# Hazard assessment for chemical substances

Toxicological and ecotoxicological hazard assessment is usually substance oriented. Thus in the NOP, too, the educts and products are assessed separately. All relevant information and the individual hazard assessment derived from it will subsequently be used for a total risk assessment of the experiment which is described in a seperate text.

## Data availability

The basis of any toxicological and ecotoxicological hazard assessment of a chemical is a preferably a complete set of experimental data on physicochemical properties and biological effects.

Therefore we first assess the data availablity for the substances used or produced in the NOP. We categorize the substances according to four categories:

1. Substances, for which - in addition to the very often determined physicochemical properties - toxicological data for mammals and ecotoxicological data are available. These substances are in the best category and thus have the most certain assessment.

2. The next category comprises substances, for which only physicochemical data and mammalian toxicity data are available. Here the hazard assessment is less certain.

3. Those substances for which no experimental toxicological data are available, are placed in the next category. For these chemicals the hazard assessment can only be based on calculated toxicological and ecotoxicological data. So there is still more uncertainty in the hazard assessment.

4. The last category is reserved for the few substances present in the NOP, which neither have an entry in the Chemical Abstracts and thus a CAS No., nor have any experimental data available at all. In these cases the total hazard assessment depends on theoretical methods and thus uncertainty is very high.

## Data availability and access

The first step to start a successful search for substance properties and effects should be to get an overview about what you already know on the chemical in question and what kind of data you are looking for. To find the needed data in literature some essential identification data have to be provided first which can then be used for further searches.

Numerous data sources on the properties and effects of chemicals are available. Also they are often very extensive so that a concise strategy is neccessary to keep searching times acceptable.

Some experience in the use of scientific libraries is absolutely neccessary to perform an effective search. Though much information is also available on the internet it has to be kept in mind that not every material published there originates from reliable sources.

## Identification of a chemical structure by names

Very important for finding information on chemicals are the so-called "rational names", which are constructed directly from the chemical structure by use rules issued by the IUPAC or the Chemical Abstracts Service. These names should provide an unambiguous identifier for the chemical structure in question, so that the structure can be redrawn only from the name - at least for a chemist with some experience in nomenclature.

In principle the naming of chemical structures ("Chemical entities") according to a rational nomenclature should be sufficient, but many of the rational names are extremely long or tongue twisters so that shorter names are often needed. Additionally for certain groups of chemicals as drugs or pesticides "non-rational" names were adopted as official names by international agencies.

Regulations, EU guidelines and laws provide another source of still more different names for one chemical entity, often because of "mixing" trivial names with rational nomenclature or incorrect application of the nomenclature rules. Because of the official nature of these texts these names often become the "official" name of a chemical.

Also there are lots of traditional trivial names that bear some relation to the technical use or the first source of the chemical, but that are not based on the chemical structure. The number of names for one chemical is boosted also by frequently changing trade names. Thus many

different trade names can be "registered trademarks" for only one chemical, e.g. for a drug with different medical indications or with different manufacturers.

## Identification of the structure and the rational name

As shown above names are a bad choice to find information on chemicals. But only a few large data bases support the direct search for a chemical structure and most of them are not freely available to students because of access charges.

To facilitate a thorough search for a chemical, its structure and its rational name have to be known beforehand. The rational name can be derived from the structure more or less easily. Usually it is also possible to draw the structure from the rational name of a chemical. Finding the chemical structure when only a trivial name or a trade name is known becomes more difficult. In this case some special handbooks will be helpful that often also list the CAS-No. The CAS-No. is an important identifier to find data on a chemical in computerized data bases - also on the internet or in commercial data bases like Beilstein Crossfire.

- Textbooks
- Chemical Abstracts Index Guide
- The Merck Index
- Römpp Chemie Lexikon (German only)
- The Dictionary of Organic Compounds (Chapman & Hall/CRC)
- Ullmanns Encyclopedia of Industrial Chemistry
- Kirk-Othmer, Encyclopedia of Chemical Technology
- Chemical catalogs

## Finding characteristic data

TThe chemical struture can be easily converted to a totals formula (line formula). This formula can be used as a starting point to scan large data pools and handbook indices like those of Chemical Abstracts and Beilstein. This procedure is very rapid because a line

formula is a very short notation and it is used by almost all handbooks and chemical encyclopedias as an index item in the form of the Hill system formula:

1. If carbon atoms are present, they are noted first, then hydrogen, and afterwards all other elements in alphabetical sequence of their symbols, e.g. $C_2H_6O$, $C_{10}H_{10}Fe$, $C_{10}H_{12}N_2O_4SSe$

2. If carbon is not present, all elements are noted in alphabetical order of their symbols. (caution: this generates some "unusual" notations for inorganic compounds) e.g. $Cl_3Fe$, $H_2O_4S$, $H_3O_4P$, $CaN_2O_6$

3. Hill line formulas are then sorted alphanumerically, e.g. $AlCl_3$ before $CH_3Cl$ before $CH_4$ before $CO_2$ before $C_2H_2$ before $Cl_2Zn$

## Finding relevant data for hazard assessment of chemicals

While data used for the characterization of chemicals - like melting point, boiling point, refractive index, optical activity are found in many handbooks and chemical encyclopedias, more specific data like solubilities, distribution coefficients, pKa values, vapor pressures are not as easily located in literature.

