Environmental Assessment Tool for Organic Syntheses

EATOS

Version 1.1

Marco Eissen
Swiss Federal Institute of Technology Zürich
Laboratory of Technical Chemistry
ETH Höngerberg, HCI G123
8093 Zürich

Jürgen O. Metzger
Carl von Ossietzky Universität Oldenburg
Fachbereich Chemie, Organische Chemie
Carl-von-Ossietzky-Str. 9-11
26111 Oldenburg

New in EATOS v1.1

The instruction manual on hand refers to EATOS v1.0. But the software EATOS v1.1 contains some few improvements that are resumed in this section.

1. Products of syntheses entered can be imported as substrates or catalysts, for instance in order to create a synthesis sequence. Now this possibility has been extended to solvents and auxiliary materials.

2. The horizontal lines of the graphical representation can be faded in and out optionally. (see Diagram → Style → Horizontal lines).

3. Furthermore the ordinate in the graphical representation will be provided with a legend, which can get brackets optionally by the user. (see Diagram → Legend → Units in brackets). Moreover the user can alter the legend by clicking the left mouse button.

4. The economic index (CI) can be indicated in Price / g or Price / kg. The choice is possible in the window "Weighting of the weightings", which can be called up under "Miscellaneous".

Contents

1   Setup Manual

1.1   Prerequisite for the Operation/Setup of the Software

1.1.1   Prerequisite for the Operation

- Hardware and system – prerequisite:

- Minimum configuration: CPU with > 200 MHz, 64 MB RAM, 10 MB free hard disk space

- Possible operating systems: all operating systems a „Java Virtual Machine" is available for, e.g., Windows 95/98/2000/NT, Linux, etc..

- An already setup version of the Java 2 Runtime Environments v1.3.x (Java 2 Runtime Environment, abbr. J2RE1.3)

- The setup can be recommended only for experienced users and, usually, should be made by the system administrator. For setup please refer to chapter 1.1.2, p. 7.

Remark: As java is an interpreted programming language, for the operation of EATOS a so called Java Virtual Machine always is mandatory. A free of charge version of such a virtual machine called „Java Runtime Environment" can be downloaded from http://java.sun.com/j2se/1.3/.

1.1.2   Software Setup

EATOS:

Edit Target Directory: By the EXPLORER you create the directory where you save the software. We recommend „C:/Programs/Eatos".

Extraction of the Program Files: Extract the archive Eatos.zip in your target directory.

Execution of EATOS: Double-clicking Eatos.jar or the linkage to be created in the next step, you start the program if JRE.1.3 is setup correctly.

Creating a linkage (optionally): Open the Explorer, change into the Eatos program directory, keep the right mouse button pressed, pull it about 1 cm to the right, release the mouse button, and select „*CREATE LINKAGE(S) HERE*" in the emerging small window. This linkage you can assign optionally the EATOS-symbol (Eatos.ico) (right mouse click on *LINKAGE* $\Rightarrow$ *CHARACTERISTICS* $\Rightarrow$ *OTHER SYMBOL*)

J2RE1.3:

Download of Java 2 Runtime Environment Standard Edition 1.3 (J2RE1.3): (Size: about 5 MB) For Windows under http://java.sun.com/j2se/1.3/jre/download-windows.html and, generally, under http://java.sun.com/j2se/1.3/. In the last case, you first must select the platform desired to use (Windows, Linux, Solaris), afterwards, you must choose the version „*US English*", or „*International*", respectively. The indicated conditions are accepted by *ACCEPT* and, usually, surveyed by „*HTTP download*". Please register the location where you save this file.

Setup of J2RE1.3: Setup is made by double clicking the „j2re-1_3_1-win.exe" just downloaded. Usually, the program is setup under the preset setup path.

Troubleshooting

In case of occurring errors please try the following steps. If you got any doubts please ask your system administrator.

1. Start the MS-DOS-Request for Input (Windows 95/98), resp., the Command-Prompt under NT and Windows 2000.

2. Input „java-version". The following lines should appear:

> Java version „1.3.1"
>
> > Java™ 2 Runtime Environment, Standard Edition (build 1.3.1-C)
> >
> > Java HotSpot™ Client VM (build 1.3.1-C, mixed mode)

If this does not appear, the J2RE is not installed correctly!

If the J2RE is installed correctly, e.g., you change with „cd c:\programs\eatos" into the EATOS-directory. There please execute „java –jar Eatos.jar". After some seconds, the message „This is Eatos v1.00 ..." should occur. It this does not appear, the program could not be started. Please regard possible error messages to recover the cause of the problem. Usually, the error should not be caused by EATOS. Please make sure that you are using the correct version of the J2RE (1.3, 1.3.1, resp.).

If you start the program as described under 3., possibly occurring program-errors produce textual outputs. In this case, these are real, non-intended errors of the program. Please contact Mr. Marco Eissen so that he can eliminate them.

Exception: Apparently, under Windows NT (4.0) EATOS can not be started by users of the main users' group, but only the system administrator himself (which means with complete rights of access). According to our experiences, this problem is not caused by EATOS but by the J2RE and can be solved by the system administrator by change in rights of access.

2   Short Operations Manual for EATOS

After the installation of EATOS, you start the program by a double-click on its symbol. With the window opened, clicking *NEW* you build up a project you can call up by *OPEN*.

