for a population of peregrine falcons (Falco peregrinus). She showed how one can estimate the economic impact of chemicals using wildlife populations. The lecture of **Mr. P. Sopasakis** overviewed his work on the development of web-tools to exemplify the importance of uncertainty of model predictions for the fate assessment of chemical

compounds.

Prof. W. Peijnenburg has closed the workshop and thanked all participants and lectors for their contributions. A post-workshop visit to BMW museum was also organized.

Acknowledgements

We thank the local organizers of the CADASTER Workshop conference, in particular Dr. E. Schlosser and Mr. S. Brandmaier, as well as members of the Chemoinformatics group, namely Miss S. Vorberg, Mr. P. Kunwar, Mr. J. Ehret, Mr. C. Skuda, for their help with preparation and implementation of the CADASTER workshop and Mr. K. Zillessen (eADMET GmbH) for his help with the preparation of a booklet with materials of the workshop. The organizers also thank all of the speakers and all participants who generously contributed their time and effort to the planning and the implementation of the workshop.

Annex 1: List of workshop materials submitted for peer-review publication in ATLA journal

1) **Environmental fate and effects of triazoles and benzotriazoles**
   Mojca Kos Durjava, Lovro Arnus, Boris Kolar, Ester Papa, Simona Kovarich, Ullrika Sahlin, Willie Peijnenburg

2) **Uncertainty in QSAR predictions**
   Ullrika Sahlin

3) **Arguments for considering QSAR uncertainty in hazard and risk assessments**
   Ullrika Sahlin, Laura Golsteijn, M Sarfraz Iqbal, Willie Peijnenburg

4) **Read Across of aquatic toxicity for the CADASTER class of Fragrances and estimation of the associated uncertainty**
   Emiel Rorije, Tom Aldenberg

5) **Species Sensitivity Distributions based on QSAR Estimates of Toxicity: Examples from CADASTER Substances**
Tom Aldenberg, Emiel Rorije, and Ullrika Sahlin

6) **Evaluation of CADASTER QSAR models for aquatic toxicity of (benzo-) triazoles and prioritization by consensus.**

Stefano Cassani, Simona Kovarich, Ester Papa, Partha Pratim Roy, Magnus Rahmberg, Sara Nilsson, Ullrika Sahlin, Nina Jeliazkova, Nikolay Kochev, Ognyan Pukalov, Igor V. Tetko, Stefan Brandmaier, Mojca Kos Durjava, Boris Kolar, Willie Peijnenburg, Paola Gramatica

7) **From descriptors to predicted properties: Experimental design using the applicability domain estimation**
Stefan Brandmaier, Sergii Novotarskyi, Iurii Sushko, Igor V. Tetko

Annex 2: List of Participants

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Annex 3: Oral presentations

Workshop lectures are publicly available at http://cadaster.eu/node/129

The abstracts of the lectures are also indicated in the booklet (see Annex 5).

Annex 4: Poster presentations

Workshop posters are publicly available at http://cadaster.eu/node/128

The abstracts of the posters are also indicated in the booklet (see Annex 5).

Annex 5: CADASTER Workshop materials

Workshop program is available at http://cadaster.eu/workshop

Workshop presentations and booklet are available at http://cadaster.eu/node/127

The booklet is provided below.

CADASTER Workshop 2012

07. – 09. October 2012

CAse studies on the Development and Application of in Silico Techniques for Environmental hazard and Risk assessment

Helmholtz-Zentrum München

Deutsches Forschungszentrum für Gesundheit und Umwelt

SEVENTH FRAMEWORK PROGRAMME

CADASTER Workshop on the development and application of QSAR models in REACH

Dear Colleague,

On behalf of the project team of the CADASTER project and the organization committee of the second CADASTER workshop, I like to welcome you to Munich. I do hope that you will not only enjoy the unique features of Munich in early October, but that you will also enjoy the scientific program offered within the workshop.

Within REACH emphasis is laid on optimizing chemical risk assessment, not only in terms of reducing costs and taking note of alternative chemicals but also in terms of reducing use of test animals. In turn, this aim requires that alternatives are available that allow for an efficient use of substitutes to common testing and common risk assessment. The CADASTER project aims at tutoring interested parties on how to optimize the integration of alternative test methods with (scarcely) available test data into a tailored risk assessment. This is done on the basis of representatives of four diverse classes of substances, in terms of chemical similarity and in terms of use patterns.

The second CADASTER (www.cadaster.eu) workshop is aimed at providing a tutorial to all interested partners on how to develop new models for the assessment of REACH-endpoints, how to use the software developed by the project participants, and how to perform integrated risk assessment.

I wish you a fruitful and challenging workshop.

Willie Peijnenburg
Coordinator of the CADASTER project



Dear Colleagues,

This is our pleasure to welcome you as a participant of the Second "CADASTER Workshop on the development and application of QSAR models with respect to the REACH guidelines". Thanks to participation of distinguished faculty and comprehensive contributions from CADASTER partners we are delighted to have an excellent scientific program.

If you are first time in Munich, we hope that you will stay 1-2 days before or after it and will enjoy a special atmosphere of this lovely city with its very special Bavarian biergartens, beautiful cafes and restaurants, world-wide known museums (in particular famous Deutsches Museum, New and Old Pinakothek, Residenz etc.) and peaceful atmosphere. In particular, if you will arrive on Sunday, you may wish to visit the last day of Oktoberfest – the largest beer festival in world.

We hope that you will enjoy your stay in Munich and will get comprehensive knowledge about the CADASTER project, its goals and results.

Igor Tetko, Eva Schlosser and Stefan Brandmaier

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Schedule

Sunday, October 7th

Time	Topic	Speaker
16:00-18:00	Registration and welcome reception at the Helmholtz Zentrum, Building 57	
19:00-22:00	Guided walk over the Oktoberfest	

Monday, October 8th

Main topic: Data collection and QSAR Model development for REACH

Time	Topic	Speaker
08:00-09:00	Registration	
09:00-09:10	Opening of the workshop. Welcome from the organizers.	Dr. Igor V. Tetko, HMGU, Germany
09:15-09:35	Overview of CADASTER: project goals, achievements and lessons	Prof. Willie Peijnenburg, RIVM, The Netherlands
09:40-10:10	Reflections on Partnering from the results of the OpenTox and CADASTER projects	Dr. Barry Hardy, Douglas Connect, Switzerland
10:15-10:45	Lessons from collection of experimental data and experimental testing in CADASTER	Dr. Mojca Kos Durjava, PHI, Slovenia
10:45-11:00	Coffee Break	
11:00-11:30	ITS for Environmental Toxicology in REACH	Prof. Gerrit Schüürmann, UFZ Leipzig, Germany
11:35-12:05	Development of models according to the OECD principles	Prof. Ester Papa, University of Insubria, Italy
12:10-12:40	Development and validation of models for TAZ/BTAZ and fragrances	Simona Kovarich, University of Insubria, Italy
12:40-14:00	Lunch	
14:00-14:30	Current and Future Methods to Group Chemicals to Perform Read-Across	Prof. M. Cronin, Liverpool John Moores University, UK
14:35-15:05	Uncertainty in QSAR predictions for probabilistic risk assessment	Dr. Ullrika Sahlin, Linneaus University, Sweden
15:10-15:40	Applicability domain assessment for QSAR models: status quo and perspectives	Dr. Iurii Sushko, eADMET GmbH, Germany
15:40-15:55	Coffee Break	
15:55-16:45	Practical training in the use of the QSPR-THESAURUS platform in application of QSAR modeling tools	Dr. Igor V. Tetko, Stefan Brandmaier, HMGU, Germany
16:45-18:15	Poster session	
19:15-20:30	Guided tour through the city center	
20:30	Workshop dinner at Augustiner Bräu	

Tuesday, October 9th

Main topic: Case studies and use of QSARs in the risk assessment

Time	Topic	Speaker
09:00-09:30	EPA's ToxCast Project: Lessons learned and future directions for use of HTS in predicting in vivo toxicology -- A Chemical Perspective	Dr. Ann Richard, Environmental Protection Agency, USA
09:35-10:05	Addressing QSPR uncertainty in chemical exposure and effect assessment - examples from the CADASTER classes	Laura Golsteijn, Radboud University Nijmegen, The Netherlands
10:05-10:15	Coffee Break	
10:15-10:45	UBA Lessons of using QSAR models with respect to REACH	Dr. Marc Brandt, Umwelt Bundesamt, Germany
10:50-11:20	Using SSD approach to quantify uncertainty from QSAR estimates of effects data - examples from the CADASTER classes	Dr. Tom Aldenberg, RIVM, The Netherlands
11:20-11:30	Coffee Break	
11:30-12:00	Read across estimates - uncertainty in the risk assessment for the CADASTER class of fragrance substances	Dr. Emiel Rorije, RIVM, The Netherlands
12:00-13:00	Lunch	
13:00-13:30	Supporting chemical risk assessments with computational methods: challenges and perspectives	Dr. Andrew Worth, JRC, Italy
13:35-14:05	QSAR integrated risk assessment – prioritization within the four CADASTER classes	Dr. Ullrika Sahlin, Linneaus University, Sweden
14:05-14:20	Coffee Break	
14:20-14:50	Modelling the costs of chemical impacts on wildlife populations: the case of peregrine falcons (Falco peregrinus) exposed to PBDEs	Dr. Aafke Schipper, Radboud University Nijmegen, The Netherlands
14:55-15:25	Use of QSAR information available at QSPR-THESAURUS for risk assessment	Pantelis Sopasakis, National Technical University of Athens, Greece
15:30-16:00	Panel discussion	Dr. Mike Comber, Mike Comber Consulting, Belgium
16:00-16:10	Closing remarks	
17:00	Visit in the BMW museum	

Legend

Invited lecture
Lecture
Case study
Practical training

Lectures and Speakers

Prof. Dr. Willie Peijnenburg
RIVM, Laboratory for Ecological Risk Assessment, Bilthoven, The Netherlands

Professor Willie Peijnenburg is Project Manager/Scientific coordinator and Professor at the Extraordinary chair "Environmental Toxicology and Biodiversity" at the University of Leiden. His current research interests contain: 1) the development and application of quantitative structure activity relationships (QSARs) for the estimation of physical chemical properties and transformation rates of chemical substances in the environment, with the aim of using these QSARs in models for ecological risk assessment; 2) the implementation of bioavailability of heavy metals in risk assessment procedures. The aim of this research is to develop methodologies for assessing soil-type and water-type specific heavy metal standards. Models are developed and validated that combine chemical insights in the area of metal speciation, with biological insights regarding uptake of metals as influenced by compartment-specific and organism-specific factors; 3) fate and effects of organic and inorganic nanomaterials in the environment: fate studies as affected by interactions with biotic and abiotic matrices, and effect studies on aquatic and benthic organisms following assessment of the bioavailable form of the nanomaterials.
Professor Peijnenburg is editor and editor-in-chief of 7 journals in the area of environmental sciences, member of various national and international peer review panels and project leader of various national and international projects in the fields of environmental risk assessment and implementation of the Water Framework Directive, amongst others to allow new EU member states to conform to the requirements of the acquis communautaire. Furthermore, he is member of various National and International Ph.D. committees, supervisor of various bachelor and master students of national and international universities and supervisor of 6 PhD students at Leiden University (CML), visiting Professor Dalian University of Technology, Dalian, China (as of April 2009), invited lecturer and session chairman/moderator at various international conferences, lecturer in various bachelor and master courses at various universities, teaching environmental chemistry, multimedia fate modeling, ecotoxicology, effect assessment.

OVERVIEW OF CADASTER: PROJECT GOALS, ACHIEVEMENTS AND LESSONS

Abstract: Implementation of REACH requires demonstration of the safe manufacture and use of chemicals. REACH aims to achieve a proper balance between societal, economic and environmental objectives, and attempts to efficiently use the scarce and scattered information available on the majority of substances. To achieve the aim of REACH to reduce animal testing by optimized use of in silico and in vitro information on related compounds, guidance is needed on how these methods should be used. The procedures include alternative methods such as chemical and biological read-across, in vitro results, in vivo information on analogues, (Q)SARs, and exposure-based waiving. Despite the fact that the concepts behinds these tools needed have been developed, additional intensive efforts are needed to translate the concept into a workable, consensually acceptable, and scientifically sound strategy. CADASTER aims at providing the practical guidance to integrated risk assessment by carrying out a full hazard assessment for chemicals belonging to four compound classes as a way of exemplifying the integration of the available tools and experimental data.
The main goal of the CADASTER project is to exemplify the integration of information, models and strategies for carrying out safety-, hazard- and risk assessments for large numbers of substances. In this contribution a general overview on the CADASTER project will be provided, including the aims of the project and the main insights and results obtained.

Dr. Barry Hardy
Director, Douglas Connect GmbH, Switzerland

Dr. Barry Hardy leads the research activities of Douglas Connect, Switzerland. He has served as coordinator for the OpenTox (www.opentox.org) project in predictive toxicology and the ToxBank infrastructure development project (www.toxbank.net).
He is also leading research activities in antimalarial drug design and toxicology for the Scientists Against Malaria project (www.scientistsagainstmalaria.net) which was developed from a pilot within the SYNERGY FP7 project on knowledge-oriented collaboration.
Dr. Hardy obtained his Ph.D. in 1990 from Syracuse University working in emerging areas of computational science. He was a National Research Fellow at the FDA Center for Biologics and Evaluation, a Hitchings-Elion Fellow at Oxford University and CEO of Virtual Environments International. He was a pioneer in the early 1990s in the development of World Wide Web technology applied to virtual scientific communities and conferences. He has developed technology solutions for internet-based communications, e-learning, laboratory automation systems, computational science and informatics, drug design and predictive toxicology. In recent years he has been active in the field of knowledge management as applied to supporting innovation, communities of practice, and collaboration.
With OpenTox[1] he has been leading the development of an open, interoperable, semantic web platform whose goal is to satisfy the needs of the predictive toxicology field through the creation of applications linking resources together for data, algorithms, models and ontologies.
As described in the recent ALTEX papers[2,3] he is motivating an international collaboration to develop an open, robust, well-maintained ontology for the field of predictive toxicology supporting the reliable use of data and concepts required for integrated analysis.

REFLECTIONS ON PARTNERING FROM THE RESULTS OF THE OPENTOX AND CADASTER PROJECTS

Abstract: In this lecture I will discuss what progress is being made on collaboration within and between European and international research projects within the field of predictive toxicology. I will also discuss the challenges and barriers to collaboration and what might be promising next directions. I will include consideration of scientific, structural, social, economic, political and environmental factors. In particular my reflections will be based on my direct experiences with the OpenTox and CADASTER projects and other initiatives.

[1] Hardy, B., Douglas, N., Helma, C., et al. (2010). Collaborative development of predictive toxicology applications. J Cheminform. 2, 7.
[2] Hardy, B., Apic, G., Carthew, P., et al. (2012). A toxicology ontology roadmap. ALTEX 29, 129-137.
[3] Hardy, B., Apic, G., Carthew, P., et al. (2012). Toxicology ontology perspectives. ALTEX 29, 139-156.

Dr. Mojca Kos Durjava

Public Health Institute Maribor, Slovenia

Mojca Kos Durjava is Senior Researcher at the Public Health Institute Maribor, Slovenia. She has been Project Leader in the Centre for Risk Assessment of Chemicals with Laboratory at the Public Health Institute Maribor since 2004. She graduated in analytical chemistry in 1996 at the University of Maribor, Slovenia. She completed her PhD study in the area of environmental chemistry in 2006 at the University of Ljubljana, Slovenia in cooperation with the University of Utrecht and the National Institute for Public Health and the Environment, RIVM, both from The Netherlands. Her present research field is in environmental chemistry and fate and effect studies of substances in the environment; effect studies on aquatic and benthic organisms. She is an expert in the area of Water Framework Directive. She is regularly presenting her achievements at conferences and in international journals.

LESSONS FROM COLLECTION OF EXPERIMENTAL DATA AND EXPERIMENTAL TESTING IN CADASTER

Abstract: Data search on all endpoints of relevance was performed for the environ¬mental risk and hazard assessment for four classes of chemicals selected in CADASTER: brominated flame retardants, fragrances, perfluorinated chemicals, triazoles and benzotriazoles. The project participants used the CADASTER QSPR-THESAURUS database on experimental parameters and (Q)SARs for chemical and biological endpoints to introduce experimental data. In general the number of experimental data is quite large; however, only limited data are available for the endpoints of primary interest for environmental risk assessment within REACH, i.e. the SIDS endpoints.

Toxicity and fate and behaviour testing was performed on a pre-selected number of chemicals selected in CADASTER. Among others, bioaccumulation tests of polybrominated diphenyl ethers (PBDE) on oligochaete species Tubifex tubifex were conducted to validate QSAR models on the bioaccumulation potential of these lipophilic organic chemicals. Selective uptake of PBDEs by oligochaete allows assessing the bioaccumulation of individual congeners in commercial mixtures. In our study the average values for BAF as well as for BCF for low and high PBDEs differed by less than an order of magnitude.

Prof. Dr. Gerrit Schüürmann

Helmholtz Center for Environmental Research (UFZ), Leipzig, Germany

Gerrit Schüürmann has studied Chemistry, Physics and Mathematics at the University of Mün¬ster in Germany followed by a doctoral thesis in Chemistry, and later completed a habilitation thesis in Ecological Chemistry at the University of Leipzig (Germany). He heads the Department of Ecological Chemistry at the Helmholtz Centre for Environmental Research in Leipzig, and is Professor of Theoretical and Ecological Chemistry at the Technical University Bergakademie Freiberg, Honorary Professor of Chemical Ecotoxicology at the University of Leipzig, and Lecturer of Toxicology at the University of Halle-Wittenberg. His research focuses on structure-activity relationships, employing computational chemistry, chemoassays, bioassays, and chemoinformatics to study and predict compound toxicity, reactivity, partitioning and degradation. Gerrit Schüürmann has published over 250 papers, has coordinated the EU project OSIRIS (2007-2011) that developed Integrated Testing

Strategies (ITS) for REACH with a particular focus on non-animal methods, and is currently chair of the expert panel "Chemical Safety" of the GDCh (German Chemical Society) and GT (German Society of Toxicology).

ITS FOR ENVIRONMENTAL TOXICOLOGY IN REACH

Abstract: Through the implementation of the European Directive REACH in 2007, alternative methods have gained an increased importance as non-animal tools for the toxicological assessment of chemical substances. In this context, the 3R principle of reducing, refining and replacing animal testing has resulted in a paradigm shift: While the original idea was to replace a given animal test by a single in vitro alternative (1:1 replacement), the integrated testing strategy (ITS) approach aims at exploiting the combined information generated from several (n) non-animal methods in order to – partly or fully – replace the respective animal experiment (1:n replacement). In the presentation, the ITS concept and its major components covering non-test (in silico) and test (in chemico, in vitro, omics) methods as well as information theory are outlined, building on respective results as developed within the EU-funded OSIRIS project.[1] For illustrating their way of application, models for predicting aquatic toxicity as implemented in the free-of-charge software ChemProp[2] are taken as example, focussing on quantitative read-across,[3] structural alerts,[4-6] implications from the model applicability domain,[7] and on consensus evaluation as a practical tool to characterize and improve the level of confidence in ITS scheme applications.

[1] OSIRIS. Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information. EU Project, contract no. GOCE-CT-2007-037017, 2007-2011. OSIRIS project website: http://www.osiris-reach.eu/. OSIRIS webtool website: http://osiris.simpple.com/OSIRIS-ITS/welcome.do.
[2] Chemical Properties Estimation Software System (ChemProp) 5.2.7, 2012. UFZ Department of Ecological Chemistry, http://www.ufz.de/index.php?en=6738.
[3] Schüürmann G, Ebert R-U, Kühne R 2011. Quantitative read-across for predicting the acute fish toxicity of organic compounds. Environ. Sci. Technol. 45: 4616-4622.
[4] Von der Ohe PC, Kühne R, Ebert R-U, Altenburger R, Liess M, Schüürmann G 2005. Structural alerts – A new classification model to discriminate excess toxicity from narcotic effect levels of organic compounds in the acute daphnid assay. Chem. Res. Toxicol. 18: 536-555.
[5] Schramm F, Müller A, Hammer H, Paschke A, Schüürmann G 2011. Epoxide and Thiirane Toxicity In vitro with the Ciliates Tetrahymena pyriformis – Structural Alerts Indicating Excess Toxicity. Environ. Sci. Technol. 45: 5812-5819.
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[7] Kühne R, Ebert R-U, Schüürmann G 2009. Chemical Domain of QSAR Models from Atom-Centered Fragments. J. Chem. Inf. Model. 49: 2660-2669.