But there are many more specific handbooks providing these data. Especially for interdisciplinary searches, many of the relevant handbooks are not found in the chemistry section of the libraries but in the medicine, biology, agricultural, engineering or other sections. Thus these sources are sometimes overlooked by students. Additional consideration should include the fact that these handbooks are often written for the specific requirements of the respective target group. Thus it can be expected, that e.g. "Ullmann's Encyclopedia of Industrial Chemistry", written primarily for engineers, contains information on technological properties of chemicals and on their use, industrial syntheses, thermodynamic data neccessary for chemical engineering. But this handbook will provide almost no data on biological effects of chemicals. In contrast a handbook of environmental chemicals will be excellent to look for toxicology and ecotoxicology of chemicals, exposition and analytical chemistry, but not for preparation methods.

We used (mainly) the following sources for gathering the data of the NOP:

- CRC Handbook of Chemistry and Physics

- The Merck Index

- BUA-Reports, of which there are currently (2012) ca. 266

- Chemical catalogs,

- Material Safety Data Sheets (MSDS), which are available from many manufacturers on CD-ROM or on the internet. A combined list of Material Safety Data Sheets of different manufacturers (portal only in German, but MSDS often in German and English) can be found at EUSDB.

More "International Chemical Safety Cards" ICSC are provided by the "Bundesinstitut für Risikobewertung" (former BgVV).

The most comprehensive compilation of toxicological data is the "Registry of Toxic Effects of Chemicals" - RTECS, which was always the primary data source for toxicological data in the NOP.

For some substances for which there is little information in the mentioned publications we sometimes succeeded in finding relevant data on the internet by using chemfinder.cambridgesoft.com or by typing in the CAS-No. (with hyphens) at search engines like Google.

## Computer assisted assessment methods

If no relevant information on a particular property of a chemical can be found, it is nowadays possible to resort to computer assisted assessment methods, which are in principle available for many substance properties. The accuracy of these computational methods often depends heavily on the specific property to be determined and on the number of experimental values that have been used to refine the computational method. The assessment of the correctness and accuracy of the computed values requires background knowledge and a lot of experience!

In the NOP we have used these methods for only three systems: For calculating physicochemical data and for properties that determine the environmental distribution and fate of chemicals, we used the program EPI Suite™.

To make use of the international expertise on structural elements in chemicals that pose a toxicological risk to humans we tested the substances of the NOP on so-called "Structural Alerts". Here we used the Software DEREK which is also broadly used in industry.

Finally some biological effects were assessed with TOPKAT®. TOPKAT uses complex algorithms based on two-dimensional descriptors. The validity of each assessment is defined by an "Optimum Prediction Space", that gives the span of values considered probable on each assessment.

## Assessment according to German TRGS 600

According to the German Toxic Substances Act ("Gefahrstoffverordnung") the employer has the liability to check if substances, preparations or products are available which pose a lower risk than those that are currently used. If it is reasonable and if it is necessary to save the life and health of the employees, he has to use the substances, preparations or products with the lower risk. This regulation can be followed practically by these steps:

- Obtain information on the substances used in the work process
- Determine the dangerous substances with unknown or not adequately known dangerous properties
- Compiling of a catalog of dangerous substances
- Check if alternate less dangerous substances or procedures are possible.

We applied this scheme to the experiments of the lab course to assess the potential danger to human health. Information on the substances has been compiled by us and is available in detail in our data base. Also the substances used or produced in the experiments can be listed in tabular form as a catalog of (dangerous) substances. To check, if alternate and less dangerous procedures or substances are available and beneficial, we must compare the alternatives in regard of their occupational safety.

We use the effect factor model of the TRGS 600 as an established and official assessment scheme for chemcials In general for this assessment scheme data are needed regarding the

toxicological endpoints acute toxicity, skin irritation, mucous membrane irritation, mutagenic potential, toxicity of repeated doses and skin sensitization. If some of these data are lacking, they are approximated by the use of a special effect factor.

If no data are available on acute toxicity, skin irritation, mucous membrane irritation or mutagenic potential and if also no permissible air concentration is assigned, the effect factor is to be set to 100.

If no data are available on toxicity of repeated doses and if also no permissible air concentration is assigned, the effect factor is to be set to 100.

If no data are available on sensitization and if also no permissible air concentration is assigned, the effect factor is to be set to 500.

The value of the effect factor is otherwise determined by the risk phrases (R phrases) and by other potential dangers to human health which are not expressed with a specific R phrase, like the substance being skin permeable, the pH value, suspected carcinogenicity etc.

For known R phrases and permissible air concentrations the effect factor of a substance can be directly found using the following table. If a substance belongs to more than one category in this table, the higher effect factor takes precedence.