In this project, please register all syntheses which should be examined. Therefore, after activating the button *NEW*, you input the appropriate stoichiometric equation. The syntheses entered in this way can be called up by *OPEN*. The quantities of the substances, the yield, and, in the case that substance-specific properties should be included into the study, toxicity data, etc., will be entered by *WEIGHTING*.

Clicking *EXPORT,* substances with all substances' data can be exported in the substance-list and are available for other examinations. By *IMPORT,* substances from the substance-list are called up and integrated into the application opened.

Instead of substances, in the register sheet Substrates and Catalysts you can import other products from other syntheses of the same project, as well. In this way, synthesis sequences are made out.

The graphic representation of the results can be achieved by *EDIT CALCULATE* (in case of emanating from an opened synthesis), and by COMPARE, if you selected one or more syntheses in the project window. In this way, syntheses, synthesis sequences, resp., can be compared with each other.

The graphic column chart indicates the input (S^{-1}) and output-1 (E), referring to a product unit, as well as the environmental indices EI_in and EI_out, which represent a weighting of the substances of the input and output with their substance specific properties according to a method described in this instruction manual. The data set the column segments are based on is output by clicking.

Using the command line, you can adjust various versions of the results. You can export the diagram by *DIAGRAM EXPORT* to insert it into other software programs as an object.

3   EATOS

3.1   Starting EATOS

3.1.1   Start

You can start the program EATOS by double-clicking the icon or calling up in the corresponding data file directory. With the following window the program starts (Figure 1, p. 11, left hand). After *GO TO*: the directory is indicated, where the program EATOS is included. The name of the up-to-date data file directory reads EATOS ⊟Eatos ▼ as well, if the program is saved in a so named directory. Besides, it is possible to change into another directory by clicking this button or the symbol ▣, which leads to the next higher hierarchy level. You arrive back to the setup directory with the symbol ▣. You can create new files with the symbol ▣.
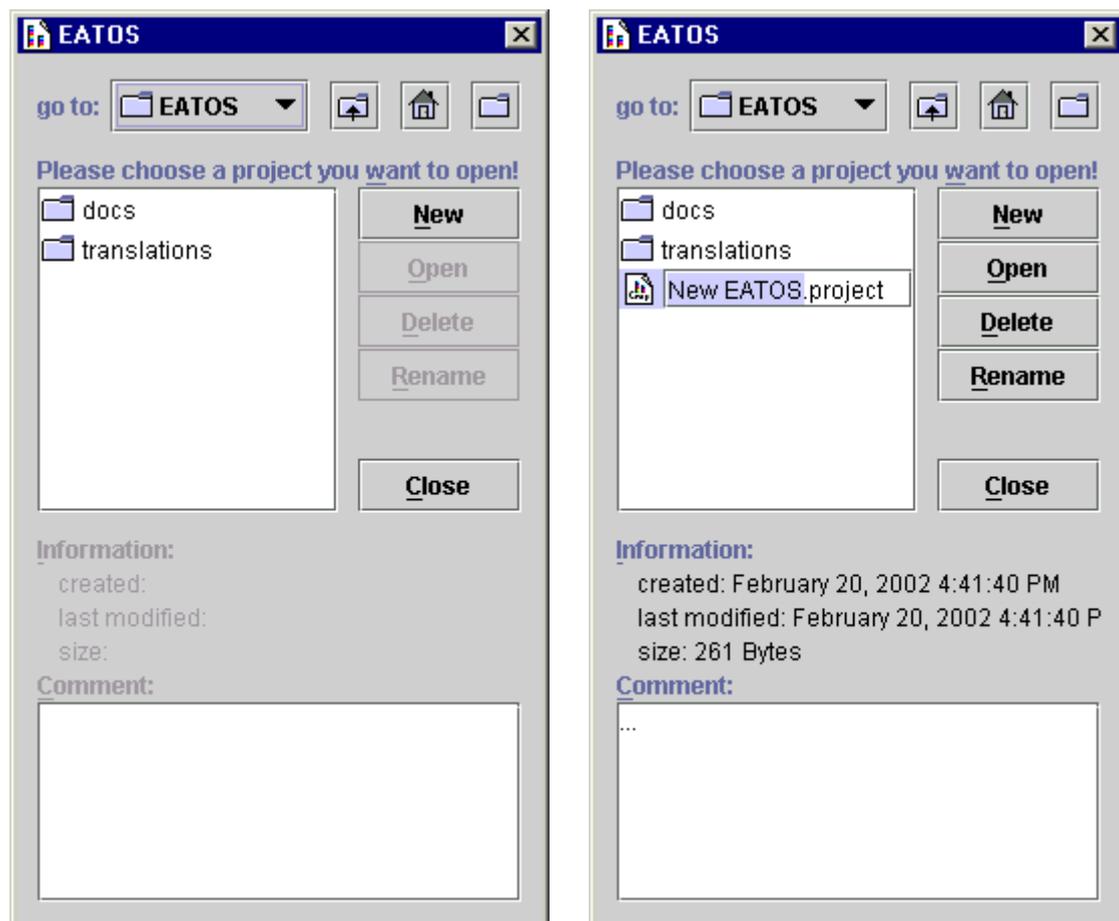
Figure 1   EATOS start window and start window with the new EATOS project

3.1.2 New EATOS Project

By clicking the button *NEW* you can make out a new so called project, where all syntheses relevant for an examination are arranged in, later (Figure 1, p. 11, right). After selecting *NEW EATOS.project* , under *INFORMATION* creating date, date with the last change, as well as the file size appear. In the comment field remarks concerning this file can be indicated.