Prof. Dr. Ester Papa
University of Insubria, Italy

Dr. Ester Papa was born in Varese (Italy) in 1977. She graduated cum Laude in Biology in 2001 at the University of Insubria (Varese, Italy) and completed in 2006 her PhD with a thesis entitled "QSAR approach to PBTs, sources of biodiversity stress", under the supervision of Prof. Paola Gramatica. During her PhD studies she was visiting student at the Liverpool John Moores University, UK (supervisor Prof. Mark T.D. Cronin), and at the Umeå University, Sweden (supervisor Dr. Patrik Andersson). Since January 2009 she is Assistant Professor (field of Environmental Chemistry) at the University of Insubria, and her research activity takes place at the Department of Theoretical and Applied Sciences in the QSAR Research Unit in Environmental Chemistry and Ecotoxicology, led by Prof. P. Gramatica. She published over 40 papers in the field of QSAR and Chemometrics, and presented over 100 among posters,

oral communications and invited talks, at scientific national and international conferences. Dr. Papa is currently involved in national and international research projects and collaborations in the field of QSAR for REACH and Green Chemistry (CADASTER, SMART-REACH Network, Center for Green Chemistry and Green Engineering-Yale University). She is referee for various international scientific journals, and chair-person at national and international scientific conferences.

DEVELOPMENT OF MODELS ACCORDING TO THE OECD PRINCIPLES

Abstract: The Organization for Economic Co-operation and Development (OECD) proposed five principles for the validation of quantitative structure-activity relationship (QSAR) models, in 2004: the compliance with all five principles has to be established for QSAR models used for regulatory purposes. This presentation illustrates the application of the five principles (1-Defined End-point, 2-Unambiguous Algorithm, 3-Defined domain of applicability, 4-Appropriate statistical validation, 5-Mechanistic interpretation, if possible) to the development of QSAR models, by using as examples some of the models generated for brominated flame retardants and perfluorinated compounds within the EU-CADASTER project. The modelling of these two classes of compounds is particularly suitable to illustrate issues related to data availability, data dimension and data homogeneity, features which influence the domain of applicability, the robustness, the predictivity, and the complexity of the models.
The application of the OECD principles during the development of QSARs is essential to deliver quality results which can be correctly documented and communicated to regulators and other users. The communication procedure is facilitated by the compilation of the QSAR Model Reporting Format (QMRF), which is a standardised format to describe the compliance of QSAR models with all the five principles.

Simona Kovarich
University of Insubria, Italy

Simona Kovarich is a PhD student in Chemical Sciences working in the QSAR Research Unit (University of Insubria, Varese) under the supervision of Prof. Paola Gramatica and Dr. Ester Papa, with a fellowship obtained by the FP7 European Project CADASTER. She graduated cum laude in Biological Science (Ecotoxicology) in 2008 at the University of Insubria with a thesis entitled "QSAR modelling of physico-chemical property and toxicity of brominated flame retardants" (Prof. Gramatica, Dr. Papa). She started her PhD studies in 2009, in the same University and still under the supervision of Prof. Gramatica and Dr. Papa. Topic of her PhD is the development of QSAR models for the characterization of environmental behaviour and toxicity of four classes of emerging pollutants (brominated flame retardants, fragrances, perfluorinated compounds and (benzo)triazoles), to be finally integrated in risk assessment procedures. During her PhD studies she spent one month at the Helmholtz Zentrum München (Germany) in the Institute of Bioinformatics and Systems Biology under the supervision of Dr. Igor Tetko, and three months at the Consulting Agency WCA Environment Ltd in Oxford (UK), under the supervision of Dr. Claire Massey and Dr. Graham Merrington. She is the author or co-author of 8 publications in international peer-reviewed journals and 40 scientific contributions to national and international meetings in the field of environmental chemistry and QSAR.

DEVELOPMENT AND VALIDATION OF MODELS FOR TAZ/BTAZ AND FRAGRANCES

Abstract: Under the EU-REACH regulation, there is an urgent need to fill data gaps as well as reduce the animal testing. In this context alternative in-silico techniques, like quantitative structure-activity relationships (QSARs), represent a valid tool for the prediction of missing

information, to be used as support tools for chemical risk assessment. The development and validation of QSAR models for four classes of emerging pollutants (brominated flame retardants, fragrances, perfluorinated compounds and (benzo)triazoles) is the central topic of Work Package 3 within the FP7 European project CADASTER.
This presentation is focused on the QSAR models developed for two chemical classes studied within the project, i.e. fragrances and (benzo)triazoles (B-TAZs). In particular, QSARs for the prediction of aquatic toxicity of B-TAZs and ready biodegradation of fragrances are presented. In the two case studies, different modeling approaches were applied starting from theoretical molecular descriptors calculated by both commercial and freely available software. QSARs were checked for their goodness-of-fit, robustness, external predictivity (also on new CADASTER experimental data) and applicability domain, in agreement with OECD principles for the validation of QSARs for regulatory purposes.
The presented case studies highlight the utility of QSARs for the prediction of environmental behavior and ecotoxicity data to be used under REACH for the hazard and risk assessment of chemicals, especially when dealing with specific chemical classes. The importance of QSAR as a valid tool for the screening and prioritization of pollutants is also stressed.

Prof. Dr. Mark T.D. Cronin

School of Pharmacy and Chemistry, Liverpool John Moores University, UK

Mark Cronin is Professor of Predictive Toxicology at Liverpool John Moores University, England. His expertise relates to the prediction of toxicity including environmental and human health effects using alternative approaches, such as the use of in silico techniques including category formation and read-across, (Q)SARs. He has long sought the development of computational models to predict toxicity based on mechanisms and modes of action. Currently he co-ordinates the EU / Cosmetics Europe COSMOS Project (part of the Seurat-1 Cluster) and is a partner in other projects including eTox, NanoBridges, AlterREACH and the development of the OECD QSAR Toolbox. Mark Cronin has published three books and over 180 papers in all areas of in silico and computational toxicology.

CURRENT AND FUTURE METHODS TO GROUP CHEMICALS TO PERFORM READ-ACROSS

Abstract: In silico, or computational, models to predict the toxicity of chemicals have obvious advantages in terms of reducing the time, cost and animal use for risk assessment. Read-across is one the simplest of in silico techniques, it relies on placing a compound into a group, or category, of chemicals. Following this, toxicity (or other) data are obtained, this potentially allows for an interpolation (the read-across) of activity. Increasingly read-across is being used, and accepted, for regulatory assessment. The key to read-across is to place a compound in a meaningful and robust category and then obtain significant high quality toxicity data for the compounds in the category. There are a number of approaches to form categories e.g. use of chemical classes, functional groups, mechanistic structural alerts etc. There are also a number of tools that help the user perform read-across, the most widely applied being the OECD QSAR Toolbox. The future of read-across depends on the ability to form and record robust categories. The real challenges are in the area of chronic toxicity prediction. Closer links are required between the chemistry and adverse effect in vivo. The use of Adverse Outcome Pathways (AOPs) is seen as being one method of providing a framework to organise the information.

Dr. Ullrika Sahlin
Linneaus University, Sweden

My research is directed towards the management of environmental systems given the current state of knowledge. Special interest is the treatment of uncertainty in scientific communication, which covers predictive inference and quantitative approaches for solving environmental problems related to decision making, and addressing questions related to decision makers perception of information and which impact uncertainty may have on the systems to be managed. The year 2010 I completed my PhD in Ecology at Lund University Sweden with the thesis From data to decision - learning by probabilistic risk analysis of biological invasions.Between 2010 and 2012 I worked as a postdoc at Linneaus University Sweden in the EU-project CADASTER on the quantification of uncertainty in QSARs for chemical regulation under REACH. During 2012 I work as a project leader of work package 4 in the EU-project CADASTER with focus on the Integration of QSARs within hazard and risk assessment. I am currently associated to the Center of Climate and Environmental research at Lund University. During 2012 and 2013 I am leading the one year project Decision making under uncertainty – towards ecological risk analysis of clupeid reduction, as part of the project PLANFISH financed by the Swedish Agency for Marine and Water Management.

UNCERTAINTY IN QSAR PREDICTIONS FOR PROBABILISTIC RISK ASSESSMENT

Abstract: Integration of QSARs in chemical safety assessment should acknowledge uncertainty following modeling predictions. Here I will describe the uncertainty in a QSAR prediction as two kinds, the predictive uncertainty describing the difference between the predicted and actual value of an endpoint, and predictive reliability, which is how confident we are in using a model to predict a particular compound. Treatment of uncertainty in predictions is context dependent, and uncertainty is to be interpreted in relation to the background information. In this talk I will demonstrate in what way a Bayesian approach provides a meaningful interpretation of uncertainty in predictions when applied in a risk assessment or other decision making contexts. I will show how different QSAR algorithms provide various approaches to assess uncertainty in QSAR predictions.

QSAR INTEGRATED RISK ASSESSMENT – PRIORITIZATION WITHIN THE FOUR CADASTER CLASSES

Abstract: Quantitative Structure - Activity or Property Relationships (QSARs) represent non-testing information that may be used in chemical regulation as replacement of experimental tested values in assessments or to guide further testing. A chemical risks assessment is based on several endpoints in need of testing, that more or less influences the regulatory decision. An efficient way to use QSARs to guide further testing ought to be one that combines several sources of non-testing information and consider their importance in relation to the regulatory decision. Predictions of chemical activities or properties based on non-testing information are, disregard if derived from expert judgments or statistical models, subject to uncertainty. An advantage with QSARs is that uncertainty in predictions given the learning algorithm and the underlying QSAR data can be quantitatively assessed by statistical principles. Uncertainty and sensitivity analysis were here done to quantify and propagate, and evaluate the influence of, the contribution of uncertainty from QSAR predictions in risk assessments. Based on QSAR integrated risk or hazard assessment, the uncertainty analysis was combined with decision model to rank chemicals after prioritization for testing within different chemical classes and the influence of considering uncertainty due to lower reliability in a prediction when a compound lies outside a QSAR's domain of applicability.

Dr. Iurii Susko

eADMET GmbH, Germany

Dr. Iurii Sushko obtained his PhD in chemoinformatics at the Technical University of Munich in 2011. His scientific interests include QSAR modeling for various toxicological endpoints (Ames test, CYP inhibition) with a particular focus on the assessment of the models' applicability domain. He designed the terminology and methodology for applicability domain assessment and showed the effectiveness of these approaches on a number of practical QSAR studies.
Dr. Sushko was one of the main developers of OCHEM - the Online Chemical Modeling Environment (ochem.eu), the free collaborative platform that allows performing the full cycle of QSAR research. In general, his interests include development of scalable integrated solutions for automation of the most demanding QSAR modeling processes. Currently, Dr. Sushko is the head of development at eADMET GmbH and he coordinates the further development of the online chemical modeling environment.

APPLICABILITY DOMAIN ASSESSMENT FOR QSAR MODELS: STATUS QUO AND PERSPECTIVES

Abstract: For any practical QSAR application, it is of crucial importance to recognize that models are not universal. Any QSAR model has its limitations and is applicable to only a small subset of the chemical space, referred to as applicability domain (AD) of the model. The assessment of applicability domain for QSAR models was a hot topic in the recent decades, which resulted into numerous scientific publications. How to identify whether the model is applicable to a particular chemical compound? How to distinguish reliable and non-reliable predictions? How to estimate the prediction accuracy for each chemical compound individually? All these questions require answers for any practical application of QSAR models.
The talk overviews the recent methodological developments for AD assessment, in particular the ones available on CADASTER web site. A focus is made on the approaches based on distances to models (DMs), the particular measures of the prediction reliability. The application of the suggested approaches is demonstrated in a number of practical modeling studies.

Dr. Igor Tetko

Helmholtz-Zentrum München, Germany

Dr. Igor Tetko is head of Chemoinformatics group at the Institute of Structural Biology and Scientific Director of eADMET GmbH. He received his MSc in physics computer science (with distinction) from Moscow Institute of Physics and Technology (USSR), PhD in chemistry from the Institute of Bioorganics and Petrochemistry (Kiev, Ukraine) and habilitation in chemoinformatics from the University of Strasbourg. His main interests include development of methodology for QSAR/QSPR studies, computer-aided drug design, in silico ADME/T property prediction, data mining and analysis of small molecules and chemical libraries, dissemination of chemical information on web. He has co-authored more than 150 publications. Dr. Tetko was recipient of HFSPO fellowship. He has also received national GO-Bio award, which led to the establishment of eADMET GmbH in 2010. He is coordinator of Marie Curie Initial Training Network "Environmental ChemOinformatics" http://www.eco-itn.eu, which is providing training to about 40 fellows across five countries in Europe. He also coordinates Virtual Computational Chemistry Laboratory (VCCLAB) http://www.vcclab.org.

Mr. Stefan Brandmaier

Helmholtz-Zentrum München, Germany

Stefan studied Bioinformatics at the Technical University and the Ludwig-Maximilian University in Munich. The main focus during this time was on protein structures and their prediction, using homology modeling techniques. His area of research within his PhD thesis is the design of experiments. The basic question within this field of research is to select a subsample of the chemical space for experimental testing, but also for QSPR model building. One of the difficulties thereby is to keep the balance between representativeness and diversity within the subsample. Another important question is, weather the quality of the selected subsample can be improved by taking prior knowledge into account. Furthermore, research areas he is interested in are: the modeling of toxicity endpoints and bioconcentration/bioaccumulation, machine learning approaches, clustering techniques and data mining.

PRACTICAL TRAINING IN THE USE OF THE QSPR-THESAURUS PLATFORM IN APPLICATION OF QSAR MODELING TOOLS

Abstract: The lecture will overview QSAR and QSPR models developed and available on the QSPR THESAURUS web site. We will show how the models can be developed, uploaded and applied to new compounds. An interpretation of model results, estimation of the accuracy of predictions will be provided. The experimental design methods will be explained and their use for selection of datasets for testing will be also demonstrated.

Dr. Ann Richard

National Center for Computational Toxicology, Environmental Protection Agency, USA

Dr. Ann Richard obtained her PhD from the University of North Carolina Chapel Hill in Theoretical Physical Chemistry in 1983. She has been a Principal Researcher within EPA's Office of Research & Development for almost 22 years, 17 of those years in the Environmental Carcinogenesis Division. In 2005 she was recruited to be a member of EPA's newly formed National Center for Computational Toxicology. Her research activities have ranged from the application of computational chemistry and structure-activity relationship (SAR) methods to problems in environmental toxicology to, more recently, the development of cheminformatics capabilities in support of predictive toxicology based on high-throughput screening for the ToxCast and Tox21 programs. Within NCCT, she is the lead for the DSSTox project and heads up chemical information management for both the ToxCast and Tox21 projects. Her current research is working to provide a foundation for improved toxico-chemoinformatics and SAR capabilities in predictive toxicology through utilization of biologically informed chemical feature sets and chemotypes that can be used to guide and inform biological modeling efforts.

EPA'S TOXCAST PROJECT: LESSONS LEARNED AND FUTURE DIRECTIONS FOR USE OF HTS IN PREDICTING IN VIVO TOXICOLOGY -- A CHEMICAL PERSPECTIVE

Abstract: U.S. EPA's ToxCast and the related Tox21 projects are employing high-throughput screening (HTS) technologies to profile thousands of chemicals, which in turn serve as probes of a wide diversity of targets, pathways and mechanisms related to toxicity. Initial models relating ToxCast Phase I HTS results to in vivo outcomes have been published, guided by biological

mechanism and pathway organizing principles, but such models have yet to incorporate chemical reactivity or QSAR considerations. The expanded ToxCast and Tox21 chemical libraries (more than 1800 and 8300 substances, respectively) are unprecedented in size, diversity, and use-case coverage (pesticides, industrial, drugs, food-additives, cosmetics, etc.), offering significantly greater opportunities for cheminformatics and QSAR contributions to toxicity modeling. However, the nature of these libraries and HTS data sets, as well as the weight-of-evidence requirements for chemical safety assessments, continue to present major challenges for statistically-based biological or QSAR modeling approaches to the toxicity prediction problem. Cheminformatics approaches and toxicity-informed feature sets, proposed for use in conjunction with biological knowledge and adverse-outcome pathway hypotheses, are being developed as a means to focus and constrain modeling efforts into potentially productive areas of chemical and biological space, thereby improving modeling success and interpretability. Abstract does not represent EPA policy.

Miss Laura Golsteijn

Radboud University Nijmegen, The Netherlands

Laura Golsteijn is a third-year PhD student at the Radboud University Nijmegen (NL), department of environmental science. In her PhD-study she focuses on methodological developments for impacts related to emissions of toxic pollutants. Laura's research is mainly built on two pillars: (1) Modeling the toxic impact of large sets of substances with (combinations of) methods and data from different disciplines. Methodologies include multimedia fate and effect modeling, bioaccumulation modeling, 'interspecies correlations estimations' for toxicity, and quantitative structure-activity relationships. (2) Quantifying the uncertainty in chemicals' toxic impact with statistical methods or probabilistic modeling. Examples of causes of uncertainty are the use of estimation methods, or the use of small experimental datasets. The research is particularly useful for Life Cycle Impact Assessment, but (parts of it) may also be used for other applications, e.g. in risk assessment context. Laura graduated in 2009 from the Radboud University in Nijmegen as MSc Biomedical Sciences with 'Occupational and Environmental Health' as her major subject. Her main interest was human and environmental risk assessment. In her MSc work placement at the Netherlands Organisation for Applied Scientific Research, she worked on a model for occupational exposure in case of spray application of liquids.

ADDRESSING QSPR UNCERTAINTY IN CHEMICAL EXPOSURE AND EFFECT ASSESSMENT - EXAMPLES FROM THE CADASTER CLASSES

Abstract: A safe maximum permissible emission (MPE) can be estimated as the ratio of the Predicted No Effect Concentration (PNEC) and the Predicted Environmental Concentration (PEC). In this study, the MPE of 8 triazoles was assessed on the basis of predicted chemical properties. We quantified the relative importance of uncertainty in the predictions of chemical properties for the overall uncertainty in the MPE. Physicochemical properties and toxic concentrations were predicted with quantitative structure-activity relationships (QSARs). Half-live categories based on chemical structure, combined with water-soil and water-sediment extrapolation, were used to predict environmental half-lives in water, soil and sediment. Parameter uncertainties were treated as probability distributions, and propagated by Monte Carlo simulations. The 90% confidence interval of the MPEs was typically four orders of magnitude. The uncertainty of the MPEs was mainly determined by uncertainty in biodegradation rates and soil sorption. Uncertainty in toxic concentrations was also relevant, but to a smaller extent. This implies that the reliability of the MPE predictions for triazoles can be improved particularly by including experimental data for biodegradation and sorption to soil.

Dr. Marc Brandt

Umwelt Bundesamt, Germany

Marc Brandt has studied Chemistry at the Humbolt-Universität Berlin from 1998 to 2003. From 2003 to 2009 he worked in the quantum chemistry group of Professor Sauer at the Humboldt University. He received his PhD in Physical and Theoretical Chemistry for his work on „DFT-calculations on selective oxidation reactions of propane and methanol with supported vanadia catalysts on silica“ in 2008. Marc Brandt works for of the Umweltbundesamt in Dessau-Rosslau, Germany, in the unit „Chemicals“ since May 2009. His work deals with the implementation of the Chemical Regulation REACH. The main focus of his work is the identification and work on substances in need of further environmental regulation.

UBA LESSONS OF USING QSAR MODELS WITH RESPECT TO REACH

Abstract: In this presentation some of the experiences the German UBA had with the use of QSAR-methods in the framework of the REACH regulation will be discussed. The first focus will be laid on the experiences with QSAR results used in the registration dossiers of substances under REACH. The second focus will highlight some of the cases where UBA uses QSAR in its regulatory work. Here some examples will be given on the use of QSAR for screening purposes and for the support of UBA regulatory proposals under REACH. Finally a first draft for an alternate form of documentation of QSAR results will be presented.

Dr. Tom Aldenberg

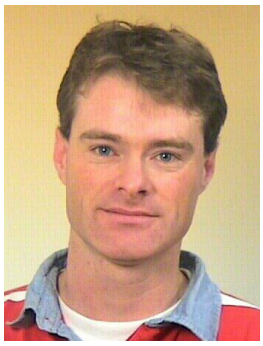
RIVM, Bilthoven, The Netherlands.

Tom Aldenberg has been working as a biomathematician for over 30 years. He graduated as a fisheries biologist at the University of Amsterdam and studied Theoretical Biology and Applied Mathematics. In the first half of his career, he specialized in ecosystem modeling: nutrient and species dynamics in eutrophied lakes, and trophic transfers of toxicants in aquatic and terrestrial foodwebs. In the second part of his career, attention shifted to Species Sensitivity Distribution (SSD) modeling, a statistical technique involving Bayesian statistics, to derive Hazardous Concentrations and Fraction of species Affected from species toxicity data. He worked on Probabilistic Environmental Risk Assessment and participated in CEFIC, EFSA, and EUFRAM EU-based projects by contributing techniques to estimate Expected Risk. Expected Risk is an improvement of the Risk Characterization Ratio (RCR), which is the basis of REACH-based Guidance to evaluate the risk of chemicals. Recently, he has been participating in the EU projects: OSIRIS and CADASTER. In OSIRIS he has built models for analyzing the information content and decision making in Repeated Dose toxicity studies, and has developed models for categorical data in order to quantify the statistical Weight-of-Evidence in Integrated Testing Strategies (ITSs) of Mutagenicity, Carcinogenicity, Skin Sensitization. Several co-authored publications have been submitted. In CADASTER, he is studying methods to build SSDs from QSAR-generated species data. This introduces a hierarchy of uncertainty layers that requires specialized statistical techniques, including Bayesian statistics.