**Table 1**: Table of effect factors

| R-phrase or other danger to human health | Effect factor |
|---|---|
| R45, R46, R49, M1, M2, K1, K2 | 50 000 |
| R26, R27, R28, permissible air concentration < 0,1 mg/m$^3$ | 1 000 |
| R32, R60, R61, RE1, RE2, RF1, RF2 | 1 000 |
| R35, R48/23, R48/24, R48/25, R42, R43 | 500 |
| R23, R24, R25, R29, R31, R34, R41, skin permeable[a] | 100 |
| R33, R40, R68, K3, M3, pH<2 bzw. pH>11,5 | 100 |
| R48/20, R48/21, R48/22, R62, R63, RE3, RF3 | 50 |
| R20, R21, R22 | 10 |
| R36, R37, R38, R65, R67 | 5 |
| R66, other R phrases or permissible air concentration >100 mg/m$^3$ | 1 |
| Substances known to have a low risk to human health | 1 |
| Permissible air concentration (PAC) between 0,1 and 100 mg/m$^3$ | 100/PAC |

[a] if R phrases R20, R21, or R22 are no given

# Ecotoxicological hazard assessment

Our ecotoxicological hazard assessment is connected to the EU classification guideline. A very similar assessment is required by the German "Umweltbundesamt" when they categorize substances and preparations into water pollution classes under the administrative regulation for water-polluting substances (German VwVwS) of 17.05.1999 - Guideline for self-categorizing. (German original: "Einstufung von Stoffen und Gemischen in Wassergefährdungsklassen gemäß Verwaltungsvorschrift wassergefährdende Stoffe (VwVwS) vom 17.05.1999 - Leitfaden für Selbsteinstufer"). For substances with the classification of R phrases R50/53, R51/53 or R52/53 the $LC_{50}$- or $EC_{50}$-values for the three main categories of aquatic organisms - fish, water fleas and algae - are used in the ways shown in the next table. The assessment is always based on the $LC_{50}$ or $EC_{50}$ for the most sensitive species. Additionally it is taken into account if the substance is bioaccumulated and how easily the substance can be biologically degraded. The last property has three categories: A substance is easily biologically degradable (according to OECD 301), if it is degraded by non-adapted soil and waste water microorganisms within 28 days for >60 % or >70 % mineralized (depending on the type of measurement 60 % for measurement of the oxygen consumption, 70 % for elimination of dissolved organic carbon). Substances are categorized as inherently biologically degradable (according to OECD 302), if they are degraded by adapted microorganisms within 28 days for more than 60 % or 70 % mineralized. (Differing from this according to OECD 302 B 70 % degradation has to be reached in 7 days.)

If data on biological degradability and on bioaccumulation are lacking, we have used theoretical prediction methods for the substances of the NOP (especially EPIWIN). The guideline of the German "Umweltbundesamt" uses in case of missing data on toxicity to aquatic organisms an estimated toxicity of <1 mg/L. In case of missing data for biological degradability it uses an estimate of "not easily degradable", and in case of missing data on bioaccumulation it uses an estimate of "high" bioaccumulation potential (BCF >100) We assess a substance with an R phrase R50 or R50/53, or with water pollution class (WGK) 3 as having high ecotoxicity. Accordingly, R phrases R51/53 or water pollution class (WGK) 2 is assessed as medium ecotoxicity, R52/53, R53 or water pollution class (WGK) 1 as low ecotoxicity. If the substance is classified by the EU and has only R phrases other than R 50-58, we estimate it to have no ecotoxicity.

**Table 2**: Assessment table

| Biological degradation | Bioaccumulation potential | EC$_{50}$ [mg/L] | | | |
|---|---|---|---|---|---|
| | | > 100 | 10 – 100 | 1 - < 10 | < 1 |
| Easily | Yes | | | R51/53 | R50/53 |
| Easily | No | | | | R50 |
| Inherently | Yes | | | R51/53 | R50/53 |
| Inherently | No | | | R51/53 | R50/53 |
| Not easily | Yes | | R52/53 | R51/53 | R50/53 |
| Not easily | No | R53 | R52/53 | R51/53 | R50/53 |

# Byproducts and impurities

   Potential byproducts of the reactions and impurities of the educts are taken into account for our (eco)toxicological hazard assessment, if they are probably present in the crude product in concentrations above the limits given in the "Preparations guideline" of the EU. These limits are:

   - ≥ 1 % for substances labeled with C (corrosive), Xn (harmful to health) or Xi (irritant), or

   - ≥ 0,1 % for substances labeled with T (toxic), T+ (very toxic) or N (dangerous for the environment).

   Substances that are carcinogenic, mutagenic, or posess reproductive toxicity in animals or man are principally labeled at least with T (toxic). Substances which are suspected carcinogens, mutagens or suspected reproductively toxic are labeled with at least Xn, if they are not acutely toxic. For substances with no available labeling (e.g. from chemical catalogs), the lower concentration limit is to be used.

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