By the button *RENAME* this *NEW EATOS.project* can receive a new name, which must be confirmed with the input key. However, the file name *project* must be maintained in any case. It offers itself, to select as a name the target product of the synthesis sequence to reflect the topic of the project. For this operations manual, the example of the synthesis of 4-methoxyacetophenone was selected, and *NEW EATOS.project* was renamed *methoxyacetophenone;4-.project*, correspondingly.

3.1.3 Delete Project

By the button DELETE the file can be removed, immediately.

3.2   Input of Synthesis Data

3.2.1   New Synthesis (Part I)

To fill this project *methoxyacetophenone;4-.project* made out new with syntheses, you select it and click the button *OPEN* (Figure 1, p. 11). In the new window, using the button *NEW*, a synthesis can be put in (see Figure 2, p. 13). For good reason, the synthesis similar to the project is named according to the product that is made. In the example continued, this is *4-methoxyacetophenone*, and, in this way, it does not distinguish from the project's name. Only by the addition ‚Organikum', which refers to the data source, - namely the book of Practical Course Organikum (20th Edition, Deutscher Verlag der Wissenschaften, Berlin, **1996**, ISBN 3-335-00492-2) – a name which is deviating a little bit, results. In the range of *Literature/Laboratory Journal* the journal source, the synthesis is based on, and its input – for this please refer to 3.4 (p. 49) – which is made later, or the experimental procedure from the lab journal, will arise.
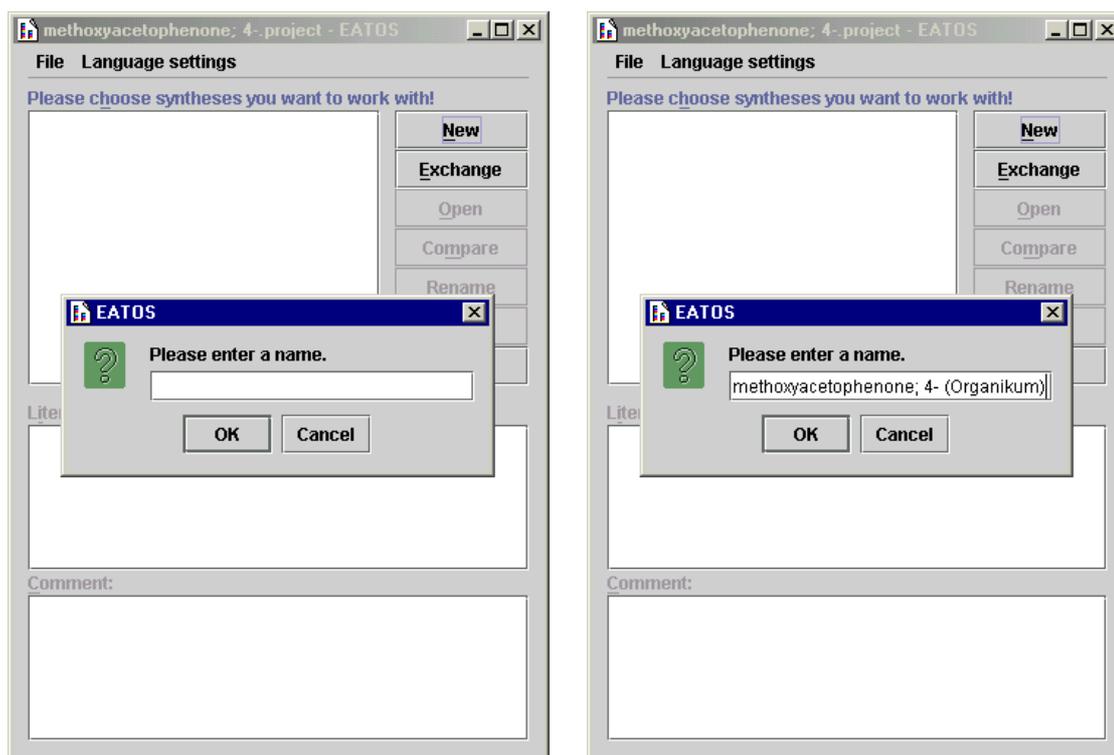
Figure 2   Make out and name new synthesis

3.2.2   Stoichiometric equation

After confirming the synthesis' name with *OK*, for ensuring a correct calculation of the material flows, in the following window you first must input the stoichiometric equation (Figure 3a, p. 14).

The considered synthesis of 4-methoxyacetophenone, according to the literature indicated in chapter 3.2.1 (p. 13), is based on the following stoichiometry.
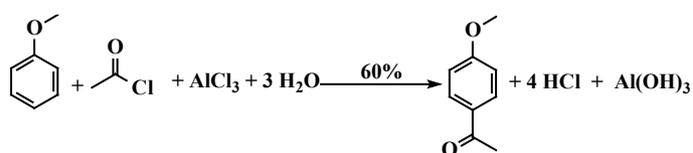
Scheme 1 Stoichiometry of the synthesis of 4-methoxyacetophenone