USING SSD APPROACH TO QUANTIFY UNCERTAINTY FROM QSAR ESTIMATES OF EFFECTS DATA – EXAMPLES FROM THE CADASTER CLASSES

Abstract: Species Sensitivity Distributions (SSDs) are mostly univariate statistical distributions for the variability of the toxicity thresholds of different biological species. This very simple model, often on the basis of the Normal (Gaussian) distribution, can be used to derive Hazardous Concentrations for a small fraction of unprotected species, and estimate the Fraction of Species Affected at given exposure concentrations. One of the weak points of the basic SSD model is that the species data are taken without error. Generally, these data derive from dose-response studies, making this claim questionable. In the CADASTER project, some or all of the species toxicity data are estimated from QSARs, which is compounded by the fact that one often has the standard number of three species only. The QSAR models are evaluated on training data involving covariates (phys-chem, descriptors, etc.) that drive the regressions. This adds several sources of uncertainty: due to the uncertainty in the coefficients and the order of the (linear) model fitted; due to the input covariate value(s) of the test substance; due to the predictive uncertainty of the model estimate and residual data; and due to the uncertainty of the (e.g. Normal) SSD fitted to the estimated species sensitivities. We present a series of hierarchical and non-hierarchical models to evaluate the uncertainties involved and to estimate the propagation of uncertainty to estimates of the ucertainty of the Hazardous Concentration.

Dr. Emiel Rorije
RIVM, The Netherlands



Emiel Rorije graduated in (theoretical) chemistry (1992), has been working on (toxicological) QSAR evaluation and development his whole career; in academia (University of Utrecht), government (RIVM) as well as industry (BASF), mostly in EU and BMBF (Germany) financed research projects. Ecotoxicology, metabolism (prediction) and (bio)degradation were the main topics of interest at BASF, whereas his current work (2005-, RIVM) focuses on the evaluation and development of human toxicological structure-activity models (skin irritation/corrosion, sensitization, reproductive and developmental toxicity). In general alternatives for in-vivo animal testing, as well as ecotoxicological model development (PBT analysis, development of a priority scoring function for PBT and Long Range Transport potential) are his working area. He was recently involved in the EU FP6 project "OSIRIS" (2008-2011) where the focus was on Integrated Testing Strategies / Weight of Evidence for Skin Sensitization. He has been playing an instrumental role in the retrospective evaluation of the multi-generation reproductive toxicity testing protocol supporting the introduction of the Extended One-Generation Reproductive Toxicity study (EOGRTs) for the OECD.

READ ACROSS ESTIMATES - UNCERTAINTY IN THE RISK ASSESSMENT FOR THE CADASTER CLASS OF FRAGRANCE SUBSTANCES

Abstract: Uncertainty in QSAR-estimated properties for use in probabilistic Risk Assessment can be extracted from the uncertainty of the underlying data set. However, the number of established QSAR models is limited, and will not cover all possible data gaps that might accor in risk assessment of substances. Within CADASTER one of the classes of substances selected to make risk assessment for using estimated properties are Fragrances. In contrast to the other three classes (PBDE, PFC and (benzo)Triazoles, this class is not defined by similar chemical structures. Fragrances can range from simple aliphatic substances to substituted poly-aromatic ring systems with all kinds of functional groups. Such a structurally diverse class of substances is not very suitable for targeted QSAR development. In the European chemicals regulation REACH, a separate possibility has been introduced to estimate properties of a substance by assuming similar behaviour of (structurally) closely related compounds. This approach is called Read Across. For several different fragrances the concept of Read Across is presented, with a simple

methodology to derive an associated uncertainty in the Read Across estimate which can be propagated in a probabilistic Risk Assessment.

Dr. Andrew Worth, MA, MSt

Joint Research Center, Bologna, Italy

Dr Andrew Worth is a senior scientific officer at the European Commission's Joint Research Centre (JRC) in Italy, where he leads the Computational Toxicology and Modelling Group within the JRC's Institute for Health & Consumer Protection (IHCP). Dr Worth has degrees in Physiological Sciences and in Linguistics from Oxford University, and a PhD in Computational Toxicology from Liverpool John Moores University. He has over 100 publications in the area of predictive toxicology, and has a particular interest in the development and assessment of computational methods and their application in the regulatory assessment of chemical safety. In addition to projects funded under the EU Framework Programme, Dr Worth regularly contributes to the activities of the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), the Organisation for Economic Cooperation and Development (OECD), as well as the European branch of the International Life Sciences Institute (ILSI EU). Dr Worth is a member of the editorial boards of Alternatives to Laboratory Animals (ATLA) and SAR and QSAR in Environmental Research (SQER). In the period January-June 2012, he was a visiting scientist at the US Food and Drug Administration (FDA) within the FDA's Center for Food Safety and Applied Nutrition (CFSAN).

SUPPORTING CHEMICAL RISK ASSESSMENTS WITH COMPUTATIONAL METHODS: CHALLENGES AND PERSPECTIVES

Abstract: This presentation will describe the role of the Threshold of Toxicological Concern (TTC) approach in chemical risk assessment. The TTC approach is being increasingly applied in the safety assessment of chemicals in consumer products, such as food additives and cosmetic ingredients, but has not found widespread application in the safety assessment of industrial chemicals. One of the merits of the TTC approach is that it provides a framework for integrating a range of computational methods in chemical risk assessment, including (Q)SARs, chemical categories and read-across, as well as physiologically-based biokinetic modelling. Chemical space analysis, by means of chemoinformatic methods, also plays an important role in establishing the applicability of the TTC approach to chemical inventories of regulatory importance (e.g. food contact materials, cosmetics). Conclusions and recommendations will be drawn in relation to the need to promote the scientific and regulatory acceptance of the TTC approach.

Dr. Aafke Schipper

Radboud University Nijmegen, The Netherlands

Dr. Aafke Schipper is a post-doctoral research fellow at the Department of Environmental Science of the Radboud University Nijmegen (The Netherlands). Her expertise is in quantifying and predicting the impacts of multiple anthropogenic and natural pressures on ecosystems, in particular wildlife populations and species assemblages. In her graduate research she combined field data collection and modelling to assess the effects of various abiotic factors (hydrology, land use and soil contamination) on plants, arthropods, birds and mammals in floodplain ecosystems. She was awarded the PhD degree at the Radboud University Nijmegen in 2011. As a post-doctoral research fellow she is extending her research beyond floodplains to further improve the understanding and prediction of species responses to multiple abiotic drivers. Based on her research activities so far, she has authored nearly 20 peer-reviewed scientific papers

MODELLING THE COSTS OF CHEMICAL IMPACTS ON WILDLIFE POPULATIONS: THE CASE OF PEREGRINE FALCONS (FALCO PEREGRINUS) EXPOSED TO PBDES

The general denial of ecosystem goods and services in decision-making processes has raised increasing concern during the past decades. This has brought about a wealth of attempts to put economic value on ecosystem properties and functions. Yet, very few studies have assessed the costs of ecosystem impairment due to chemical pollution. We developed an approach to calculate the costs of chemical impacts on wildlife populations. Quantitative exposure-response relationships are combined with a wildlife demographic model to compute the impacts of chemical substances on the equilibrium size of the population. Subsequently, cost estimates are obtained by quantifying the number of captive-reared individuals needed per year in order to maintain a user-defined equilibrium population size at a given pollution level. Using long-term monitoring data, we applied our approach to calculate the costs associated with the impacts of polybrominated diphenyl ethers (PBDEs) on a population of peregrine falcons (Falco peregrinus). In this presentation we will outline the approach and present the results of the peregrine falcon case study.

Mr. Pantelis Sopasakis

National Technical University of Athens, Greece

Pantelis Sopasakis received his Diploma in Chemical Engineering in 2007 and his Master's degree in Applied Mathematics – with scepial emphasis on Mathematical Analysis and Differential Equations – in 2009 from the National Technical University of Athens, Greece. He has participated in the EU research project "OpenTox" as a research associate and he was appointed as a Research Fellow in the Helmholtz research centre in Munich, Germany under a Marie-Curie scholarship.
He is currently working on his Ph.D. thesis on Modeling and Control of Biological and Physiological Systems in NTU, Athens. His research interests include MPC algorithms, Impulsive Control Systems, Optimization, and Machine Learning algorithms while he has published a number of relevant scientific articles.

STATISTICAL INFERENCE WEB TOOL FOR THE ENVIRONMENTAL RISK ASSESSMENT USING QSAR MODELS

Statistical Inference methodologies and QSAR/QSPR models are used to answer key questions in environmental cheminformatics. The whole setting leads to a statistical inference mechanism that can be used to assess the environmental damage that can be possibly caused by the emission of certain chemicals to the ecosystem. The computational tool for this calculation has been implemented as a RESTful web service and a user interface has been set up to allow end-users to easily access the functionality offered. A Monte-Carlo simulation is performed and the user is returned a probability distribution function (PDF) for the environmental concentration, the persistency and the Long-Range Transport (LRTP).

Dr. Mike H I Comber, BA
Mike Comber Consulting, Belgium

Mike Comber has over 40 years of experience in the chemical/petrochemical industry and has been involved for much of this time in international groups examining the fate and effects of chemicals. He has managed teams of shift analysts, ECETOC Work Groups and Industry research programmes. He has been involved in the assessment of the state of the science in risk assessment, modelling techniques and alternative technologies. His involvement in work groups has covered OECD, EU (both new and existing substances and REACH RIPs), international research teams and Industry activities.
Mike is supporting Industry businesses by helping them obtain environmental data for risk/hazard assessment of products and processes, for Global registration programmes. He has developed skills in the area of risk assessment – hazard, PBT identification, fate and emission assessments and alternative methodology including category formation, read-across, (Q)SAR and in-vitro methodology.

Poster Abstracts

QSAR / QSPR modeling

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PERFORMANCE, RELIABILITY AND ROBUSTNESS - A COMPARISON OF SEVERAL EXPERIMENTAL DESIGN STRATEGIES

Authors: Stefan Brandmaier and Igor V. Tetko

Keywords: Experimental design, QSAR modeling, statistical evaluation

Abstract: The goal of the design of experiments is to reduce a large collection of relevant instances to a smaller set of representative and informative instances. Thereby experimental design is an adequate way to efficiently manage resources and to save costs in experiments, aiming to systematically explore the space of interest. The selected instances are usually experimentally measured and afterwards used, to build a statistical model on them. Apart from a good performance, reliability and robustness, both against small variations in the dataset and structural outliers are required from that model. A variety of approaches aiming to realize a meaningful selection is available, but for chemical applications, they all work in the descriptor space.
We developed two adaptive approaches for a representative subset selection and compared it to several commonly used experimental design strategies. Like Bayesian approaches, adaptive approaches take information about the target property into consideration, but instead of using preliminary available information, they make use of the accumulating information, that is gathered in a stepwise procedure. The adaptive approaches we implemented combine an iterative refinement of the descriptor space with known sampling concepts, like similarity and dissimilarity selections. We evaluated the approaches on a variety of chemical datasets and our results (see Fig. 1) show, that stepwise approaches can significantly improve the performance of a selection and the resulting models. Furthermore, they provide a higher adaptiveness to small variations in the dataset, which makes them more capable of structural outliers, than the classic approaches. Additionally, we found indications, for a correlation between the flexibility of a selection approach and the balance between the performance and the reliability of the resulting model.

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QSAR MODELING OF THE ANTIISOPRENALINE ACTIVITY OF POTENTIAL β-BLOCKERS

Authors: Katarína Boronová, Jozef Lehotay and Ružena Čižmáriková

Keywords: QSAR, antiisoprenaline activity, aryloxyaminopropanol derivatives, artificial neural network, support vector machine

Abstract: The aim of this work is designing of QSAR models for derivatives of aryloxyaminopropanol using advanced chemometrical techniques. The properties of these compounds predestinate them as potential betablockers; they exhibit strong pharmacological

effects and might be used in the treatment of various cardiovascular diseases. β-blockers are drugs have a chiral structure with a single stereogenic centre.
Antiisoprenaline activity, pA2, selected as the target variable, was predicted the mentioned kind of compounds by means of thoroughly selected descriptors provided by the applied Dragon software. The most important type of descriptors were constitutional indices, molecular descriptors, topological indices and information indices. For calculation and validation of efficient QSAR models different modelling methodologies were applied based on ANN (artificial neural network) and SVM (support vector machine) techniques. Both methods exhibit high ability for successful prediction of the atiisoprenaline activity of the studied molecules.

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DEVELOPMENT OF QSAR MODEL PREDICTING THE PET INHIBITORY ACTIVITY FOR THE SET OF FUROPYRROLE DERIVATIVES

Authors: Peter Nemecek and Renata Gasparova

Keywords: PET inhibitory activity, artificial neural networks, genetic algorithm

Abstract: The aim of this work is a QSAR study of furopyrrole derivatives exhibiting biological activity- inhibition of photosynthetic electron transport (PET). Model development process included utilization of modern optimization tools, such as genetic algorithms (GA) and artificial neural networks (ANN). The number of input descriptors was reduced as a crucial step of QSAR modelling. Molecular descriptors were calculated by software Dragon and their optimal subset was selected by GA or sensitivity analysis from ANN. Both reduction approaches were compared according the prediction ability of the developed models. From the amount of 4885 descriptors available in Dragon, just 37 were selected for the final QSAR model. Prediction ability of developed models was evaluated by QF32, the predictive squared correlation coefficient proposed by Todeschini. GETAWAY descriptors, 2D Autocorrelations and Drug like indices were proved as the most suitable groups of descriptors related to the biological activity. In the final phase of the QSAR study an 18 new derivates of furopyrrole (not yet synthesised) were suggested and their expected PET inhibitory activity was predicted by the best developed QSAR model (QF32=0,980).
Acknowledgement: This study was supported by the Slovak grant agency VEGA-1/0233/12 and FPPV-21-2012.

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MODELING THE α-GLUCOSIDASE INHIBITION BASED ON A 3D-MORSE APPROACH AND MACHINE LEARNING TOOLS

Authors: Khairedine Kraim, Djameleddine Khatmi, Youcef Saihi and Fouad Ferkous

Keywords: 3D-MoRSE, QSAR, DRAGON 6, machine learning, xanthone and curcuminoid, α-glucosidase inhibitors

Abstract: The α-glucosidase enzymes (EC 3.2.1.20, 3.2.1.10, 3.2.1.48 and 3.2.1.106) have drawn a special interest of the pharmaceutical research community since it was revealed that the inhibition of its catalytic activity led to the retardation of glucose absorption and the decrease in postprandial blood glucose level.

This indicates that the effective α-glucosidase inhibitors may serve as chemotherapeutic agents for clinic use in the treatment of diabetes, hypertension, dyslipidemia, obesity and cardiovascular diseases inpatients with metabolic syndrome.
Quantitative structure–activity relationship (QSAR) models are useful in understanding how chemicals structure relates to the biological activity of natural and synthetic chemicals and for design of newer and better therapeutics.
In the present study, we have selected dataset composed of 57 molecules derived from two natural and promising scaffolds: xanthone and curcuminoid. The inhibitory of these derivatives over the α-glucosidase enzyme was expressed by the cytotoxicity IC50.
A several machine learning methods (MLR; ANN; SVM; GA) have been applied in combination with 3D Molecule Representation of Structures Based on Electron Diffraction descriptors (3D-MoRSE), on DRAGON 6 software, to modeling the inhibitory activity ofα- glucosidase with dataset composed of 57 molecules derived from the xanthone and cucumioids as two natural promising scaffolds.
The models obtained were capable of describing over 80.50% of the variance in the experimental activity of 45 analogues of these compounds with the use of the mentioned approaches and dataset. The predictive activity of the models was evaluated by means of external validation set and the Y- randomization technique, and its structural chemical domain has been verified by the leverage approach. In comparison with other descriptor classes on DRAGON 6, the model relative to the 3D- MoRSE descriptors was considered as the best.

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IN SILICO PREDICTION OF INTERNAL TTC

Authors: Falko Partosch, Ralf Stahlmann and Ursula Gundert-Remy

Keywords: Internal TTC, Munro, ELINCS, in silico

Abstract: The TTC approach is a non-animal tool for risk assessment. Recently EFSA has published a Scientific Opinion on Threshold of Toxicological Concern (TTC) (EFSA Journal 2012;10(7):2750 [103 pp.]). The TTC value which is the lower 5th percentile of an empirical distribution of NOAEL/safety factor of 100 is used for risk assessment purposes in the absence of data on a specific chemical. This approach has been helpful in some cases. However the application of the approach to non-oral exposure is hampered by route to route extrapolation. In vitro methods are available (OECD TG 428) for testing dermal absorption, thus allowing for determination of internal dose. TTC values are derived from studies with external dosing, e.g. Munro database, European List of Notified Chemical Substances (ELINCS). Therefore direct comparison of internal exposure by the dermal route with external TTC values seems appropriate. We used an in silico approach to convert external NOAELs to internal NOAELs in order to derive an internal TTC value.
Physicochemical properties (pKa, logPow, molecular weight) were taken from documents (ELINCS) or published sources. If not available we calculated with the software program ACD Percepta (ACD Labs, Ontario, Canada). The fraction absorbed was also calculated with the software program ACD Percepta. NOAELs for 613 chemicals were taken from the Munro database and for 556 chemicals from the ELINCS database. Multiplying the NOAELs by the fraction absorbed results in internal NOAELs we constructed the empirical distribution of the internal NOAELs of both databases and determined the lower fifth percentile in order to derive an internal TTC value after adjustment using the traditional safety factor of 100. The TTC value based on the data for the external dosing is 2.5 µg/kg/d and for the internal dose 0.07 µg/kg/d based on the whole Munro database. The values for the ELINCS database are 21 and 0.015 µg/kg/d.
High variability in the ratio between internal and external TTC is observed which in addition is different when different databases are looked at. Overall the internal TTC is remarkably lower than the external TTC. Hence, for route to route extrapolation it is necessary to use internal TTC

values. The same applies for the definition of a negligible absorption as mentioned in the REACH legislation.

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PREDICTIVE UNCERTAINTY MAY BE IMPROVED BY EFFICIENT USE OF EXPERIMENTAL INFORMATION FOR QSARS – WEIGHTING VERSUS AVERAGING IN LINEAR REGRESSION

Authors: Marit Marsh Strömberg and Ullrika Sahlin

Keywords: Regression, experimental uncertainty, predictivity, information

Abstract: Experimental values of physiochemical properties or activities used to build QSARs are subject to both uncertainty and variability, which more or less affect the uncertainty in QSAR predictions. One source of variation comes from having experiments done at different labs, or at different times, and with different practices. QSARs are mostly developed by using only one value for each compound even though there may be more than one experimental value for a given compound. Here we investigate whether an inclusion of more information, i.e. of multiple point estimates, of endpoint values instead of averages may enhance predictive performance of a QSAR regression. Regressions built on averages for each compound are compared to weighted regressions built on all experimental values where each weight is assigned such that all compounds are given equal weights in total, but also on regressions build on all experimental values. Predictive performances were compared for QSAR data from models in Papa et al. (2008). For two of the four models the weighted model showed an improved predictivity as compared to the average model indicating that uncertainty in QSAR predictions may be improved by using weighting instead of averaging. In order to make general conclusions a simulation experiment was done on artificially generated QSAR data sets. The comparisons between modeling approaches were done on models judged as having good predictivity on average, which were those with R^2>0.6 for the training data, and where at least one of the approaches succeeded reasonably well in assessing the predictive uncertainty. None of the three modeling approaches had always better predictive performance than the others, and the difference in predictive performance as judged by Kullback-Leibler divergences were mostly found within the "barely worth mentioning" zone. Weighted linear regression performed on average worse than the others and the performance got worse with increasing expected number of experimental values per compound (p-value less than 0.001). The model using all data points instead of only averages had a slightly lowered performance with increasing expected experimental values as well (p-value less than 0.01). Neither the number of compounds per descriptor nor expected total variance influenced the relative performances of the models. The general conclusion is that there is no specific model type that is always in favor in terms of model predictivity, and which approach that is best depends on the specific data set. Therefore it could be worthwhile to consider all three types when developing a QSAR by linear regression.