In the register sheets *SUBSTRATES*, *PRODUCTS*, and *COUPLED PRODUCTS* you input the substances taken part with their appropriate stoichiometric coefficients of Scheme 1 and their formulas (Figure 3 b - d). By clicking the buttons *MORE* and *FEWER*, the number of substances and coupled products can be varied. If the data of particular compounds is already present in the internal list of substances (refer to chapter 3.5, p. 50), they can be merged here by clicking the button *IMPORT* (refer to chapter 3.6, p. 51), so that name of substance, formula, and material parameter are already present and must not be input once again. More details concerning the topic substance list are explained in these chapters.
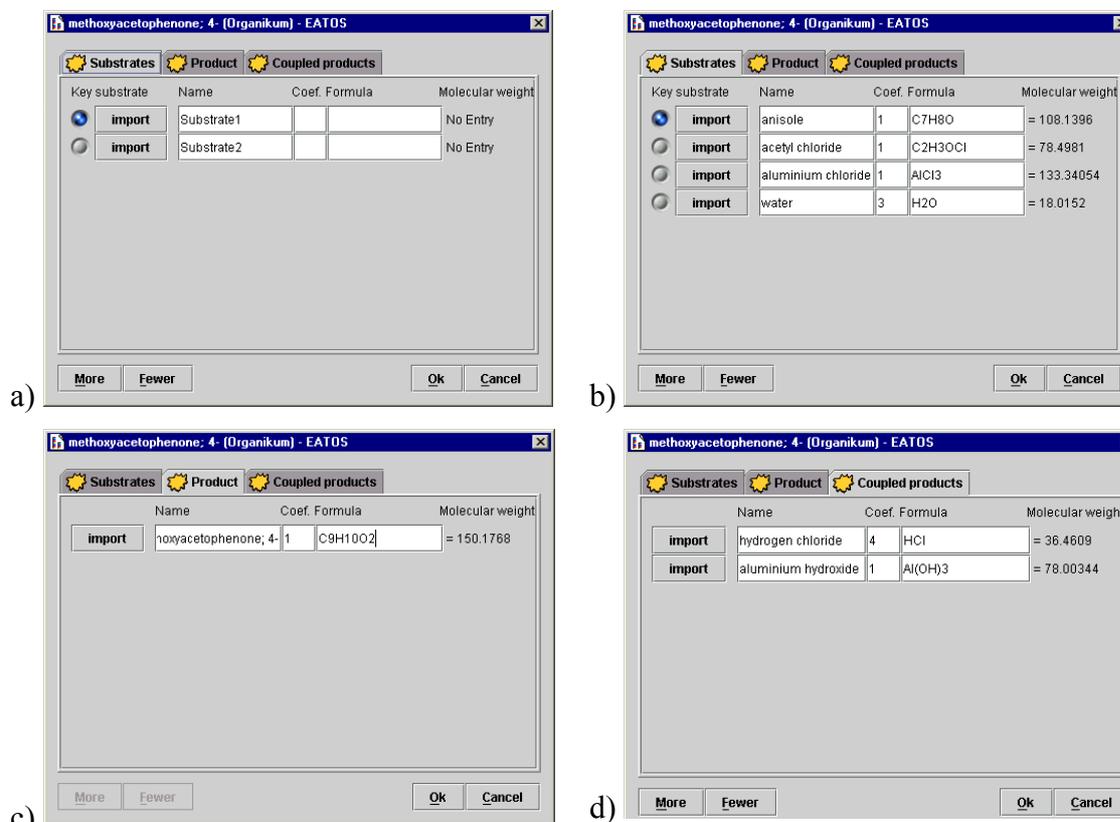
Figure 3   Input of the stoichiometric equation of a synthesis

The substrate to which the yield, as well as a possibly determined conversion are referred – the so called key substrate – will be marked with a blue point (click to the left of *IMPORT*). By clicking *OK* after complete input of substrates, product, and coupled products, the correctness of the stoichiometric equation will be checked internally and determined for the synthesis' name constantly. If, subsequently, a modification of the stoichiometric equation or the determination of the key substrate is necessary, you will have to input a completely new synthesis including all data by clicking *NEW* (Figure 2, p. 13). Therefore, already during the input of the stoichiometry of the equation, you absolutely have to pay attention to the correct allocation of the key substrate.