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APPLICATION OF DESIRABILITY ANALYSIS FOR FINDING THE OPTIMAL LEVELS OF THE MOLECULAR DESCRIPTORS IN QSAR MODELS

Authors: Vesna Rastija, Sonja Nikolić and Vijay H. Masand

Keywords: Desirability, analysis, inhibition, antimalarial

Abstract: Desirability analysis was performed in order to find a set of levels of the predictor variables (molecular descriptors) that maximizes the desirability of the responses on the dependent variable (studied inhibitory activities). The best QSAR models for the inhibition of α-glucosidase by polyphenols and anti-malarial activity of synthetic tri-pyrrole derivatives (prodiginines) were used for analysis.
Predicting responses on the dependent variable were obtained by fitting the observed responses using an equation based on the levels of the independent variables (descriptors). Subsequently, the levels of the independent variables that simultaneously produce the most desirable predicted responses on the dependent variable were found. Overall desirability was computed as the geometric mean of the individual desirability.
Desirability profiles consist of a series of graphs, one for each independent variable, of overall desirability scores at different levels of one independent variable, holding the levels of the other independent variables constant at specified values. Inspection of the desirability profiles shows which levels of the predictor variables produce the most desirable predicted responses on the dependent variable. Spline method was selected for fitting the desirability function and contours maps. The contour plots show the levels of overall response desirability produced in different regions of the plane defined by pairs of independent variables. Each region of the plane represents a different combination of the levels of the two variables.
Desirability analysis was carried out with STATISTICA 7.0.

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PRIORITIZATION OF EMERGING POLLUTANTS ON THE BASIS OF CHEMICAL STRUCTURE

Authors: Simona Kovarich, Ester Papa, Barun Bhhatarai, Stefano Cassani and Paola Gramatica

Keywords: Prioritization, design of experiments, QSAR, emerging pollutants

Abstract: The prioritization of hazardous chemicals is a useful procedure for the identification of critical substances and the optimization of experiments. This procedure became of particular relevance within the EU-REACH regulation, which encourages the minimization of animal testing also by the use of alternative in vitro and in silico methods. Among these methods quantitative structure-activity relationships (QSARs) can predict missing data for the unknown activities and properties necessary to prioritize existing or not yet synthesized chemicals. The prioritization of four classes of emerging pollutants (brominated flame retardants, fragrances, perfluorinated compounds and (benzo)triazoles) is one of the topics of the FP7 European project CADASTER (CAse studies on the Development and Application of in-Silico Techniques for Environmental hazard and Risk assessment). The final goal of the project is to exemplify the integration of information, models and strategies for carrying out hazard and risk assessments for large numbers of substances, organized in the four representative chemical classes.
The prioritization applied to CADASTER chemicals was crucial to focus the experimental design on critical substances on the basis of their chemical structure and potential ecotoxicological hazard.

The aim of this poster is to summarize the prioritizations performed within CADASTER project, also by applying "ad hoc" QSAR/QSPR models developed so far (WP3) for the four classes of compounds under investigation. Different prioritization procedures were applied to over 1000 chemicals by combining, through different approaches (similarity analysis, multivariate ranking methods, factorial design), the structural information, encoded in theoretical molecular descriptors, and the data (experimental or predicted) available for different toxicological and ecotoxicological endpoints. Chemicals belonging to the ECHA pre-registration list were also studied in the prioritizations. Priority compounds were suggested for focusing the experiments executed by other CADASTER partners (WP2).

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QSAR AND QSPR MODELS FOR EMERGING POLLUTANTS: WP3 ACTIVITIES WITHIN THE FP7 EUROPEAN PROJECT CADASTER

Authors: Simona Kovarich, Barun Bhhatarai, Ester Papa, Magnus Rahmberg, Sara Nilsson, Tomas Oberg, Nina Jeliazkova, Nikolay Kochev, Ognyan Pukalov, Wolfram Teetz, Stefan Brandmaier, Igor V. Tetko and Paola Gramatica

Keywords: QSAR, alternative methods, REACH, emerging pollutants

Abstract: The EU-REACH regulation encourages the use of alternative in vitro and in silico methods in order to minimize animal testing, costs and time. Among these, quantitative structure-activity relationships (QSARs) represent a useful tool to predict unknown activities/properties for existing or even not yet synthesized chemicals. The development and validation of QSAR models for four classes of emerging pollutants (brominated flame retardants, fragrances, perfluorinated compounds and (benzo)triazoles is the central topic of Work Package 3 (WP3) within the FP7 European project CADASTER (CAse studies on the Development and Application of in-Silico Techniques for Environmental hazard and Risk assessment). The final goal of the project is to exemplify the integration of information, models and strategies for carrying out hazard and risk assessments for large numbers of substances, organized in the four representative chemical classes.
The aim of this poster is to summarize the WP3 activities within CADASTER project and the QSAR/QSPR models developed so far for the four classes of compounds under investigation. This modeling activity involved different project partners in universities and research institutes across Europe (University of Insubria, Linnaeus University, IVL Swedish Environmental Research Institute, Ideaconsult Ltd. and Helmholtz Zentrum München), and was realized by different modeling approaches.
For each class, ad hoc QSARs were developed for all the available experimental data (i.e. physico-chemical properties, environmental and mammalian toxicity) in order to characterize environmental behavior and activity profile of the chemicals. In agreement with the OECD principles for the validation of QSARs for regulatory purposes, all the proposed models were checked for their robustness, external predictivity and applicability domain.
QSAR predictions, together with structural analysis (e.g. similarity analysis and multivariate ranking methods), were used for the identification of priority compounds (also among the ECHA pre-registration list) to optimize the experimental testing to be performed in WP2.

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QSPR MODELS FOR PREDICTIONS AND DATA QUALITY ASSURANCES: MELTING POINT AND BOILING POINT OF PERFLUORINATED CHEMICALS

Authors: Barun Bhhatarai, Wolfram Teetz, Tomas Öberg, Nina Jeliazkova, Nikolay Kochev, Ognyan Pukalov, Igor V. Tetko, Simona Kovarich, Ester Papa and Paola Gramatica

Keywords: QSAR, REACH, perfluorinated compounds, consensus

Abstract: Quantitative Structure Property Relationship (QSPR) studies on physico-chemical properties of per- and polyfluorinated chemicals (PFCs) are presented. The experimental data for the PFCs for the Melting Point and the Boiling Point used for developing the QSPR models were selected from Syracuse PhysProp database1 and from other literatures. The data sets were split into training, for model development, and prediction sets, for predictivity check, in two different ways: a) by random selection of response values, and b) by structural similarity verified by Self Organizing Map (SOM). This helps to propose reliable predictive models developed on the training set and externally verified on the prediction set (Test I). Multiple linear regression (MLR), partial least squares (PLS) and (ANN) were used for QSPR modeling. Individual models based on 0D-2D dragon descriptor, E-state descriptors and fragment based descriptors and their prediction as well as consensus model predictions will be presented and compared.
In addition, the predictive performances of the developed models were verified on a blind external validation set (EV-set) prepared from experimental values available from PERFORCE database2. This database contains only long chain perfluoro-alkylated chemicals, particularly monitored by regulatory agencies like US-EPA3 and EU-REACH4. QSPR modeling using different approaches, internal and external validation on two different prediction sets and study of applicability domain highlights the robustness and higher accuracy of the proposed models. Finally, Melting Point for additional 397 PFCs and Boiling Point for 364 PFCs for which experimental measurements are unknown were predicted, verifying their applicability domain.

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QSAR MODELS FOR AQUATIC TOXICITY OF TRIAZOLES AND BENZOTRIAZOLES: WP3 RESULTS WITHIN THE FP7 EUROPEAN PROJECT CADASTER

Authors: Stefano Cassani, Ester Papa, Simona Kovarich, Partha Pratim Roy, Magnus Rahmberg, Sara Nilsson, Nina Jeliazkova, Nikolay Kochev, Ognyan Pukalov, Igor Tetko and Paola Gramatica

Keywords: QSAR, alternative methods, REACH, emerging pollutants

Abstract: Under the EU-REACH regulation, there is an urgent need to fill data gaps as well as reduce the costs and number of animals sacrificed for testing. In this context alternative in-silico techniques, like quantitative structure-activity relationships (QSARs), represent a valid tool for the prediction of missing information, to be used as support tools for chemical risk assessment (RA). The integration of QSAR in RA procedures is one of the goals of the EU-FP7 project CADASTER. The project is focused on four classes of emerging pollutants, including triazoles and benzotriazoles ((B)TAZs). These chemicals are synthetic molecules with industrial and pharmaceutical uses. (B)TAZs have been found distributed throughout the environment, mainly in water compartments, where they are cause of concern for their possible effects on aquatic organisms.
This study summarizes the QSAR models for the aquatic toxicity of (B)TAZs, developed within the CADASTER project by the different partners. The presented QSARs were realized by different

modeling approaches (e.g. MLR-OLS, PLSR, Kohonen Neural Network) starting from theoretical molecular descriptors calculated by commercial and freely available software (DRAGON, PaDEL-Descriptor, CADASTER web). The studied end-points were EC50 (72h) in Pseudokirchneriella subcapitata, EC50 (48h) in Daphnia magna, and LC50 (96h) in Onchorhynchus mykiss, since these data for algae, zooplankton and fish are among the key data required for risk assessment of chemicals. QSARs were checked for their goodness-of-fit, robustness, predictivity and applicability domain, in agreement with OECD principles for the validation of QSARs for regulatory purposes. The proposed models showed high robustness (range Q2LOO=0.70-0.88) and external predictive ability (range Q2ext=0.71-0.91). Additionally, predictions by consensus were obtained combining results from different models and approaches. Models were also applied for the screening of more than 300 (B)TAZs without experimental data, many of them included in the European Chemicals Agency (ECHA) pre-registration list and therefore to be registered under REACH. This screening allowed for identification of the most problematic compounds for the aquatic environment. Finally, a comparison with ECOSAR predictions showed a higher prediction accuracy of the local models developed within the CADASTER project.
Concluding, this work highlights the utility of QSARs for the prediction of eco-toxicity data to be used under REACH for the hazard and risk assessment of chemicals, especially when dealing with specific chemical classes (like (B)TAZs). The importance of QSAR as a valid tool for screening and prioritization of pollutants is also stressed.

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DEVELOPING ROBUST CHEMICAL CATEGORIES FOR READ-ACROSS RELATING TO CHRONIC TOXICITY

Authors: Mark Cronin, Steven Enoch, Judith Madden, Mark Nelms, Przemyslaw Piechota and Andrea-Nicole Richarz

Keywords: Category formation, adverse outcome pathways, chronic toxicity

Abstract: Recently there has been a great deal of interest in the use of read across, from within rationally-derived chemical categories, as a non-animal alternative to predict toxicity. One method used to group similar compounds together, for the prediction of human organ level toxicity, is to consider the presence of reactive fragments that are associated with known mechanisms of toxicity e.g. reactive hepatotoxicity. Structural rules, fragments and properties, associated with specific mechanisms of toxic action have been identified and coded (either as SMARTS or CSRML) into a KNIME Workflow. Thus a chemical can be searched for a particular structural rule and then compounds with the same rules (and hence putative mechanism of action) can be identified. The same methodology can be applied, implicitly or explicitly, to the metabolites of the chemicals of interest, where it is the metabolite rather than the parent that is responsible for the toxicity. Relevant databases can be searched using the KNIME Workflow and toxicological data retrieved for chemicals within the category. The Adverse Outcome Pathway (AOP) approach has been promoted as a means to identify and verify relevant mechanisms of action. AOPs record information relating to the perturbation of biological systems (for example disruption of biochemical pathways) that can result in an adverse effect. Targeted in vitro or in chemico assays can help to identify areas of chemical space that are associated with a specific AOP. This can be used to develop rationally-derived chemical categories associated with the adverse outcome. This study exemplifies the use of such a workflow in the prediction of organ-level toxicity. The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n° 266835 and from Cosmetics Europe. The funding of the IMI-JU eTOX prject (grant agreement no. 115002) is gratefully acknowledged.

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MODELLING THE ACUTE AQUATIC TOXICITY OF SULFUR-CONTAINING COMPOUNDS: IDENTIFICATION AND PROFILING OF ELECTROPHILES

Authors: Mark Cronin, Terry Schultz and Andrea-Nicole Richarz

Keywords: Acute aquatic toxicity, QSAR, profiling

Abstract: Covalent protein binding is an important molecular initiating event (MIE) for a number of toxicological endpoints, e.g. skin sensitisation, mutagenicity and excess aquatic toxicity above narcosis. The computational prediction of the protein binding potential of a compound will therefore contribute to the toxicity assessment of the chemical. It thus allows for the rapid and inexpensive screening of new and existing chemicals for their toxic potential. The OECD QSAR Toolbox is a computational tool to group chemicals and make predictions of toxicity. Chemical profilers are used to assist in the grouping of chemicals. Protein binding profilers in the OECD QSAR Toolbox are a compilation of 2-D chemical fragments (known as structural alerts), based on organic chemistry reactions, that are known to bind covalently to biological proteins. Most often these reactions target either the thiol (SH) moiety of cysteine or the primary amine (NH2) moiety of lysine in proteins in the target organism. Using the protein binding profilers in version 3.0 of the OECD QSAR Toolbox, a series of sulfur-containing industrial organic compounds were profiled for protein binding potential and reaction mechanism as well as their protein binding potency. They belong to several chemical classes: mercaptans (RSH), sulfides (RSR'), disulfides (RSSR'), sulfoxides (RS(=O)R'), sulfones (RS(=O)(=O)R'), sulfonates (ROS(=O)(=O)R') and sulfates (ROS(=O)(=O)OR'). In order to verify the in silico prediction of toxicity based on structural alerts and the applicability domain for sulfur-containing compounds, 27 chemicals were tested experimentally with the in chemico glutathione (GSH) and in vitro Tetrahymena pyriformis (TETRATOX) assays. In silico prediction identified which sulfur-containing chemicals were reactive or non-reactive in the GSH assay and if they would exhibit toxicity in excess of baseline in the TETRATOX assay. The experimental data show that the in silico profiler predictions were generally correct for all chemical classes where testing was possible. Importantly, the in silico profilers were also able to distinguish between reaction mechanisms associated with the relative degree of (un)saturation in the compounds. The funding of European Chemicals Agency (ECHA) Service Contract No. ECHA/2008/20/ECA /203, from the European Community's 7th Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n°266835 and from Cosmetics Europe is gratefully acknowledged.

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EXTERNALLY PREDICTIVE QSAR MODELS: THRESHOLDS OF ACCEPTANCE BY VARIOUS EXTERNAL VALIDATION CRITERIA AND CRITICAL INSPECTION OF SCATTER PLOTS

Authors: Nicola Chirico, Ester Papa and Paola Gramatica

Keywords: QSAR, external validation, statistical criteria, thresholds

Abstract: The evaluation of linear regression QSAR models performances, both in fitting and external prediction, is of pivotal importance. In the last decade different external validation parameters have been proposed: Q2F1 (Shi), Q2F2 (Schuurmann), Q2F3 (Todeschini), average r2m (Roy) and the Golbraikh –Tropsha (GT) method. Recently, the concordance correlation coefficient (CCC, Lin) has been proposed by our group as an external validation parameter to be used in QSAR studies. In our recent work, published in 2011 on JCIM, we have shown that,

comparing with the commonly used acceptance thresholds (Q2Fn=0.6, average r2m=0.5), the concordance correlation coefficient threshold value (=0.85) is usually the most restrictive in the acceptance of QSAR models as externally predictive. This fact suggested that the CCC could be used as the preferred validation parameter in a precautionary approach, if the aim of QSAR developers is to have the smallest differences among the experimental data and the predictions of the external data set.
In this new work, we have studied and compared the general trends of the various criteria in dependence of different possible bias in the external data distributions (scale and location shifts), by means of a wide range of different simulated scenarios. This study highlighted, also by visual inspections of the experimental vs. predicted plots, some problems related to a few criteria; in particular, average r2m, if based on the proposed cut-off, could be prone to accept also not predictive models. This analysis allowed also to propose recalibrated, and inter-comparable, new thresholds for each criteria in the definition of a QSAR model as externally predictive. Two additional relevant topics emerged from the analysis of the results: 1) the scatter plot of the external predictions must always be evaluated and 2) the root mean squared error (RMSE) must also be calculated, as it is usually done in the good QSAR practice. In fact, we have verified that the sensitivity of the various validation criteria to RMSE often differs.
An additional important topic, here considered and applicable only to CCC, was to check by hypothesis test if the value of the calculated CCC is statistically significant. This procedure allowed, consequently, to determine also the minimum acceptable size of the external data set, an important point in QSAR studies, where the data set sizes are often small.

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COMPARATIVE MODELLING OF BIODEGRADABILITY DATA

Authors: Susann Vorberg and Igor V. Tetko

Keywords: Biodegradability, QSAR modeling, OCHEM

Abstract: Biodegradability is a crucial property to estimate a compounds long-term impact on the environment. This endpoint is difficult to model and one reason therefore is amongst others the lack and inconsistency of available experimental data.
We collected about 2500 measurements from sources, such as the CHRIP and ECHA database, as well as from a study derived by Chen et al. [1], cleaned them from ambiguities or duplicates and uploaded a final number of 1971 measurements to the Online CHEmical database and Modeling environment (OCHEM)[2]. The data is comprised of discrete values and additional continuous measurements and is freely available.
We applied several machine learning methods to the derived datasets. We used numerous descriptor sets to give an exhaustive overview of possible representations of the under- lying compounds and optimized the parameterization of the respective machine learning tools. Various elaborate approaches have been employed successfully to improve the per- formance of the initial models. After the exclusion of about 50 outliers with the most unrelieable predictions using applicability domain methods, the combination of descriptor sets and the inclusion of regression modelling, we achieved QSAR models at more than 87% balanced accuracy. Ongoing work is concerned with further analysis of underlying concepts explaining the relationship between characteristic compound properties and biodegradation.

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environ- ment (OCHEM): web platform for data storage, model development and publishing of chemical information.

21

BECOME ONE: UNIFIYING QSARS IN SOIL ECOTOXICOLOGY

Authors: Daniel Giesen and Kees C.A.M. van Gestel

Keywords: Soil ecotoxicology, risk assessment, polar vs. non-polar narcosis, chemical descriptors, liposome-water partition coefficient, bioavailability

Abstract: Two main factors constrained the unifications of Quantitative Structure-Activity Relationship (QSAR) toxicity models dealing with polar and non-polar compounds and different soils. First, established QSAR for non-reactive compounds distinguish between narcosis I (non-polar) and narcosis II (polar), which exhibit different toxicities when based on their respective LogKow, with the implication that polar compounds are more toxic. Secondly, freely dissolved bioavailable concentrations used in the models had to be estimated by using organic carbon-water partition coeffecients (logKoc) and the fraction of organic carbon in the soils. In order to resolve these limitation and optimize QSARs for risk assessment, compound membrane interactions, the liposome-water partition coefficient (logKlipw) and soil-specfic logKoc were determined for a subset of eight chlorobenzenes and 4 chloroanilines. Actual bioavailable concentration for the EC50 values for the effect on reproduction of Folsomia candida were measured with polyacrylate solid-phase micrextraction (SPME) and used in the QSAR instead of estimated concentrations. The QSAR corrected for the chemical descriptors effectively closed the gap between polar and non-polar narcosis, however, still distinguished the two soils. A single QSAR, predicting toxicity for all compounds in both soils, was only accomplishable after the incorporation of the measured concentrations and the total water volume in the respective soils as integral part of the test matrix.

22

COMPOUND LIPOPHILICITY AS A DESCRIPTOR TO PREDICT METABOLIC AFFINITY (KM) IN MAMMALS

Authors: Alessandra Pirovano, Mark A.J. Huijbregts, Isabel A. O'connor, Ad M.J. Ragas and A. Jan Hendriks

Keywords: Biotransformation, binding affinity, lipophilicity

Abstract: In bioaccumulation models, biotransformation is one of the processes decreasing the concentration of chemicals in an organism. The enzymatic action of metabolism involves two processes. Firstly, the chemical needs to reach the enzyme and bind with it; secondly, a catalytic reaction must take place. The binding of the chemical and its successive catalysis are described by two enzymatic parameters: the Michaelis constant (Km) and the maximum rate of the reaction (Vmax), respectively. Measured Km and Vmax data are lacking for many chemicals and species.
The aim of this study was to estimate the relationships between binding affinity, represented by 1/Km (1/μM), and lipophilicity, expressed by the octanol-water partitioning coefficient (Kow), for in vitro oxidations catalysed by alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), flavin-containing monooxygenase (FMO), and cytochrome P450 (CYP). The focus was on finding generic patterns of metabolism across enzymes. The knowledge of the underlying biochemical mechanisms is useful to further develop models for whole-body biotransformation.
For the regressions developed, 1/Km always increased with the Kow, as expected from the partitioning theory. The binding to FMO was not well correlated to the compound Log Kow,

possibly because of its different reaction mechanism involving a nucleophilic attack. If strong interactions such as covalent or ion bonds are important, distribution of chemicals is expected to be weakly related to their Kow. Good correlations were found for the substrates of ADH, ALDH, and CYP, after excluding specific classes of outliers. These correlations suggested that the enzyme affinity of the chemicals is driven by weak, in particular hydrophobic, interactions with these enzymes. The slopes of these regressions did not statistically deviate from the typical slope (ranging from 0.46 to 0.70) that correlates protein-water distribution (Log Kpw) and Log Kow.