3.2.3   New Synthesis (Part II)

Confirming the stoichiometric equation with *OK* in Figure 3 (p. 14) leads back to the window of project where the input synthesis appears with its name (Figure 4, p. 15, left hand).
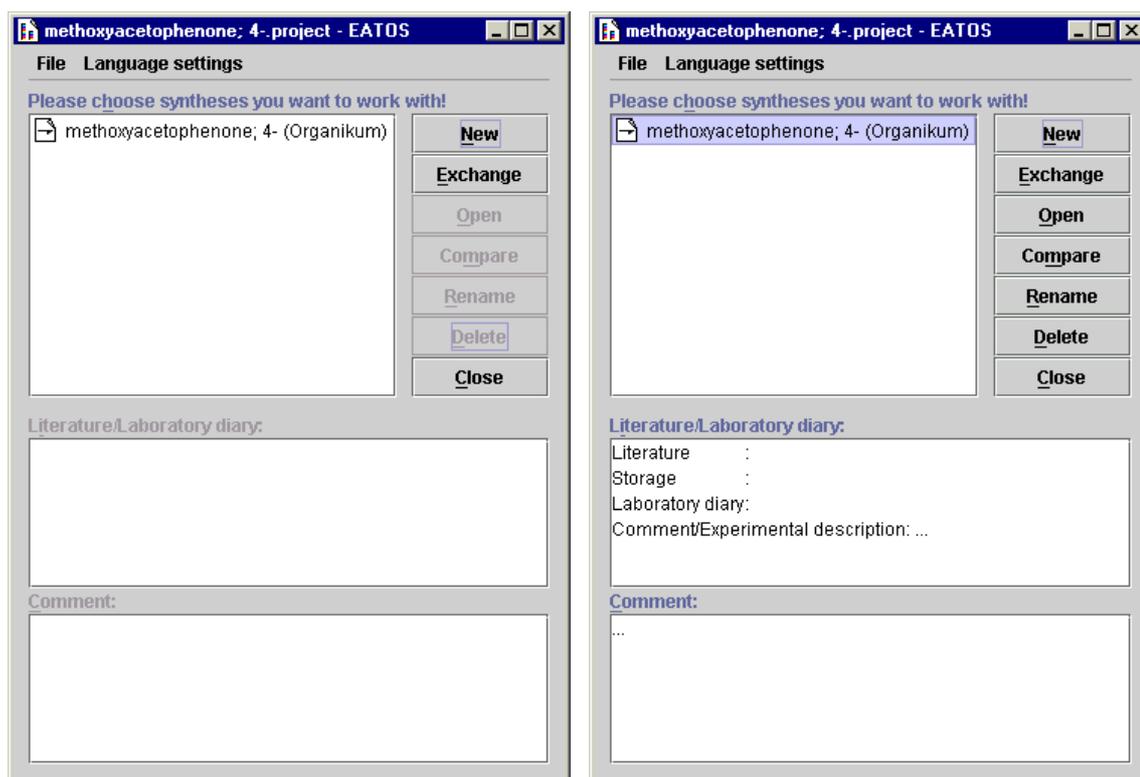
Figure 4   Edit a new synthesis

Further syntheses, e.g. of the same product by other methodologies, similarly can be added by *NEW* or *EXCHANGE* of corresponding syntheses, which are input in other

projects, already. But more concerning the topic *EXCHANGE* you can find in chapter 3.2.3, p. 30). By clicking *CLOSE* you will return to the start window.

But normally, the synthesis input is processed following directly, to input and examine synthesis data and substance properties. By selecting the synthesis, you can operate with the buttons gray underlaid so far (Figure 4, p. 15, right hand) and rename or delete the synthesis as usual. Via the button *COMPARE* several syntheses can be compared (chapter 3.7, p. 57). Clicking the button *OPEN*, a new window appears, where you input all further data concerning the synthesis and the substance properties (Figure 6, p. 19).

3.2.3.1 Command line for the editing of the synthesis

Figure 5   Edit synthesis and substance properties

The command line consists of *FILE*, *EDIT*, *SYNTHESIS SEQUENCE*, and *?*.

Under *FILE* you can save the project or, as well as the synthesis, change it or terminate the program.

EDIT makes it possible, after the input of all data, to *CALCULATE* and visualize a graphic flip chart to the synthesis, among other things, mediating information on material input and output. This function corresponds to *COMPARE* in Figure 4 (p. 15), with the difference that only the synthesis opened at present is indicated. Further functions under *EDIT* are *WEIGHTING* (see chapter 3.3, p. 32), *LITERATURE* (see chapter 3.4, p. 49), *SUBSTANCE LIST* (see chapter 3.5, p. 50), and *MODE*). The mode

of the window in Figure 6 (p. 19) can be changed from *SIMPLE* into *EXTENDED*. However, the simple mode is completely sufficient to the full functionality of EATOS! Even it is sufficient to only input the substance quantities of all materials used (substrates, catalysts, solvents, and auxiliary materials) in [g] and the yield in [%]. However, specifications of volume always force the specification of the density. For a clearer reproduction of the substrate names in the detail views of the results' diagram (chapter 3.7, p. 57), there is the possibility to indicate an abbreviation, e.g., DMSO instead of dimethyl sulfoxide. Adjusting the mode on *EXTENDED*, you can input into the investigation further knowledge concerning the synthesis. In this way, *RECYCLABLE QUANTITIES* and *EMISSIONS* known from a procedure can be integrated, and specifications on the degree of purity of the materials used can be refer to both, to an actually pollution not known in detail, and to substances in a material mixture, *ADDITIONAL INGREDIENTS* can be specified (see chapter 3.2.3.11, p. 28). There exist further special input options, possible by the extended mode, for catalysts (chapter 3.2.3.5, p. 19), product (chapter 3.2.3.8, p. 25), coupled (chapter 3.2.3.9, p. 27), and byproducts (chapter 3.2.3.10, p. 27).

Clicking *SYNTHESIS SEQUENCE* you can take over newly data changes in a selected substance of a synthesis in a synthesis sequence (also compare chapter 3.6.3, p. 53) characterized by an imported product (also compare chapter 3.6.2, p. 52) of another synthesis of the project opened, by *REIMPORT*, if this raw data file still exists. *REIMPORT (RECURSIVE)* means that all data of the synthesis opened will be updated. On the other hand, *REIMPORT (RECURSIVE, FOR ALL SUBSTANCES)* really causes an updating for all substances of the total synthesis sequence.

With *? HELP*, a schematic overview of the *MASS-BALANCE REGIONS* and information on the program EATOS is callable.

3.2.3.2 Toolbar weighting, literature, substance list

Clicking *WEIGHTING* you can input material parameters, such as R-phrases and toxicological data for the synthesis' substances, for internally determining load factors which make possible a weighting of the material balance in view of environmentally relevant aspects for an estimation of the synthesis' danger potential. A description of the *WEIGHTING* is given in chapter 3.3 (p. 32). Additionally, please refer to chapter 3.4 (p. 49) and chapter 3.5 (p. 50) for detailed explanations concerning the input of the literature and editing the substance list.

3.2.3.3 Comment field

The comment field on a register sheet of the window in Figure 6, p. 19) serves for making notes concerning the respective substance in connection with the presently opened synthesis.

3.2.3.4 Substrates

The first view after opening (*OPEN*) a (new) synthesis according to Figure 4 (p. 15), is the register sheet *SUBSTRATES* (Figure 5, p. 16). At the lower end, this register sheet is differentiated in the substrates input before, which are callable, respectively. The substrate marked with a blue point is the key substrate, where yield and, if need be, conversion refer to. In case you determined the key substrate wrongly when inputting the stoichiometric equation (see Figure 3, p. 14) ($\rightarrow$ check!), you cannot correct this for the synthesis opened. Instead of this you must input the synthesis again!

In the simple mode, if meaningful, firstly you can determine an abbreviation which possibly later will allow a more clearly orientation in the detail view. The quantity indication can be made in different units and must be of one value > 0. Using the symbol ![symbol], instead of [g], you can select [mol] or [ml], as well. In the last case, however, the indication of the density is necessary. According to literature, for the example of the synthesis of 4-methoxyacetophenone you input 1 mole ansiole, 1.05 mole acetyl chloride, and 1.2 mole $AlCl_3$. With 500 g ice the necessary destruction of the keto-aluminum complex takes place. 3 moles can be ascribed to the substrates and the rest to the *AUXILIARIY MATERIALS* (chapter 3.2.3.7, p. 24).

The button *IMPORT* makes it possible to overwrite the regarded substrate by a substance already saved in the substance list with a possibly more extensive data file with exception of the comment field, which inputs are preserved thereby. So that you do not need to search for the substrate in the total substance list, only substances with the same molecularly weight are displayed. Additionally, this button represents the central interface, which syntheses (under formation of a synthesis sequence) can be linked by with each other! For this purpose, you choose another synthesis in the same project, its product, now regarded as intermediate, enters the synthesis opened as substrate. A product already input in the project in form of a synthesis can be imported as well when making out a subsequent synthesis using this product as synthesis, when inputting its stoichiometric equation (see Figure 3, p. 14). Further information concerning the topic *IMPORT* you will find in chapter 3.6.2 (p. 52).

By the button *EXPORT* you can export substances into the substance list, so that they are available for other applications with their total data file.

By the button *RENAME* you assign another name to a substance. By *RESET* you delete the register sheet-data input before.

In the extended mode (Figure 6, p. 19), further information concerning the substrates can be brought in. If substrates are used in excess, and regained when processing or by the reaction guidance, you can indicate the *RECYCLABLE QUANTITY*. In case of available information concerning materials emitted during a procedure, you can input them under *EMISSIONS*. For the sake of the characterization, there exists the possibility to indicate the *CAS-NUMBER* of the substance (but the *CAS-NUMBER* has no further program-internal effects). Regarding the key substrate you can input the grade of the

conversion, as far as known by gaschromatographical experiments. Internally, this indication automatically is ascribed to the other substrates, as well. Thereby and by the substrate excess the quantity of the non-converted substrates is determined internally. Generally, we recommend to follow preparative conversions gaschromatographically to be able to judge on the process of the synthesis. Additionally, you can consider the purity of the used substrates, which does not only exclusively mean the impurity only constituting little per cent points and being unknown in detail, but also additional ingredients, which can be indicated in detail in case of material mixtures. More information concerning the input of *ADDITIONAL INGREDIENTS* is described in chapter 3.2.3.11 (p. 28).

Figure 6   Extended mode at the example of the input of the substrates

3.2.3.5   Catalysts

With the name *CATALYSTS* not only do we mean real catalysts in this program. Furthermore, this register sheet is intended as well for initiators and activators which, generally, are used substoichiometric , but derived from the synthesis partially changed. In the example of the synthesis of 4-methoxyacetophenone– $AlCl_3$ is regarded as substrate – we use no catalysts, so that the register sheet *CATALYSTS* is explained by another example, that of the dibenzoyl peroxide induced hydrobromination of 10-undecylenic acid (A. Vogel, „Testbook of Practical Organic Chemistry", Longman London & New **1978**, ISBN 0-582-44250-8). In this radical addition reaction, under

formation of 11-bromounedecanoic acid, dibenzoyl peroxide causes the chain initiation and converts itself into benzene and carbon dioxide (Scheme 2).