23

PREDICTING THE ORAL UPTAKE EFFICIENCY OF CHEMICALS IN MAMMALS: EXTENSION TO THE HYDROPHILIC RANGE

Authors: Isabel Oconnor, Mark Aj Huijbregts, Alessandra Pirovano, Ad Mj Ragas and A Jan Hendriks

Keywords: Bioaccumulation, uptake model, hydrophilic compounds

Abstract: Environmental risk assessment requires models for estimating the bioaccumulation of untested compounds. So far, bioaccumulation models have focused on lipophilic compounds, and only few have included hydrophilic compounds. Our aim was to extend an existing bioaccumulation model to estimate the oral uptake efficiency of pollutants in mammals for compounds over a wide Kow range with an emphasis on hydrophilic compounds, i.e. compounds in the lower Kow range. Usually, most models use octanol as a single surrogate for the membrane and thus neglect the bilayer structure of the membrane. However, compounds with polar groups can have different affinities for the different membrane regions. Therefore, an existing bioaccumulation model was extended by dividing the diffusion resistance through the membrane into a outer and inner membrane resistance, where the solvents octanol and heptane were used as surrogates for each membrane region, respectively. The model was calibrated with uptake efficiencies of environmental pollutants measured in different mammals during feeding studies combined with human oral absorption efficiencies of pharmaceuticals. The new model estimated the uptake efficiency of neutral (RMSE=14.6) and dissociating (RMSE=19.5) compounds with logKow ranging from -10 to +8. The inclusion of the Khw improved uptake estimation for 33% of the hydrophilic compounds (logKow<0) (r2=0.51, RMSE=22.8) compared to the model based on Kow only (r2=0.04, RMSE=34.9), while hydrophobic compounds (logKow>0) were estimated equally by both model versions with RMSE=15.2 (Kow&Khw) and RMSE=15.7 (Kow only). The model can be used to estimate the oral uptake efficiency for both hydrophilic and hydrophobic compounds

Risk assessment

3

RANKING OF CONCERN FROM PERSISTENCE, BIOACCUMULATION AND TOXICITY IN THE ENVIRONMENT OF PHARMACEUTICALS AND PERSONAL CARE PRODUCTS

Authors: Sheyla Ortiz de García, Ruben Irusta Mata and Pedro Garcia Encina

Keywords: Pharmaceuticals and personal care products, QSAR, persistence, bioaccumulation, toxicity, ranking of concern

Abstract: A wide range of Pharmaceuticals and Personal Care Products (PPCPs) are present in the environment and many of its adverse effects are unknown. Therefore, the aim of this study was to estimate the persistence, bioaccumulation and toxicity potential, by using (US-EPA) Quantitative Structure - Activity Relationships (QSARs) models and databases, to generate, by means of Decision Analysis by Ranking Techniques (DART), a ranking of concern of ninety five PPCPs. Hormones, antidepressants (and its metabolites), blood lipid regulators and all personal care products, considered in this study were in highest levels of risk according to total and partial rankings. It is necessary further improvement and incorporate useful tools to environmental impact assessment of PPCPs, while cost and time in experimental evaluations are being optimized.

4

THE INFLUENCE OF UNCERTAINTY IN QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIPS ON PERSISTENCE AND LONG-RANGE TRANSPORT POTENTIAL: THE CASE OF POLYBROMINATED DIPHENYL ETHERS (PBDES)

Authors: M Sarfraz Iqbal, Laura Golsteijn, Tomas Öberg, Ullrika Sahlin, Ester Papa, Simona Kovarich and Mark A. J. Huijbregts

Keywords: Non-testing strategy, chemical regulation, risk assessment, uncertainty analysis, applicability domain

Abstract: In cases where experimental data on chemical-specific input parameters are lacking, chemical regulations allow the use of alternative methods to testing, such as in silico predictions based on Quantitative Structure-Property Relationships (QSPRs). QSPR predictions are often given as point estimates; however, little is known about to what extent uncertainties associated with QSPR predictions contribute to uncertainty in fate assessments. In this study, QSPR-induced uncertainty in overall persistence (Pov) and long-range transport potential (LRTP) was studied by integrating QSPRs into probabilistic assessments of five polybrominated diphenyl ethers (PBDEs), using the multimedia fate model Simplebox. The uncertainty analysis considered QSPR-predictions of the fate input parameters' melting point, water solubility, vapor pressure, organic

carbon-water partition coefficient, hydroxyl radical degradation, biodegradation, and photolytic degradation. Uncertainty in Pov and LRTP was dominated by the uncertainty in direct photolysis and biodegradation half-life in water. The remaining QSPRs, developed specifically for physico-chemical properties, had a relatively low contribution to uncertainty. Our findings suggest that the reliability of the ranking of PBDEs on the basis of Pov and LRTP can be substantially improved by developing better QSPRs to estimate degradation properties. This case study on QSPR-integrated fate assessment for PBDEs demonstrates the use of uncertainty and sensitivity analysis in non-testing strategies, and highlights the need for guidance when compounds fall outside the applicability domain of a QSPR.

5

RELIABILITY IN PREDICTIVE MODELS UNDER ALTERNATIVE TREATMENTS OF PREDICTIVE UNCERTAINTY – QSPRS IN CHEMICAL SAFETY ASSESSMENTS

Authors: Ullrika Sahlin

Keywords: Uncertainty, reliability, predictions

Abstract: In the absence of experimentally tested physicochemical endpoints, European chemical regulation REACH allows the use of non-testing strategies such as Quantitative Structure-Property Relationships (QSPR) to predict the required information. A QSPR may be more or less reliable for predicting a property of a chemical compound. Reliability ought to be higher for compounds inside the applicability domain of a QSPR and for which the model predict by higher accuracy. Quantitative measures of reliability support the decision on whether a model is reliable enough to use for prediction, but also to judge if a compound falls inside the applicability domain of a specific QSPR. The integration of non-testing strategies into decision calls for evaluated approaches to treat predictive uncertainty and thereby reliability of QSPR predictions. The practical impact of treatment of epistemic uncertainty on decision making was illustrated by asking if, and in what way, the reliability of QSPR for decision making is changed under alternative approaches to assess predictive uncertainty. Predictive uncertainty from a QSPR regression of melting point received alternative treatment based on posterior distribution by Bayesian modeling, estimates of predictive variance from re-sampling, and interval estimation by sensitivity analysis. A comparison of global and local reliability estimates showed that the Bayesian and re-sampling assessment of uncertainty gave similar judgments of reliability. Using more robust estimates such as Robust Bayes made it more difficult to distinguish between low and high reliability. The non-probabilistic treatment of predictive uncertainty had low similarity with the other reliability judgments. I have illustrated the practical impact of the treatment of epistemic uncertainty on decision-making by showing how uncertainty in predictions from QSPRs transfers to the judgment of compounds as being more or less inside the applicability domain of a predictive model.

PREDICTING CARCINOGENICITY, MUTAGENICITY AND REPRODUCTIVE TOXICITY BY AVAILABLE NON-TESTING TOOLS – HOW USEFUL ARE THESE FOR IDENTIFYING CHEMICALS OF CONCERN?

Authors: Aleksandra Rybacka, Christina Rudèn and Patrik Andersson

Keywords: Carcinogenicity, mutagenicity, reproductive toxicity, CLP, REACH, industrial chemicals, prioritization, expert system

Abstract: Industry is responsible for the risk assessment of industrial chemicals as regulated in the legislation REACH[1]. Based on Annex III in REACH, chemicals will be prioritized for further testing if they are being classified as carcinogenic (C), mutagenic (M) or toxic to reproduction (R) or are identified as persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB). In REACH the use of non-testing methods is encouraged, especially for the purpose of prioritization of the low volume chemicals. Existing studies[2,3,4,5] on the utility of non-testing approaches for predicting CMR properties do not focus on application of results for CLP[6] classification. In this study we focused on one criteria of Annex III and analyzed a number of in silico tools including (Q)SAR Toolbox, LAZAR, Toxtree, DEREK, CAESAR, VEGA and TEST on their use to predict various CMR related properties. In total 50 models were studied using 94 chemically diverse organic chemicals selected from the priority lists assigned by the Commission according to the Existing Substances Regulation[7]. Data on the models sensitivity, specificity and accuracy were calculated and compared. Furthermore, the chemicals were studied on a chemical map including European high and low production volume chemicals. This map, described in detail elsewhere[8], was constructed using PCA and a range of chemical descriptors and revealed that the studied chemicals are representative for current use industrial chemicals. The study showed accuracy for carcinogenicity up to 92 % for the best model, but significantly worse statistics for mutagenicity and reproductive toxicity. For certain models, a large share of compounds were defined as out of applicability domain. In particular this was observed for (Q)SAR Toolbox, where e.g. 88% of chemicals were classified as out of domain in the model predicting estrogen receptor binding. In addition, we found a group of compounds being predicted as false negatives by most models. The study proves that there is a need for improving available non-testing models especially for predicting mutagenicity and reproductive toxicity. One possible option to decrease the number of false positives and negatives may be to integrate available tools to derive consensus predictions.

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Social Events

Oktoberfest

The Munich Oktoberfest is the largest folk festival in the world and has its origin in the wedding ceremonies of crown prince Ludwig – later King Ludwig I. of Bavaria – with Princess Therese of Sachsen-Hildburghausen in the year of 1810. The citizens of Munich were invited to attend the festivities held on the fields in front of the city gates to celebrate the happy royal event. The fields were named Theresienwiese ("Theresa's meadow") in honor of the Crown Princess, and have kept that name ever since, although the locals have since abbreviated the name simply to the "Wies'n". Horse races in the presence of the Royal Family marked the close of the event that was celebrated as a festival for the whole of Bavaria. The decision to repeat the horse races in the subsequent year gave rise to the tradition of the Oktoberfest.

In 2012, the Oktoberfest will be celebrated for the 179th time. Since 1850, the bronze statue of Bavaria has watched the Oktoberfest. This worldly Bavarian patron was first sketched by Leo von Klenze in a classic style and Ludwig Michael Schwanthaler romanticised and "Germanised" the draft. The statue was constructed by Johann Baptist Stiglmaier and Ferdinand von Miller.

Since 1950, there has been a traditional festival opening: The entry of the festival hosts and breweries. During the ceremonial opening of the fest, the families of the festival hosts in coaches adorned with flowers, the bands of the festival tents, the waitresses on decorated carriages and the magnificent horses and carts of the Munich breweries enter the festival grounds. A twelve gun salute and the tapping of the first keg of Oktoberfest beer at 12:00 by the incumbent Mayor of Munich with the cry "O' zapft is!" ("It's tapped!" in the Austro-Bavarian language) opens the Oktoberfest. The Mayor then gives the first beer to the Minister-President of the State of Bavaria. The Oktoberfest is one of the most famous events in Germany with more than 6 million people from around the world attending the event every year to descend on the beer tents of Munich to celebrate the 16-day Oktoberfest extravaganza.

Augustiner Bräu

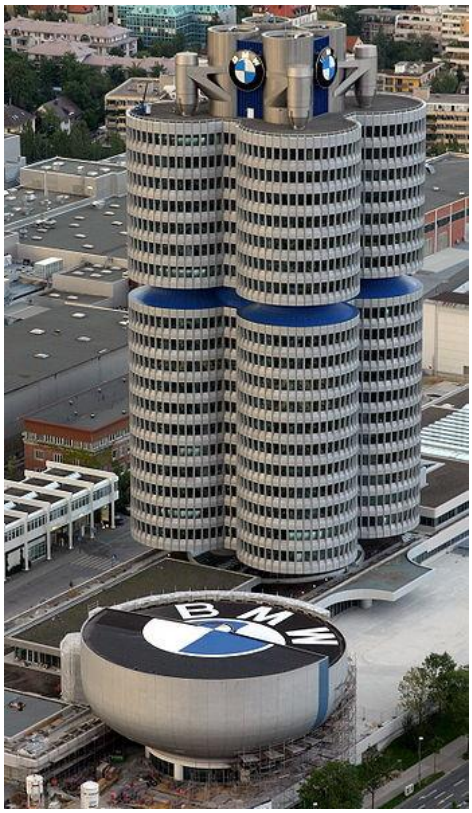
The history of Augustiner-Bräu, due to about 680 years of tradition Munich's oldest brewery, has begun in 1294, when the cornerstone of the Augustinian monastery was laid at the Haberfeld next to the Neuhauser Gasse. Documentary proof exists that already in 1328 an excellent beer was brewed within the walls of the freshly completed building. A major fire raged in Munich that year as well and the monastery is known to have been spared, therefore 1328 is considered the foundation date of the Augustiner brewery, thereby being the oldest of all existing breweries resident in Munich.

From the brewing house's first days on until the secularisation in 1803, when Napoleon's reforms put many Bavarian monasteries under state control, the very renowned beer had continually been brewed there. It had been sold in the internal tavern, very popular because of the reigning high spirits, as the monastery hold both brewing and selling rights. Worth mentioning is also that the Bavarian prince had not given them only both rights, but also exempted the monks from any taxes to reward them for the extraordinary quality of their beer.

After the takeover of the monastery by the state and the departure of the brotherhood, the brewery was denationalized and eventually moved to 275, Neuhauser Straße in 1817 (in the meantime nr. 27 and in Munich's central pedestrian precinct). The company stayed there only until 1885, when the "Stammhaus" was turned into a restaurant that has persisted until today, even though a major rearrangement, directed by the well-known architect Emanuel von Seidl, has taken place at the beginning of the 19th century.

In the course of history, Augustiner-Bräu survived a privatisation, some wars and many extensions without ever forgetting its philosophy or risking about the quality of its beer. This has made Augustiner-Bräu an important element for Munich's culture and the city's restaurants and beer gardens - mainly the Augustiner Keller and the Hirschgarten - places still representing the cosiness and traditional social life of ancient Munich.

BMW-Museum



The BMW Museum is one of the most popular company museums in Germany. And of all the companies sights in Munich, only the Deutsches Museum and the Neue Pinakothek (New Gallery) attract more visitors. Each year some 250,000 people from all over the world come to the BMW Museum - a story of success for which there are good reasons, because the BMW Museum does not just present the history of BMW and the engines, motorcycles and automobiles manufactured by the company in the course of its first 75 years.

Rather, the BMW Museum achieves an entirely different goal. It enables its visitors to marvel at the horizons of transport technology through the eyes of five generations, from the early days at the beginning of this century and into the next millenium. Horizons which show the development of ideas, dreams, philosophies, work, society and the individual mobility made possible by technology. In this way the BMW Museum possibly makes it a bit easier to understand the present as the future of our past and as the past of our future.

The BMW Museum was built at the same time as the Olympic Stadium with its famous tent roof and the BMW Building. Construction started in 1971 and the Museum was opened in 1973. The museum is designed as a "self-supporting body": the reinforced concrete shell supports the roof. The spiral path inside the Museum rest entirely on the columns also supporting the four platforms which constantly increase in size the further up you go. The shell expands in size from a diameter of less than 20 metres (66 ft) to 41 metres (134.5 ft) at the top. In all - it is 19 metres (62 ft) high. Flying over the area in an aircraft you will see a huge BMW logo on the roof of the Museum.

Known as the salad bowl or white cauldron, the silver futuristic building was designed by the architect of the BMW Headquarters, the Viennese Professor Karl Schwanzer. The roughly circular base is only 20 meters in diameter, the flat roof about 40 metres. The entrance is on the ground floor and consists of a cloakroom (in basement) and reception. First, the visitor ascends on a spiral upward in the building to visit the exhibits. Slideshows and smaller, in-depth exhibits are located on four "islands" inside the building. After "looping" the actual exhibition visitors reach the upper floor, where there are individual exhibits, a small cinema hall and several interactive exhibits that explain the technology further. An escalator leads visitors finally back into the ground floor.

Sightseeing and History

München

Munich is the capital and the largest city of the German state of Bavaria. It is located on the River Isar north of the Bavarian Alps. Munich is the third largest city in Germany, behind Berlin and Hamburg. About 1.42 million people live within the city limits. Munich was the host city of the 1972 Summer Olympics. Its native name, München, is derived from the Old High German Munichen, meaning "by the monks' place". The city's name derives from the monks of the Benedictine order who founded the city; hence the monk depicted on the city's coat of arms. Black and gold—the colours of the Holy Roman Empire—have been the city's official colours since the time of Ludwig the Bavarian. Modern Munich is a financial and publishing hub, and a frequently top-ranked destination for migration and expatriate location in livability rankings. Munich achieved 4th place in frequently quoted Mercer livability rankings in 2011. For economic and social innovation, the city was ranked 15th globally out of 289 cities in 2010. In 2010, Monocle ranked Munich as the world's most livable city (in 2012, Munich was ranked fifth in Monocle's ranking, yet remained the highest ranked city in Germany).

The year 1158 is assumed to be the foundation date, which is only the earliest date the city is mentioned in a document. The document was signed in Augsburg. By that time the Guelph Henry the Lion, Duke of Saxony and Bavaria, had built a bridge over the river Isar next to a settlement of Benedictine monks—this was on the Salt Route and a toll bridge. In 1175, Munich was officially granted city status and received fortification. In 1180, with the trial of Henry the Lion, Otto I Wittelsbach became Duke of Bavaria and Munich was handed over to the Bishop of Freising. (Wittelsbach's heirs, the Wittelsbach dynasty, would rule Bavaria until 1918.) In 1240, Munich was transferred to Otto II Wittelsbach and in 1255, when the Duchy of Bavaria was split in two, Munich became the ducal residence of Upper Bavaria. Duke Louis IV was elected German king in 1314 and crowned as Holy Roman Emperor in 1328. He strengthened the city's position by granting it the salt monopoly, thus assuring it of additional income. In the late 15th century Munich underwent a revival of gothic arts—the Old Town Hall was enlarged, and Munich's largest gothic church, now a cathedral—the Frauenkirche—constructed in only twenty years, starting in 1468.

When Bavaria was reunited in 1506, Munich became its capital. The arts and politics became increasingly influenced by the court (see Orlando di Lasso, Heinrich Schuetz and later Mozart and Richard Wagner). During the 16th century Munich was a centre of the German counter reformation, and also of renaissance arts. Duke Wilhelm V commissioned the Jesuit Michaelskirche, which became a centre for the counter-reformation, and also built the Hofbräuhaus for brewing brown beer in 1589. The Catholic League was founded in Munich in 1609. In 1623 during the Thirty Years' War Munich became electoral residence when Maximilian I, Duke of Bavaria was invested with the electoral dignity but in 1632 the city was occupied by Gustav II Adolph of Sweden. When the bubonic plague broke out in 1634 and 1635 about one third of the population died. Under the regency of the Bavarian electors Munich was an important centre of baroque life but also had to suffer under Habsburg occupations in 1704 and

1742. In 1806, the city became the capital of the new Kingdom of Bavaria, with the state's parliament (the Landtag) and the new archdiocese of Munich and Freising being located in the city. Twenty years later Landshut University was moved to Munich. Many of the city's finest buildings belong to this period and were built under the first three Bavarian kings. Later Prince Regent Luitpold's years as regent were marked by tremendous artistic and cultural activity in Munich (see Franz von Stuck and Der Blaue Reiter).

Following the outbreak of World War I in 1914, life in Munich became very difficult, as the Allied blockade of Germany led to food and fuel shortages. During French air raids in 1916, three bombs fell on Munich. After World War I, the city was at the centre of much political unrest. In November 1918 on the eve of revolution, Ludwig III and his family fled the city. After the murder of the first republican premier of Bavaria Kurt Eisner in February 1919 by Anton Graf von Arco auf Valley, the Bavarian Soviet Republic was proclaimed. When Communists had taken power, Lenin, who had lived in Munich some years before, sent a congratulatory telegram, but the Soviet Republic was put down on 3 May 1919 by the Freikorps. While the republican government had been restored, Munich subsequently became a hotbed of extremist politics, among which Adolf Hitler and the National Socialism rose to prominence.

In 1923 Hitler and his supporters, who were then concentrated in Munich, staged the Beer Hall Putsch, an attempt to overthrow the Weimar Republic and seize power. The revolt failed, resulting in Hitler's arrest and the temporary crippling of the Nazi Party, which was virtually unknown outside Munich. The city once again became a Nazi stronghold when the National Socialists took power in Germany in 1933. The National Socialist Workers Party created the first concentration camp at Dachau, 10 miles (16 km) north-west of the city.

The city is known as the site of the culmination of the policy of appeasement employed by Britain and France leading up to World War II. It was in Munich that British Prime Minister Neville Chamberlain assented to the annexation of Czechoslovakia's Sudetenland region into Greater Germany in the hopes of sating the desires of Hitler's Third Reich. Munich was the base of the White Rose, a student resistance movement from June 1942 to February 1943. The core members were arrested and executed following a distribution of leaflets in Munich University by Hans and Sophie Scholl. The city was heavily damaged by allied bombing during World War II—the city was hit by 71 air raids over a period of six years.