Scheme 2 Dibenzoyl peroxide induced hydrobromination of 10-undecylenic acid
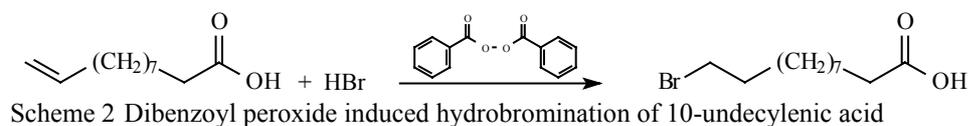
You input the catalysts in the corresponding register sheet by firstly inputting the name (Figure 7).
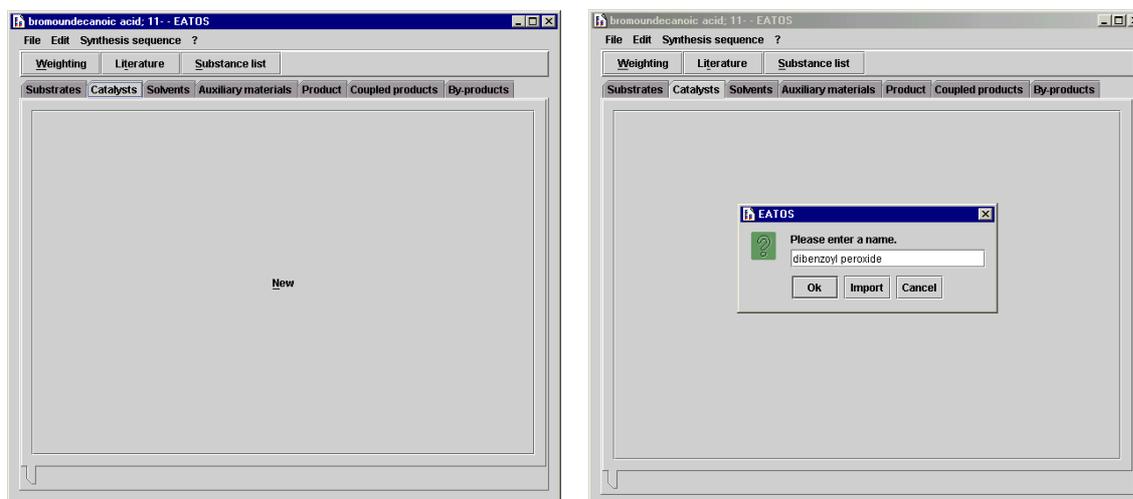
Figure 7   Input of a catalyst

Afterwards, you input the further indications, analogously to the substrates – also in the unit [mol %]. Figure 8 already shows the extended mode.

Figure 8   Register sheet for catalysts in the extended mode

In addition to the input possibilities described in chapter 3.2.3.4 (p. 18) (*SUBSTRATES*), you can consider subsequent products resulting from the catalyst. The byproducts resulting from the conversion of dibenzoyl peroxide are benzene and carbon dioxide and can be input under *BYPRODUCTS (CATALYST) SPECIFY... .*
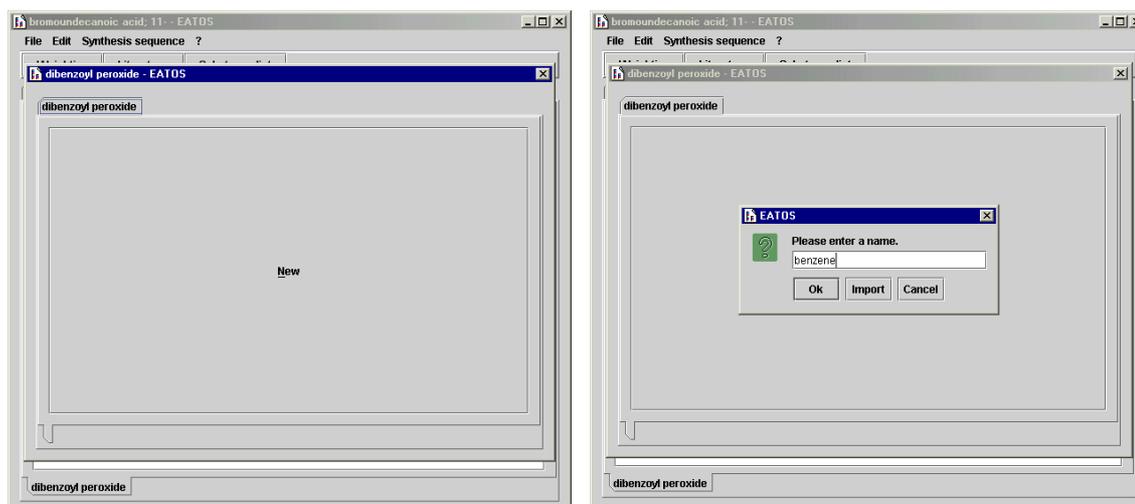
Figure 9   Specification of byproducts of the catalyst I

After naming of a byproduct (Figure 9), you put in the formed quantity and/or emissions (Figure 10).