After US occupation in 1945, Munich was completely rebuilt following a meticulous and – by comparison to other war-ravaged West German cities – rather conservative plan which preserved its pre-war street grid. In 1957 Munich's population passed the 1 million mark. Munich was the site of the 1972 Summer Olympics, during which Israeli athletes were assassinated by Palestinian terrorists in the Munich massacre, when gunmen from the Palestinian "Black September" terrorist group took hostage members of the Israeli Olympic team.

Munich enjoys a thriving economy, driven by the information technology, biotechnology, and publishing sectors. Environmental pollution is low, although as of 2006 the city council is concerned about levels of particulate matter (PM), especially along the city's major thoroughfares. Today, the crime rate is low compared to other large German cities, such as Hamburg or Berlin. This high quality of life and safety has caused the city to be nicknamed "Toytown" amongst the English-speaking residents. German inhabitants call it "Millionendorf", an expression which means "village of a million people".


1. Siegestor
2. University
3. Hofgarten
4. Theatiner Kirche
5. Feldherrenhalle
6. Max-Joseph-Platz
7. Maximilianeum
8. Dallmayr
9. Alter Peter
10. Old City Hall
11. New City Hall
12. Frauenkirche
F. Augustiner

Places of Interest

Siegestor

The Siegestor (Victory Gate) in Munich, is a three-arched triumphal arch crowned with a statue of Bavaria with a lion-quadriga, similar in style to the Arch of Constantine in Rome, the Marble Arch in London, the Arc de Triomphe in Paris and the Brandenburger Tor in Berlin. It is located between the Ludwig Maximilian University and the Ohmstraße, where the Ludwigstraße (south) ends and the Leopoldstraße (north) begins. It thus sits at the boundary between the two Munich districts of Maxvorstadt and Schwabing.

The gate was commissioned by King Ludwig I of Bavaria, designed by Friedrich von Gärtner and completed by Eduard Mezger in 1852. The quadriga was created by Martin von Wagner. Lions were likely used in the quadriga, instead of the more usual horses, because the lion was a symbol of the House of Wittelsbach, the ruling family of the Bavarian monarchy. The gate was originally dedicated to the glory of the Bavarian army (dem bayerischen Heere zum Ruhme). Today the Siegestor is a monument and reminder to peace. After sustaining heavy damage in World War II, the gate was - similar to the Kaiser-Wilhelm-Gedächtniskirche in Berlin - reconstructed and restored only partially. The inscription on the back side is by Wilhelm Hausenstein and reads Dem Sieg geweiht, vom Krieg zerstört, zum Frieden mahnend, which translates as "Dedicated to victory, destroyed by war, reminding of peace". In the last couple of years, the statues that remained were meticulously cleaned and restored. The Siegestor is 21 meters high, 24 meters wide, and 12 meters deep.

Ludwig Maximilian Universität

The Ludwig Maximilian University of Munich, commonly known as the University of Munich or LMU, is a university in Munich, Germany. A public research university, it is amongst Germany's oldest universities. Originally established in Ingolstadt in 1472 by Duke Ludwig IX of Bavaria-Landshut, the university was moved in 1800 to Landshut by King Maximilian I of Bavaria when Ingolstadt was threatened by the French, before being relocated to its present-day location in Munich in 1826 by King Ludwig I of Bavaria. In 1802, the university was officially named Ludwig-Maximilians-Universität by King Maximilian I of Bavaria in his as well as the university's original founder's honour.

The University of Munich has, particularly since the 19th century, been considered as one of Germany's as well as Europe's most prestigious universities; with 34 Nobel laureates associated with the university, it ranks 13th worldwide in terms of Nobel laureates. Among these were Wilhelm Röntgen, Max Planck, Werner Heisenberg, Otto Hahn and Thomas Mann. Pope Benedict XVI was also a student and professor at the university. The LMU has recently been conferred the title of "elite university" under the German Universities Excellence Initiative.

The LMU is currently the second-largest university in Germany in terms of student population; in the winter semester of 2009/2010, the university had a total of 45,539 matriculated students. Of these, 7,801 were freshmen while international students totalled 6,743 or almost 15% of the student population. As for endowments, the university records in 2008 a total of 458.8 million Euros in funding without the university hospital; with the university hospital, the university has a total funding amounting to approximately 1 billion Euros.

Feldherrnhalle

The Feldherrnhalle (sometimes also written Feldherrenhalle, "Field Marshals' Hall") is a monumental loggia in Munich, Germany. It was built between 1841 and 1844 at the southern end of Munich's Ludwigstrasse next to the Palais Preysing and east of the Hofgarten. Friedrich von Gärtner built the Feldherrnhalle at the behest of King Ludwig I of Bavaria after the example of the Loggia dei Lanzi in Florence. The Feldherrnhalle was a symbol of the honours of the Bavarian Army. It contains statues of military leaders Johann Tilly and Karl Philipp von Wrede. The central sculptural group was added in 1882, after the Franco-Prussian War.

On Friday morning, 9 November 1923, the Feldherrnhalle was the scene of a confrontation between the Bavarian State Police and an illegally organized march by the followers of Adolf Hitler. When ordered to stop the marchers continued; the State Police felt threatened and opened fire. Four policemen and sixteen marchers were killed and a number were wounded, including Hermann Göring. As a result, Hitler was arrested and sentenced to a prison term. This was one of the efforts by the Nazis to take over the Bavarian State, commonly referred to as the Beer Hall Putsch. A relief picture of the Feldherrnhalle also appears on the Blood Order medal of the Nazi party.

Hofgarten

The Hofgarten (Court Garden) is a garden in the center of Munich, Germany, located between the Residenz and the Englischer Garten. The garden was built in 1613–1617 by Maximilian I, Elector of Bavaria as an Italian style Renaissance garden. In the center of the garden is a pavilion for the goddess Diana, built in 1615 by Heinrich Schön the elder. A path leads from each of the eight arches. On the roof of the Diana pavilion is the replica of a sculpture of Bavaria by Hubert Gerhard, created in 1623. The original is in the Kaisersaal of the Residenz. Facing the Hofgarten on the east side is the Bavarian Staatskanzlei ("State Chancellery"), housed in the former Army Museum, with the addition of glass wings left and right of the original building. The repurposed building was completed in 1993. A few steps more eastwards the Hofgartenkaserne was located from 1801 to 1899. In the north east corner, a square black granite memorial stands to the White Rose group, whose members were executed for a non violent campaign against Hitler's regime.

The garden was destroyed during World War II, and was rebuilt with a partial redesign which compromised between the landscape garden character it had acquired in the nineteenth century and the original formal design of the seventeenth century. Nowadays the garden is open to the public, and is very

popular with both residents and tourists alike. The nearest Munich U-Bahn station is Odeonsplatz, located directly west of the garden.

Theatiner Kirche

The Theatine Church of St. Cajetan is a Catholic church in Munich, southern Germany. Built from 1663 to 1690, it was founded by Elector Ferdinand Maria and his wife, Henriette Adelaide of Savoy, as a gesture of thanks for the birth of the long-awaited heir to the Bavarian crown, Prince Max Emanuel, in 1662.

The church was built in Italian high-Baroque style, inspired by Sant'Andrea della Valle in Rome, designed by the Italian architect Agostino Barelli. His successor, Enrico Zuccalli, added two towers, originally not planned, and then finished the 71 meter high dome in 1690. The facade in Rococo style was completed only in 1768 by François de Cuvilliés. Its Mediterranean appearance and yellow coloring became a well known symbol for the city and had much influence on Southern German Baroque architecture. The interior has a rich stucco decoration, executed by Nicolò Petri (1685–1688), Wolfgang Leutner being responsible for the stucco figures. The great black pulpit is a work of Andreas Faistenberger (1686). The altars house paintings of Caspar de Crayer, Carlo Cignani, George Desmareés and Joachim von Sandrart. Balthasar Ableithner created the statues of Saint Marcus and Saint John.

Ludwigstrasse

The Ludwigstrasse in Munich is one of the city's four royal avenues. Principal was King Ludwig I of Bavaria, the avenue is named in his honour. The city's grandest boulevard with its public buildings still maintains its architectural uniformity envisioned as a grand street "worthy the kingdom" as requested by the king. The Ludwigstrasse has served also for state parades and funeral processions.

The avenue begins at Odeonsplatz and runs from south to north, it leads from the Feldherrnhalle in the south to the Siegestor in the north, skirting the Ludwig-Maximilians-Universität, the St. Ludwig church, the Bayerische Staatsbibliothek (Bavarian State Library) and numerous state ministries and palaces. The southern part of the avenue was constructed in Italian renaissance style by Leo von Klenze from 1816 onwards. The northern part was then constructed since 1827 in line with a plan of Klenze's rival Friedrich von Gärtner, the appearance is strongly influenced by Italian romanesque architecture. Some buildings were constructed during the Third Reich, such as the Bavarian Department of Agriculture. The opening in the middle of the Ludwigstrasse for the new circular road Altstadtring after World War II disturbs the appearance. Its extension north of the Siegestor in Schwabing is called Leopoldstrasse.

Max-Joseph-Platz

Max-Joseph-Platz is a large square in central Munich which was named after King Maximilian Joseph. Max-Joseph-Platz serves as the western starting point of the royal avenue Maximilianstraße.

The square was constructed with the erection of the National Theatre Munich at its east side, which was opened in 1818. Opposite to its Corinthian columns at the west side are middle-class houses. The north side is framed by the Königsbau of the Munich Residence. King Ludwig I of Bavaria instructed his architect Leo von Klenze to build the King's tract in the south of his palace in the style of the Florentine Palazzo Pitti. The facade of the Residenz Theatre is situated between the Königsbau and the National Theatre. The south of Max-Joseph-Platz is dominated by the Neo-Renaissance arcades of the former Palais Toerring-Jettenbach, a rococo mansion which originates from 1747. The monument Max-Joseph Denkmal before the Königsbau was created in the middle of the square as a memorial for King Maximilian Joseph by Christian Daniel Rauch and carried out by Johann Baptist Stiglmaier. It was only revealed in 1835 since the king had rejected to be eternalized in sitting position. After World War II a subterranean garage was constructed below the Max-Joseph-Platz, its gateway disturbs the neo-classical appearance of the square.

Maximilianstrasse

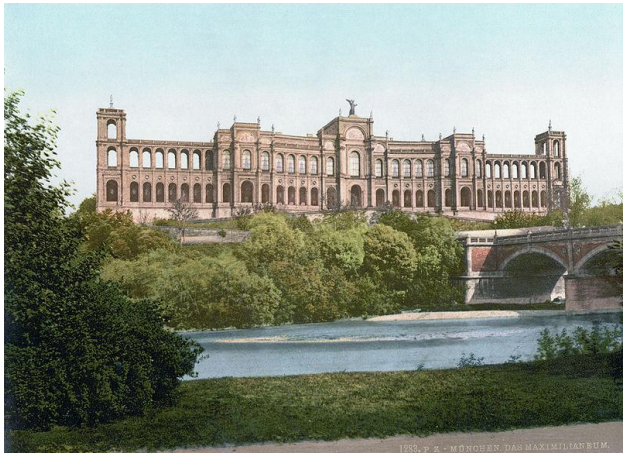
The neo-Renaissance Maximilianstraße in Munich is one of the city's four royal avenues. It starts at Max-Joseph-Platz, where the Residenz and the National Theatre are situated, and runs from west to east. Principal was king Maximilian II of Bavaria, who started the project in 1850, the avenue is named for his honour. Leading architect was Friedrich Bürklein.

With this project, the king also aimed to "invent" a new architectural style which would combine the best features of historical models combined with then modern building technology. The avenue is framed by mostly neo-Gothic buildings influenced by the English Perpendicular style.
Opposite to the National Theatre the north facade of the Old Mint Yard got its neogothic decoration when the Maximilianstrasse was built to fit it with the concept of this royal avenue. The new buildings house, among others, in the western portion of the street the Schauspielhaus (built by Max Littmann, 1901) and in the eastern portion several state buildings like the building of the district government of Upper Bavaria (Friedrich Bürklein, 1856–1864), the Völkerkundemuseum (Museum of Ethnology, built by Eduard Riedel, 1858–1865) and the building of the Wilhelmsgymnasium (built by Carl Leimbach, 1875–1877). After crossing the river Isar further east, the avenue circles the palatial Maximilianeum (Friedrich Bürklein, 1857–1874), home of a gifted students´ foundation and the Bavarian Landtag (state parliament). The opening in the middle of the Maximilianstrasse for the new circular road Altstadtring after World War II still disturbs the appearance. The Maxmonument in the middle of the eastern part of the avenue is dedicated to King Maximilian II of Bavaria and was sculpted by Kaspar von Zumbusch. In the south the dome of St. Lukas is visible.

The western portion of Maximilianstrasse is known for its galleries, designer shops, luxury boutiques, jewellery stores, and one of Munich's foremost five-star hotels, the Hotel Vier Jahreszeiten (Kempinski, built by Rudolf Gottgetreu, 1856–1858). Dolce & Gabbana, Versace, Louis Vuitton, Dior, Chanel, Escada, Hugo Boss, Gucci, Gianfranco Ferré, Bulgari and many other famous shops keep branches in the Maximilianstrasse. They have increasingly ousted the traditional shops, art galleries and restaurants.

Maximilianeum

The Maximilianeum, a palatial building in Munich, was built as the home of a gifted students' foundation and has also housed the Bavarian Landtag (state parliament) since 1949.



The principal was King Maximilian II of Bavaria, who started the project in 1857. The leading architect was Friedrich Bürklein. The building is situated on the bank of river Isar before the Maximilian Bridge and marks the eastern end of the Maximilianstrasse, one of Munich's royal avenues which is framed by neo-Gothic palaces influenced by the English Perpendicular style. Due to statical problems the construction was only completed in 1874 and the facade of the Maximilianeum which was originally planned also in neo-Gothic style had to be altered in renaissance style under the influence of Gottfried Semper. The building was extended on its back for new parliament offices, several modern wings were added in 1958, 1964, 1992 and again in 2012.

Dallmayr

Dallmayr is a luxury delicatessen food store in Munich, Germany, dating back to the 17th century. Its reputation is comparable to Fauchon in Paris, Fortnum & Mason in London, or Meiji-ya in Tokyo. About 2.5 million people visit the main store every year. Besides luxury food, Dallmayr also sells a luxury brand of coffee, includes a restaurant, a party service, and other food related services. The revenue of 2004 was 455 million euro with about 2,500 employees. The main competitor in Munich is Feinkost Käfer.

The main store, completed in 1950 with a neo classic facade, is located in the Dienerstrasse in Munich between the Marienplatz and the Odeonsplatz. About 2.5 million people visit the main store every year, including VIPs and tourists. (Other sources state 1.3 million people per year, which in any case are still more than Neuschwanstein with 1.1 Million). The list of regular customers includes Queen Sirikit Rajini of Thailand. Besides the first-rate food, the store is also known for its indoor fountain, stocked with live crayfish. Different from a supermarket, there is no central cashier, rather the products are always purchased in the individual departments. The building is known Germany-wide due to the Dallmayr television advertising, prominently featuring the building since 1980, including the staff in blue blouses and white aprons and the historic porcelain vessels. Having a TV spot run three times per day costs the company about 20 million euro per year. Currently, a staff of about 300 is employed in the main store.

The main store dates back to the 17th century, with a Spezereien-Handlung of the Munich citizen and chandler Christian Reitter. The store was established in the current location in the Dienerstrasse between 1671 and 1700. The exact date is not known, a surviving document dates from his death in 1700. After his death his

two daughters inherited the store and the chandler guild membership. The name Dallmayr comes with a new owner in 1870, Alois Dallmayr, a merchant from Wolnzach in Bavaria. Alois Dallmayr did not have any heir and therefore in 1895 sold the store to Anton Randlkofer, who died only two years later. The Alois Dallmayr KG is despite its size still a family business. The owners are Wolfgang Wille (born ca. 1940 or 1941), married to Marianne Wille since 1971, and Georg Randlkofer (born 1948).

Alter Peter

St. Peter's Church is a Roman Catholic church in the inner city of Munich, southern Germany. It is also the oldest church in the district. Before the foundation of Munich as a city in 1158, there had been a pre-Merovingian church on this site. 8th century monks lived around this church on a hill called Petersbergl. At the end of the 12th century a new church in the Bavarian Romanesque style was consecrated, and expanded in Gothic style shortly before the great fire in 1327, which destroyed the building. After its reconstruction the church was dedicated anew in 1368. In the early 17th century the 92 meter spire received its Renaissance steeple top and a new Baroque choir was added. The interior is dominated by the high altar to which Erasmus Grasser contributed the figure of Saint Peter. Among other masterpieces of all periods are five Gothic paintings by Jan Polack and several altars by Ignaz Günther. The ceiling fresco by Johann Baptist Zimmermann (1753–1756) was re-created in 1999-2000. The parish church of Saint Peter, whose tower is commonly known as "Alter Peter" - Old Peter - and which is emblematic of Munich, is the oldest recorded parish church in Munich and presumably the originating point for the whole city.

Altes Rathaus

The Old Town Hall, until 1874 the domicile of the municipality, serves today as a building for the city council in Munich. The Old Town Hall bounds the central square Marienplatz on its east side. The building, documented for the first time in 1310, had its Grand Hall (Großer Saal) constructed in 1392/1394. The former Talburg Gate (Talburgtor) of the first city wall serves as spire. The Old Town Hall was re-designed in late-gothic style by Jörg von Halsbach 1470-1480.

The Grand Hall was decorated by the Morris dancers, created by Erasmus Grasser. After alterations of the facade during the Renaissance the building was restored in neo-gothic style 1861-1864. In 1874 the municipality moved to the New Town Hall. For the passage of increased road traffic the Old Town Hall was tunneled in 1877 and 1934. During World War II the building was severely damaged and the spire was reconstructed in 1971-1974. Parts of the neo-Gothic elements, especially the statues of Ludwig the Bavarian (west facade) and Henry the Lion (east facade) and the gable design are preserved.

Neues Rathaus

The New Town Hall is a town hall at the northern part of Marienplatz in Munich, Bavaria, Germany. It hosts the city government including the city council, offices of the mayors and part of the administration. In 1874 the municipality had left the Old Town Hall for its new domicile.

It was built between 1867 and 1908 by Georg von Hauberrisser in a Gothic Revival architecture style. It covers an area of 9159 m^2 having 400 rooms. The 100 meters long main facade towards the Marienplatz is richly decorated. It shows the Guelph Duke Henry the Lion, and almost the entire line of the Wittelsbach dynasty in Bavaria and is the largest princely cycle in a German town hall. The central monument in the center of the main facade between the two phases at Marienplatz above the guard house, is an equestrian statue of Prince Regent Luitpold. The bay of the tower contains statues of the first four Bavarian kings.

The main facade is placed toward the plaza, while the back side is adjacent to a small park (Marienhof). The basement is almost completely occupied by a large restaurant called Ratskeller. On the ground floor, some rooms are rented for small businesses. Also located in the ground floor is the major official tourist information. The first floor hosts a big balcony towards the Marienplatz which is used for large festivals such as football championships or for concerts during the Weihnachtsmarkt. Its main tower has a height of 85 m and is available for visitors with an elevator. On the top thrones the Münchner Kindl. The Rathaus-Glockenspiel, performed by an apparatus daily on 11am, 12pm and 5pm, is a tourist attraction.

Frauenkirche

The Frauenkirche (full name Dom zu Unserer Lieben Frau, "Cathedral of Our Dear Lady") is a church in the Bavarian city of Munich that serves as the cathedral of the Archdiocese of Munich and Freising and seat of its Archbishop. It is a landmark and is considered a symbol of the Bavarian capital city. The church towers are widely visible because of local height limits. According to the narrow outcome of a local pleviscite, city administration prohibits buildings with a height exceeding 99 m in the city center. Since November 2004, this prohibition has been provisionally extended outward and as a result, no buildings may be built in the city over the aforementioned height. The south tower is open to those wishing to climb the stairs and offers a unique view of Munich and the nearby Alps.

Right next to the town's first ring of walls, a romanesque church was added in the 12th century, serving as a second city parish following Alter Peter church (nicknamed 'Ole Pete'), which is the oldest. The current construction replaced this older church and was commissioned by Duke Sigismund and the people of Munich. The cathedral was erected in only 20 years time by Jörg von Halsbach. For financial reasons and due to the lack of a nearby stone pit, brick was chosen as building material. Construction began in 1468. Since the cash resources were exhausted in 1479 Pope Sixtus IV granted an indulgence.

The two towers (north tower 98,57 m, south tower 0,12 m less) were completed in 1488 and the church was consecrated in 1494. However, for yet another lack of money, the originally planned tall open-work spires so typical for the gothic style could not be built and the towers had to stay uncovered until 1525. Hartmann Schedel printed a view of Munich including the uncovered towers in his famous Nuremberg Chronicle, better known as Schedel's World Chronicle.
By then, nonetheless since more and more rainwater irrupted through the two tower's ceilings, a decision was finally made to catch up, however in a much more budget-priced design. This way the building got it's famous domes atop each tower and the church became such an non-interchangeable landmark. Their design was modelled on the Dome of the Rock in Jerusalem, which in turn took a lead from late Byzantine architecture.

Most remakably and besides from having another (first) parish church, Munich had only 13,000 inhabitants but erected a simple (second) parish church that was able to house a crowd of 20,000! (One has to leave away the church benches in the naves, something most unusual at that time and being a much later addition.) The cathedral suffered severe damage during World War II — the roof collapsed and one of the towers suffered severe damage. A major restoration effort began after the war and was carried out in several stages, the last of which coming to an end in 1994.

The Frauenkirche was constructed from red brick in the late Gothic style within only 20 years. The building is designed very plainly, without rich Gothic ornaments. An attraction that survived WWII is the Teufelstritt, or Devil's Footstep, at the entrance. This is a black mark resembling a footprint, which according to legend was where the devil stood when he curiously regarded and ridiculed the 'windowless' church that Halsbach had built. (In baroque times the high altar would obscure the one window at the very end of the church on can spot now when standing in the entrance hall.) In another version of the legend, the devil made a deal with the builder to finance construction of the church on the condition that it contain no windows. The clever builder, however, tricked the devil by positioning columns so that the windows were not visible from the spot where the devil stood in the foyer. When the devil discovered that he had been tricked, he could not enter the already consecrated church. The devil could only stand in the foyer and stomp his foot furiously, which left the dark footprint that remains visible in the church's entrance today.

The four kings

Maximilian I

Maximilian I (also known as Maximilian Joseph) (27 May 1756 – 13 October 1825) was duke of Zweibrücken from 1795 to 1799, prince-elector of Bavaria (as Maximilian IV Joseph) from 1799 to 1805, king of Bavaria (as Maximilian I) from 1806 to 1825. He was a member of the House of Palatinate-Zweibrücken-Birkenfeld, a branch of the House of Wittelsbach.

Maximilian, the son of the count palatine Frederick Michael of Zweibrücken-Birkenfeld and Maria Francisca of Sulzbach, was born at Schwetzingen – between Heidelberg and Mannheim. He was carefully educated under the supervision of his uncle, Duke Christian IV of Zweibrücken, became Count of Rappoltstein in 1776 and took service in 1777 as a colonel in the French army and rose rapidly to the rank of major-general. From 1782 to 1789 he was stationed at Strasbourg, but at the outbreak of the French Revolution he exchanged the French for the Austrian service, taking part in the opening campaigns of the revolutionary wars.

On 1 April 1795 he succeeded his brother, Charles II, as duke of Zweibrücken, however, his duchy was entirely occupied by the French. On 16 February 1799 Maximilian Joseph became Elector of Bavaria and Count Palatine of the Rhine, the Arch-Steward of the Empire, and Duke of Berg on the extinction of the Palatinate-Sulzbach line with the death of the elector Charles Theodore.
The sympathy with France and with French ideas of enlightenment which characterized his reign was at once manifested. In the newly organized ministry Count Max Josef von Montgelas, who, after falling into disfavour with Charles Theodore, had acted for a time as Maximilian Joseph's private secretary, was the most potent influence, an influence wholly "enlightened" and French. Agriculture and commerce were fostered, the laws were ameliorated, a new criminal code drawn up, taxes and imposts equalized without regard to traditional privileges, while a number of religious houses were suppressed and their revenues used for educational and other useful purposes. He closed the University of Ingolstadt in May 1800 and moved it to Landshut.
In foreign politics Maximilian Joseph's attitude was from the German point of view less commendable. With the growing sentiment of German nationality he had from first to last no sympathy, and his attitude throughout was dictated by wholly dynastic, or at least Bavarian, considerations. Until 1813 he was the most faithful of Napoleon's German allies, the relation being cemented by the marriage of his eldest daughter to Eugène de Beauharnais. His reward came with the Treaty of Pressburg (26 December 1805), by the terms of which he was to receive the royal title and important territorial acquisitions in Swabia and Franconia to round off his kingdom. He assumed the title of king on 1 January 1806. On 15 March he ceded the Duchy of Berg to Napoleon's brother-in law Joachim Murat.

The new king of Bavaria was the most important of the princes belonging to the Confederation of the Rhine, and remained Napoleon's ally until the eve of the Battle of Leipzig, when by the Treaty of Ried (8 October 1813) he made the guarantee of the integrity of his kingdom the price of his joining the Allies.
By the first Treaty of Paris (3 June 1814), however, he ceded Tyrol to Austria in exchange for the former Grand Duchy of Würzburg. At the Congress of Vienna, which he attended in person, Maximilian had to make further concessions to Austria, ceding Salzburg and the quarters of the Inn and Hausruck in return for the western part of the old Palatinate. The king fought hard to

maintain the contiguity of the Bavarian territories as guaranteed at Ried but the most he could obtain was an assurance from Metternich in the matter of the Baden succession, in which he was also doomed to be disappointed.
At Vienna and afterwards Maximilian sturdily opposed any reconstitution of Germany which should endanger the independence of Bavaria, and it was his insistence on the principle of full sovereignty being left to the German reigning princes that largely contributed to the loose and weak organization of the new German Confederation. The Federal Act of the Vienna Congress was proclaimed in Bavaria, not as a law but as an international treaty. It was partly to secure popular support in his resistance to any interference of the federal diet in the internal affairs of Bavaria, partly to give unity to his somewhat heterogeneous territories, that Maximilian on 26 May 1818 granted a liberal constitution to his people. Montgelas, who had opposed this concession, had fallen in the previous year, and Maximilian had also reversed his ecclesiastical policy, signing on 24 October 1817 a concordat with Rome by which the powers of the clergy, largely curtailed under Montgelas's administration, were restored. The new parliament proved to be more independent than he had anticipated and in 1819 Maximilian resorted to appealing to the powers against his own creation; but his Bavarian "particularism" and his genuine popular sympathies prevented him from allowing the Carlsbad Decrees to be strictly enforced within his dominions. The suspects arrested by order of the Mainz Commission he was accustomed to examine himself, with the result that in many cases the whole proceedings were quashed, and in not a few the accused dismissed with a present of money. Maximilian died at Nymphenburg Palace, near Munich, on 13 October 1825 and was succeeded by his son Ludwig I. Maximilian is buried in the crypt of the Theatinerkirche in Munich.

Under the reign of Maximilian Joseph the Bavarian Secularization (1802–1803) led to the nationalisation of cultural assets of the Church. The Protestants were emancipated. In 1808 he founded the Academy of Fine Arts Munich.
The city of Munich was extended by the first systematic expansion with the new Brienner Strasse as core. In 1810 Max Joseph ordered construction of the National Theatre Munich in French neo-classic style. The monument Max-Joseph Denkmal before the National Theatre was created in the middle of the square Max-Joseph-Platz as a memorial for King Maximilian Joseph by Christian Daniel Rauch and carried out by Johann Baptist Stiglmaier. It was only revealed in 1835 since the king had rejected to be eternalized in sitting position.
In 1801 he led the rescue operation when a glassmaker's workshop collapsed, saving the life of Joseph von Fraunhofer, a 14 year-old orphan apprentice. Max Joseph donated books and directed the glassmaker to give Fraunhofer time to study. Fraunhofer went on to become one of the most famous optical scientists and artisans in history, inventing the spectroscope and spectroscopy, making Bavaria noted for fine optics, and joining the nobility before his death at age 39.
He was elected a Royal Fellow of the Royal Society in 1802.

In private life Maximilian was kindly and simple. He loved to play the part of Landesvater, walking about the streets of his capital en bourgeois and entering into conversation with all ranks of his subjects, by whom he was regarded with great affection. Maximilian married twice and had a total of thirteen children.

Ludwig I

Ludwig I (25 August 1786 – 29 February 1868) was a German king of Bavaria from 1825 until the 1848 revolutions in the German states. Born in Strasbourg, he was the son of Count Palatine Maximilian Joseph of Zweibrücken (later Maximilian I Joseph of Bavaria) by his first wife Augusta Wilhelmine of Hesse-Darmstadt. At the time of his birth, his father was an officer in the French army stationed at Strasbourg. He was the godson and namesake of Louis XVI of France.

Ludwig's rule was strongly affected by his enthusiasm for the arts and women and by his overreaching royal assertiveness. An enthusiast for the German Middle Ages, Ludwig ordered the re-erection of several monasteries in Bavaria which had been closed during the German Mediatisation. He reorganized the administrative regions of Bavaria in 1837 and re-introduced

the old names Upper Bavaria, Lower Bavaria, Franconia, Swabia, Upper Palatinate and Palatinate. He changed his royal titles to Ludwig, King of Bavaria, Duke of Franconia, Duke in Swabia and Count Palatine of the Rhine. His successors kept these titles.

Ludwig moved the Ludwig-Maximilians-Universität from Landshut to Munich in 1826. The king also encouraged Bavaria's industrialization. He initiated the Ludwig Canal between the rivers Main and the Danube. In 1835 the first German railway was constructed in his domain, between the cities of Fürth and Nuremberg. Bavaria joined the Zollverein in 1834. As Ludwig had supported the Greek fight of independence his second son Otto was elected king of Greece in 1832. Otto's government was initially run by a three-man regency council made up of Bavarian court officials.

After the July Revolution in France 1830, his previous liberal policy became more and more repressive. The Hambacher Fest in 1832 showed the discontent of the population with high taxes and censorship. In connection with the unrest of May 1832 142 political processes were initiated. The seven death sentences converted by the king in long terms of imprisonment. In his reign, there were about 1,000 political processes. Ludwig stricter censorship which he had abolished in 1825 and provoked the opposition of the population.

In 1837, the Roman Catholic supported clerical movement, the Ultramontanes, came to power in the Bavarian parliament and began a campaign of change to the constitution, which removed civil rights that had earlier been granted to Protestants, as well as enforcing censorship and forbidding the free discussion of internal politics. On 14 August 1838 the King dictated against considerable odds with the "squat adopting" the military back a squat in front of the Blessed Sacrament at Corpus Christi processions and church services. This squat had been the practice until 1803 in what was still almost purely Catholic Bavaria, but was then removed with the inclusion of Protestant areas. The Ultramontanes regime ended due to their demands against the naturalization of Ludwig I's Irish-born mistress Eliza Gilbert (better known by her stage name Lola Montez). Ludwig resented this move and the Ultramontanes under Karl von Abel were pushed out.

Already in 1844 Ludwig was confronted with the Beer riots in Bavaria. During the revolutions of 1848 the king faced increasing protests and demonstrations by the students and the middle classes. The King had ordered to close the university in February and on 4 March a large crowd assaulted the Armory to storm the Munich Residenz. Ludwig's brother Prince Karl managed to appease them, but now the royal family and the Cabinet turned against Ludwig. He had to sign the so-called "March Proclamation" with substantial concessions. On 16 March 1848 it was followed by renewed unrest because Lola Montez had returned to Munich after a short exile. Ludwig had to let her search by the police on 17 March, what was the worst humiliation for him. Not willing to rule as a constitutional monarch, Ludwig abdicated on 20 March 1848 in favour of his eldest son, Maximilian. He died at Nice, and was buried in St. Boniface's Abbey, Munich.

As admirer of ancient Greece and the Italian renaissance Ludwig patronized the arts as principal of many neoclassical buildings, especially in Munich, and as fanatic collector. Among others he had built were the Walhalla temple, the Befreiungshalle, the Ludwigstrasse, the Bavaria statue,

the Ruhmeshalle, the Glyptothek, the Old and the New Pinakothek. His architects Leo von Klenze and Friedrich von Gärtner also strongly influenced the cityscape of modern Athens.

Already as crown prince Ludwig collected especially Early German and Early Dutch paintings, masterpieces of the Italian renaissance, and contemporary art for his museums and galleries. He also placed special emphasis on collecting Greek and Roman sculpture. Through his agents, he managed to acquire such pieces as the Medusa Rondanini, the Barberini Faun, and, in 1813, the figures from the Aphaea temple on Aegina. One of his most famous conceptions is the celebrated "Schönheitengalerie" (Gallery of Beauties), in the south pavilion of his Nymphenburg Palace in Munich. A collection of 36 portraits of the beautiful women painted between 1827 and 1850 mostly by Joseph Karl Stieler. Also after his abdication, Ludwig remained an important and lavish sponsor for the arts. This caused several conflicts with his son and successor Maximilian. Finally Ludwig financed his projects from his own resources.

Ludwig was an eccentric and notoriously bad poet. He would write about anything, no matter how trivial, with strings of rhyming couplets. For this the king was teased by Heinrich Heine who wrote several mockery poems in Ludwig's style. Ironically Ludwig's Walhalla temple added Heine's bust to its collection in 2009. In private life Ludwig was, in spite of his royal assertiveness, modest and companionable and was even known for his often shabby attire. Ludwig was hard of hearing and had a birthmark on his forehead which was often concealed in portraits. Ludwig had several extramarital affairs and was one of the lovers of Lady Jane Digby, an aristocratic English adventuress. Ludwig also became tainted with scandals associated with Lola Montez, another of his mistresses. It seems likely that his relationship with her contributed greatly to the fall from grace of the previously popular king.

Maximilian II

Maximilian II of Bavaria (28 November 1811 – 10 March 1864) was king of Bavaria from 1848 until 1864. He was son of Ludwig I of Bavaria and Therese of Saxe-Hildburghausen. After studying at Göttingen and Berlin and travelling in Germany, Italy and Greece, he was introduced by his father into the council of state (1836). From the first he showed a studious disposition, declaring on one occasion that had he not been born in a royal cradle his choice would have been to become a professor. As crown prince, in the chateau of Hohenschwangau near Füssen, which he had rebuilt with excellent taste, he gathered about him an intimate society of artists and men of learning and devoted his time to scientific and historical study.

When the abdication of Ludwig I (20 March 1848) called him suddenly to the throne, his choice of ministers promised a liberal regime. Although, however, from 1850 onwards his government tended in the direction of absolutism, he refused to become the tool of the clerical reaction, and even incurred the bitter criticism of the Ultramontanes by inviting a number of celebrated men of learning and science (e.g. Geibel, Liebig and Sybel) to Munich, regardless of their religious views.
Maximilian II responded also to the demands of the people for a united German state, by attending the Frankfurt Assembly which intended to create such a state. The progress of the revolution, however, gave him pause. In 1849 an uprising in the Bavarian Palatinate was broken down with the support of Prussian forces. The king strenuously opposed the unionist plans of the Frankfurt Parliament, refused to recognize the imperial constitution devised by it, and assisted Austria in restoring the federal diet and in carrying out the federal execution in Hesse and Holstein. In the aftermath of the failure of the Frankfurt Assembly, Prussia and Austria continued to debate of which monarchy had the inherent right to rule Germany. The dispute between Austria and the Electoral Prince of Hesse-Kassel (or Hesse-Cassel) was used by Austria and its allies (including Bavaria) to promote the isolation of Prussia in German political affairs. This diplomatic insult almost led to war when Austria, Bavaria and other allies moved troops through Bavaria towards Hesse-Kassel in 1850. However, the Prussian army backed down and accepted the principle of dual leadership. This event was known as the Punctation of Olmütz but also known as the "Humiliation of Olmütz" by Prussia. This event solidified the Bavarian kingdom's alliance with Austria against Prussia.

In his German policy Maximilian was guided by the desire to maintain the union of the princes, and hoped to attain this as against the perilous rivalry of Austria and Prussia by the creation of a league of the "middle" and small states - the so-called Trias. In 1863, however, seeing what he thought to be a better way, he supported the project of reform proposed by Austria at the Furstentag of Frankfurt. Attempts by Prussia to reorganize the loose and un-led German Confederation, were opposed by Bavaria and Austria while taking part in its own discussions with Austria and other allies in 1863 in Frankfurt without Prussia and its allies attending. The failure of this proposal, and the attitude of Austria towards the Confederation and in the Schleswig-Holstein Question, disillusioned him; but before he could deal with the new situation created by the outbreak of the war with Denmark he died suddenly at Munich, on 10 March 1864. He is buried in the Theatinerkirche in Munich.

Maximilian offered Paul Heyse and other writers from North Germany large stipends. Hans Christian Andersen visited "King Max" (as he called him) in his castle Starnberg, and write of him as a young, highly amiable man. The King, having read his novels and fairy tales, let Andersen know that he was deeply impressed by The Improvisator, En Digters Bazar, The Little Mermaid and Paradisets Have. Next to Hohenschwangau Castle also the Hambach Castle was reconstructed from 1844 for Crown Prince Maximilian by August von Voit. In 1849 King Maximilian II instructed the architect Eduard Riedel to redesign the Castle Berg in neo-gothic style with several towers and a crenellate. Maximilian II was the principal of the Maximilianstrasse and the Bavarian National Museum in Munich. Compared to his father Maximilian preferred a new architectural style with strong reference to the Gothic Revival architecture which would combine the best features of historical models combined with then modern building technology. The hiking path in Upper Bavaria called Maximiliansweg is named after him, as he made a longer hike in the Bavaria alps in the summer of 1858.

Maximilian was a man of amiable qualities and of intellectual attainments far above the average, but as a king he was hampered by constant ill health, which compelled him to be often abroad, and when at home to live much in the country. By his wife, Marie Friederike Franziska Hedwig, daughter of Prince William of Prussia, whom he married in 1842, he had two sons, Ludwig II of Bavaria and Otto of Bavaria, both of whom became king, were declared insane, and deposed.

Ludwig II

Ludwig (25 August 1845 – 13 June 1886) was King of Bavaria from 1864 until shortly before his death. He is called the Märchenkönig, (Fairy tale King). Ludwig is sometimes also called "Mad King Ludwig", though the accuracy of that label has been disputed. His younger brother, Otto, was considered insane, thus the claim of hereditary madness was convenient. Because Ludwig was deposed on grounds of mental incapacity without any medical examination, questions about the medical "diagnosis" remain controversial. Adding to the controversy are the mysterious circumstances under which he died. King Ludwig and the doctor assigned to him in captivity at Castle Berg on Lake Starnberg were both found dead in the lake in waist-high water, the doctor with unexplained injuries to the head and shoulders, the morning after the day Ludwig was

deposed. One of Ludwig's most quoted sayings was "I wish to remain an eternal enigma to myself and to others."

Ludwig is best known as an eccentric whose legacy is intertwined with the history of art and architecture. He commissioned the construction of two extravagant palaces and a castle, the most famous being Neuschwanstein, and was a devoted patron of the composer Richard Wagner. King Ludwig is generally well-liked and even revered by many Bavarians today, many of whom note the irony of his supposed madness and the fact that his legacy of architecture and art and the tourist income they generate help to make Bavaria the richest state in Germany.

Crown Prince Ludwig had just turned 18 when his father died after a three-day illness, and he ascended the Bavarian throne. Although he was not prepared for high office, his youth and brooding good looks made him popular in Bavaria and elsewhere. One of the first acts of his reign, a few weeks after his accession, was to summon composer Richard Wagner to his court in Munich. Wagner had a notorious reputation as a revolutionary and a philanderer and was constantly on the run from creditors. Ludwig had admired Wagner since first seeing his opera, Lohengrin, at the impressionable age of 15½, followed by Tannhäuser ten months later.

A year after meeting the King, Wagner presented his latest work, Tristan und Isolde, in Munich to great acclaim. But the composer's perceived extravagant and scandalous behaviour in the capital was unsettling for the conservative people of Bavaria, and the King was forced to ask Wagner to leave the city six months later, in December 1865. Between 1872 and 1885, the King had 209 private performances (Separatvorstellungen) given for himself alone or with a guest, in the two court theatres, comprising 44 operas (28 by Wagner, including eight of Parsifal), 11 ballets and 154 plays (the principal theme being Bourbon France) at a cost of 97,300 marks.

The greatest stresses of Ludwig's early reign were pressure to produce an heir, and relations with militant Prussia. Both issues came to the forefront in 1867. Ludwig became engaged to Duchess Sophie in Bavaria, his cousin and the youngest sister of his dear friend, Empress Elisabeth of Austria.[8] The engagement was publicized on 22 January 1867, but after repeatedly postponing the wedding date, Ludwig finally cancelled the engagement in October. Throughout his reign, Ludwig had a succession of close friendships with men, including his chief equerry and Master of the Horse, Richard Hornig (1843–1911), Hungarian theatre actor Josef Kainz, and courtier Alfons Weber (born c.1862). He began keeping a diary in which he recorded his private thoughts and his attempts to suppress his sexual desires and remain true to his Roman Catholic faith. Ludwig's original diaries from 1869 were lost during World War II, and all that remains today are copies of entries during the 1886 plot to depose him. These diary entries, along with private letters and other surviving personal documents, show Ludwig's lifelong struggle with his orientation.

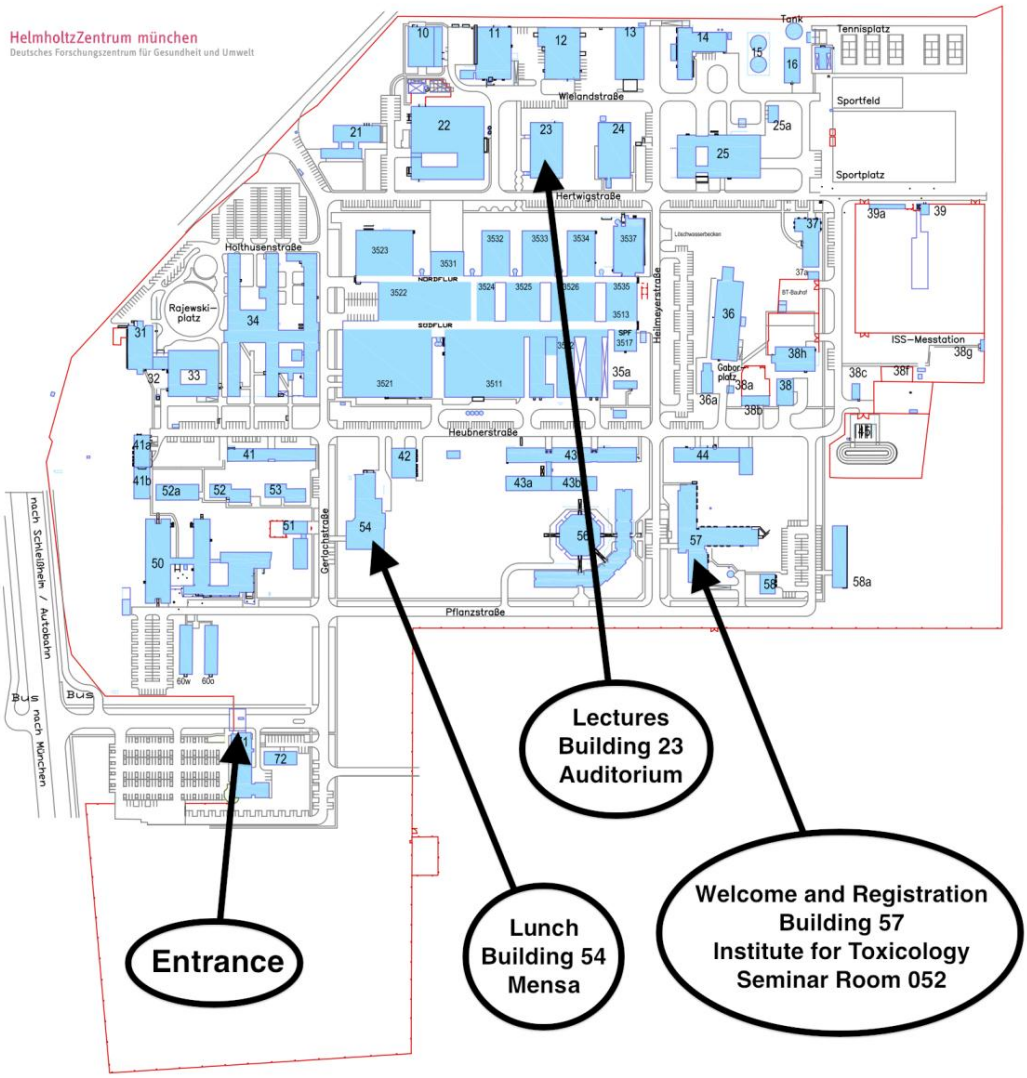
Ludwig was notably eccentric in ways that made serving as Bavaria's head of state problematic. He disliked large public functions and avoided formal social events whenever possible, and preferred a life of seclusion that he pursued with various creative projects. He last inspected a military parade on 22 August 1875 and last gave a Court banquet on 10 February 1876. His mother had foreseen difficulties for Ludwig when she recorded her concern for her extremely introverted and creative son who spent much time day-dreaming. These idiosyncrasies combined with the fact that Ludwig avoided Munich and participating in the government there at all costs, caused considerable tension with the king's government ministers, but did not cost him popularity among the citizens of Bavaria. The king enjoyed traveling in the Bavarian countryside

and chatting with farmers and laborers he met along the way. He also delighted in rewarding those who were hospitable to him during his travels with lavish gifts.

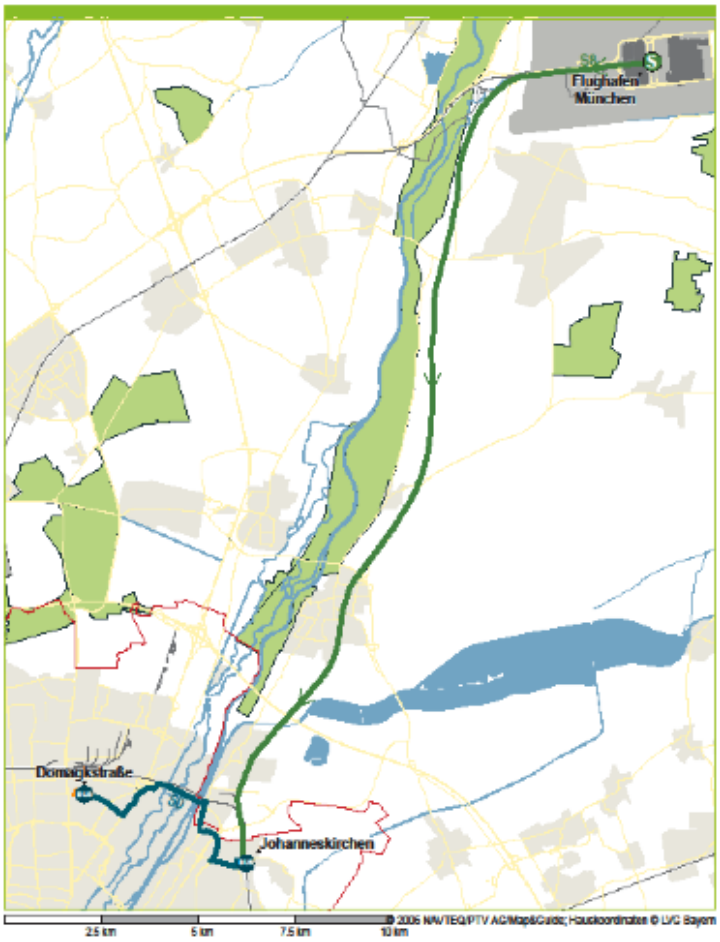
At 4 a.m. on 10 June 1886, a government commission including Holnstein and von Gudden arrived at Neuschwanstein to formally deliver the document of deposition to the king and place him in custody. Ludwig's death three days later was officially ruled a suicide by drowning, but the official autopsy report indicated that no water was found in his lungs. Ludwig was a very strong swimmer in his youth, the water was approximately waist-deep where his body was found, and he had expressed suicidal feelings during the crisis.

Maps

The Helmholtz Campus



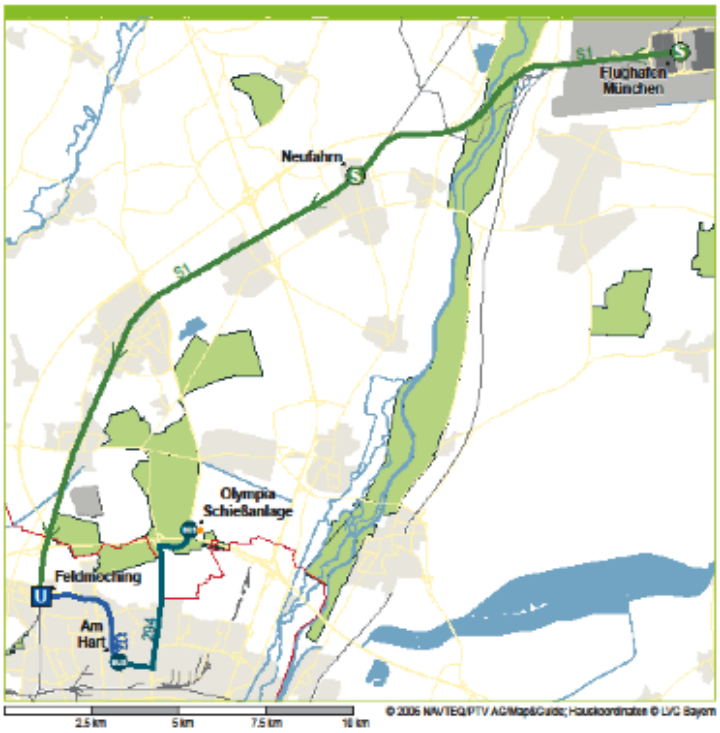
From Munich airport to the Star Inn



- **S-Bahn S8** from Flughafen München to Johanneskirchen
- **MetroBus 50** from Johanneskirchen to Domagkstrasse

You can find connections at http://www.mvv-muenchen.de

From Munich airport to Hotel Olympia



- **S-Bahn S1** from Flughafen München to Feldmoching
- **U-Bahn U2** from Feldmoching to Am Hart
- **Regionalbus 294** from Am Hart to Olympia Schießanlage

ATTENTION: Regionalbus 294 is not available on Sundays !!!

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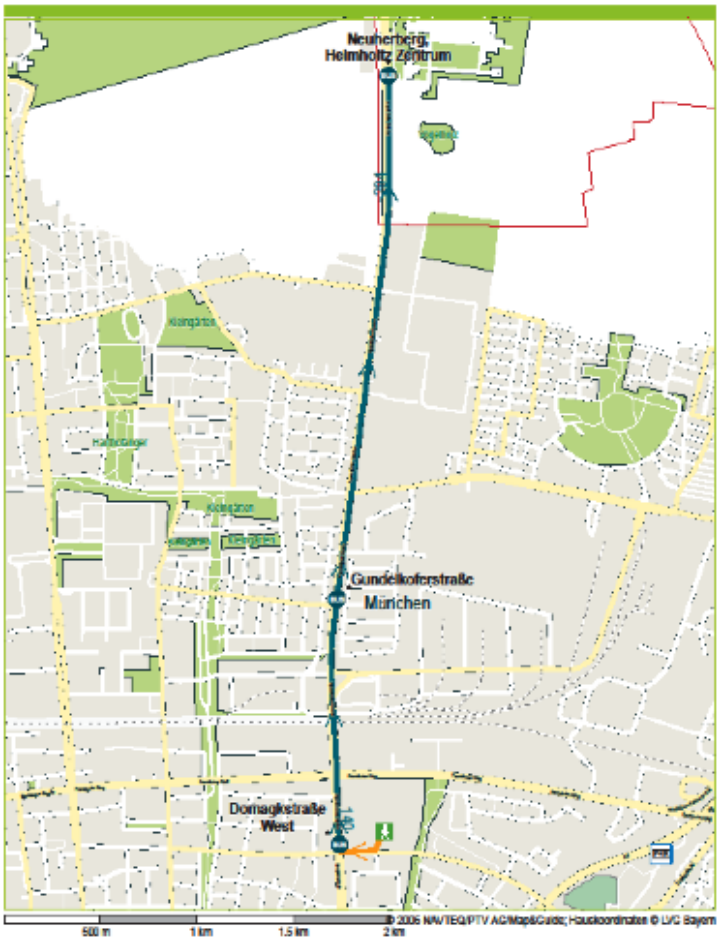
From Star Inn Hotel to the Helmholtz Zentrum



- **StadtBus 140** from Domagkstraße West to Gundelkoferstraße
- **Regionalbus 294** from Gundelkoferstraße to Neuherberg, Helmholtz Zentrum

ATTENTION: Regionalbus 294 is not available on Sundays !!!

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From the central station to Hotel Olympia

- **U-Bahn U2** from Hauptbahnhof to Am Hart
- **Regionalbus 294** from Am Hart to Olympia Schießanlage

ATTENTION: Regionalbus 294 is not available on Sundays !!!

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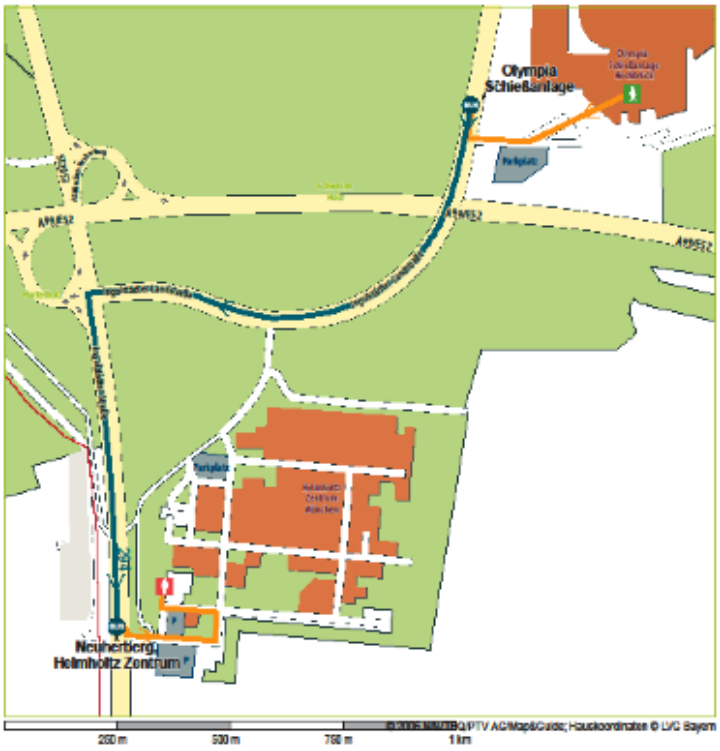
From the Helmholtz Zentrum to Hotel Olympia



- **Regionalbus 294** from Neuherberg, Helmholtz Zentrum to Olympia Schießanlage

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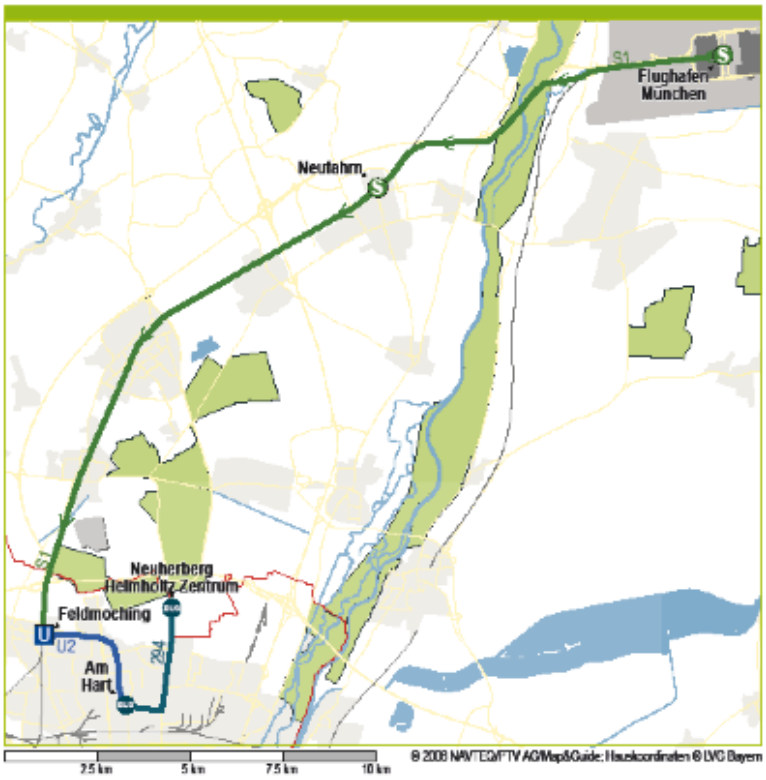

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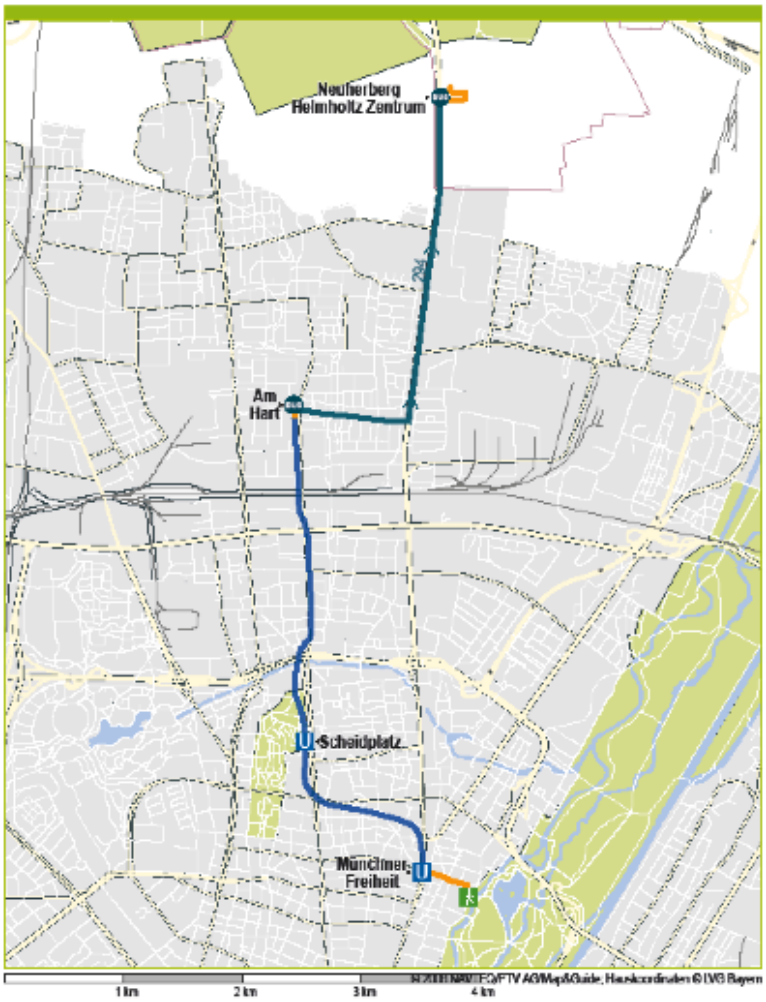
From the central station to the Katholische Akademie

- **S-Bahn S1-S8** from Hauptbahnhof to Marienplatz
- **U-Bahn U3/U6** from Marienplatzt to Münchner Freiheit
- **Walk** from Münchner Freiheit into Feilitzschstraße, then left into Mandlstraße

You can find connections at http://www.mvv-muenchen.de

From the Katholische Akademie to the Helmholtz Zentrum



- **Walk** from Mandlstrasse to Münchner Freiheit
- **U-Bahn U3/U6** from Münchner Freiheit to Am Hart
- **Regionalbus 294** from Am Hart to Neuherberg, Helmholtz Zentrum

ATTENTION: Regionalbus 294 is not available on Sundays !!!

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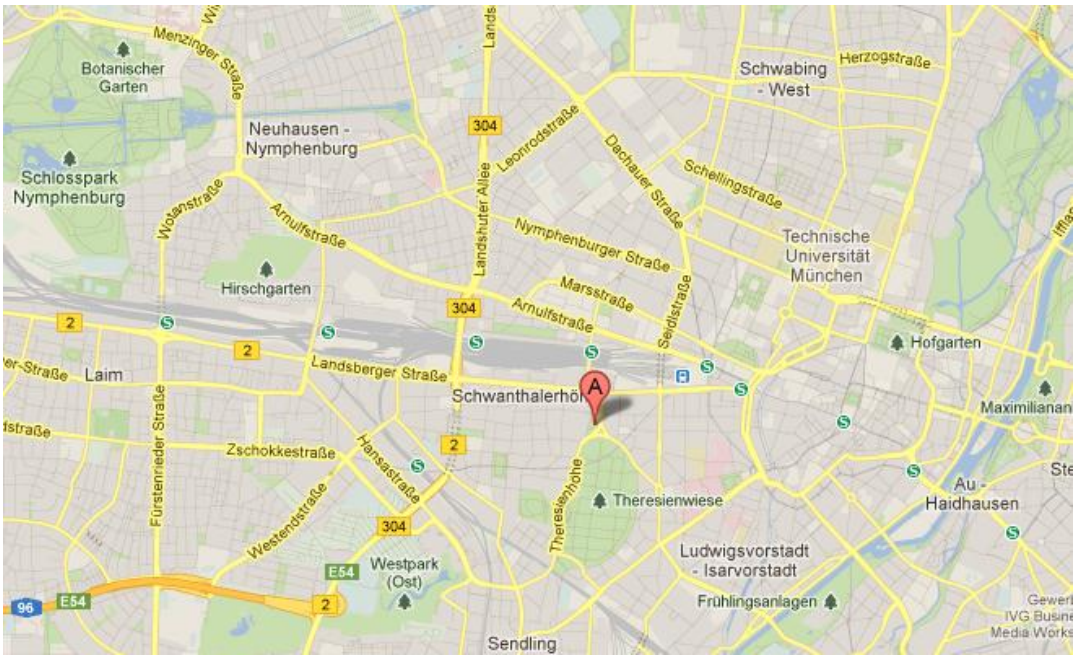
Maps for the Oktoberfest



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Police
110

Emergency call
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Important for those who are accommodated in Hotel Olympia

In case you missed the last bus, the most convenient solution to get home is to take the subway U2 to Feldmoching (final destination). Usually several Taxis are waiting in front of the exit 'Josef-Frankl-Straße'. The costs for this ride are approximately 15€.