Figure 10   Input of byproducts resulting from the catalyst I

In case of the decompostition of dibenzoyl peroxide you can assume that about 64 % of the quantity converts into benzene. This amount approximately corresponds to the mass of two benzene rings in dibenzoyl peroxide. In this way, the remaining 36 % can be allocated to the emitting carbon dioxide. If you omit to input carbon dioxide, however, you also can indicate 100 % with the statement that the whole amount of dibenzyol peroxide converts into the substance benzene, at least. The mass difference is program-internally ascribed to the quantity of the unknown byproducts from the catalyst. The input of the aspect that two molecules benzene per molecule dibenzoyl peroxide are formedis made under *#BYPRODUCT / #CATALYST*, i.e., 2/1. The symbol ‚#' represents the term ‚number'. Thereby, the internal calculation by indication of *#BYPRODUCT / #CATALYST* refers to the molecular weights. Therefore, in this case you must input the formula of the catalyst as well as those of the byproduct, what can be omitted otherwise. Subsequently, by *NEW* you correspondingly input the other byproduct carbon dioxide with an amount of 36 % (Figure 11 and Figure 12).
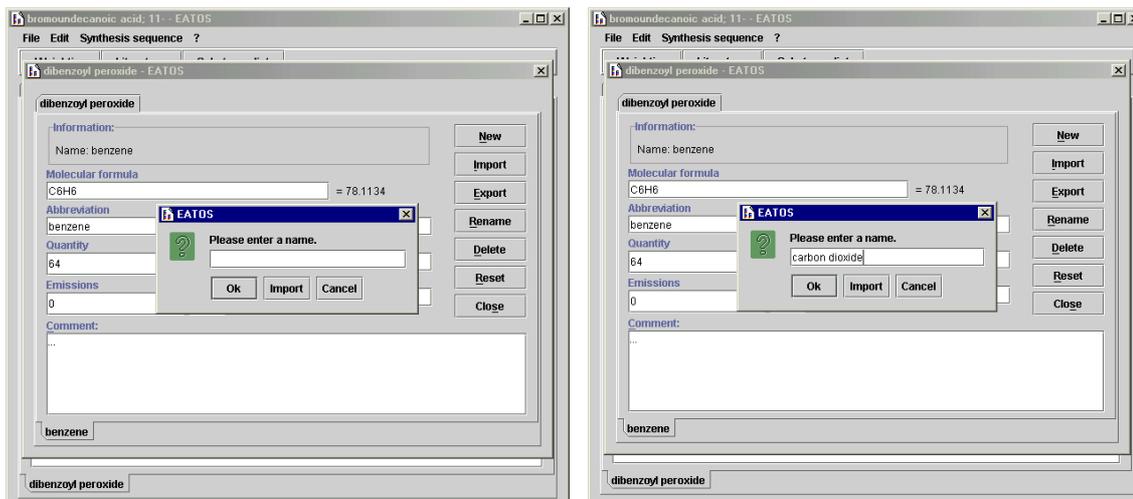
Figure 11   Specifying byproducts of the catalyst II

Of course, few materials used input under *CATALYST* convert into other substances. Such in the true sense catalytic working materials are input under *CATALYST* and no additional decomposition products are described. As examples we indicate heterogeneous catalysts such as Pd/C for hydration, or Nafion H, or K 10 for acid catalyzed reactions, or homogeneous catalysts like the Grubbs's metathesis catalyst.

The toolbar *IMPORT* (see chapter 3.6.2 p. 52) allows the involvement of a substance already present in the substance list as well as of a product saved in the project! In this way, synthesized catalysts inclusively the materials being necessary for their production can be integrated into the regarded synthesis. However, generally it is not possible to indicate *RECYCLABLE QUANTITIES*. For this reason, you should input only the really needed quantity.
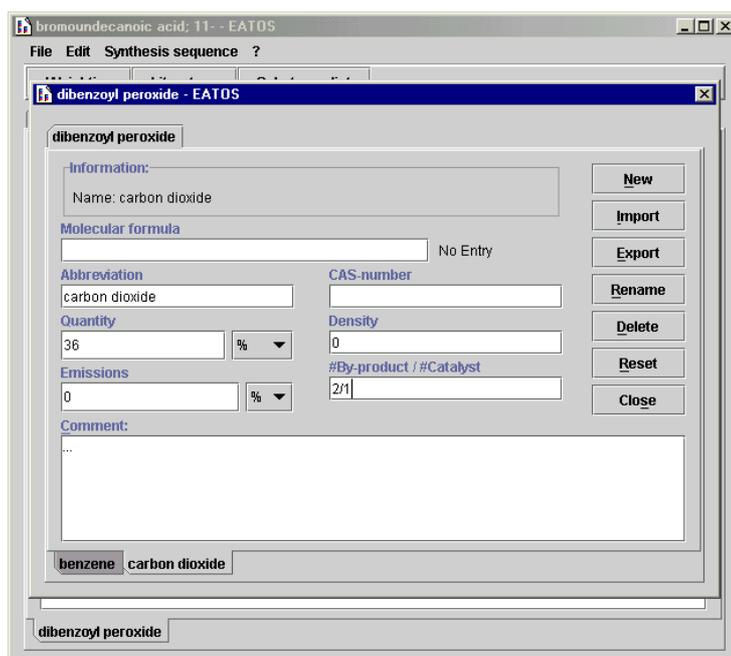
Figure 12   Input of byproducts resulting from the catalyst II

3.2.3.6 Solvents

Similarly, as described in chapter *SUBSTRATES* 3.2.3.4 (p. 18), you input *SOLVENTS* in the corresponding register sheet. According to literature, the quantity of the solvent 1,2-dichloroethane used for the synthesis of 4-methoxyacetophenone amounts to 400 ml.

3.2.3.7 Auxiliary materials

Under *AUXILIARY MATERIALS* all further substances are indicated, which must be spent for the synthesis of the product. Among other things, there belong to reagents situated in the reaction vessel, which are not ascribed to the catalysts or solvents, as well as auxiliary materials which are needed for the isolation of the product as, e.g., washing water, extraction solvents, etc. Certainly, it is optional, e.g., to input all solvents in the register sheet *SOLVENTS*, also when they were used during the isolation. We differentiate between four miscellaneous mass balance regions: *REACTION*, *ISOLATION*, *WASTE PRETREATMENT*, and *WASTE TREATMENT*. If information is available, you can consider as well materials used for the pretreatment or treatment of the current waste material and assign it to the mass balance regions, correspondingly. In the command line under *?* the mass balance regions are presented in an overview:
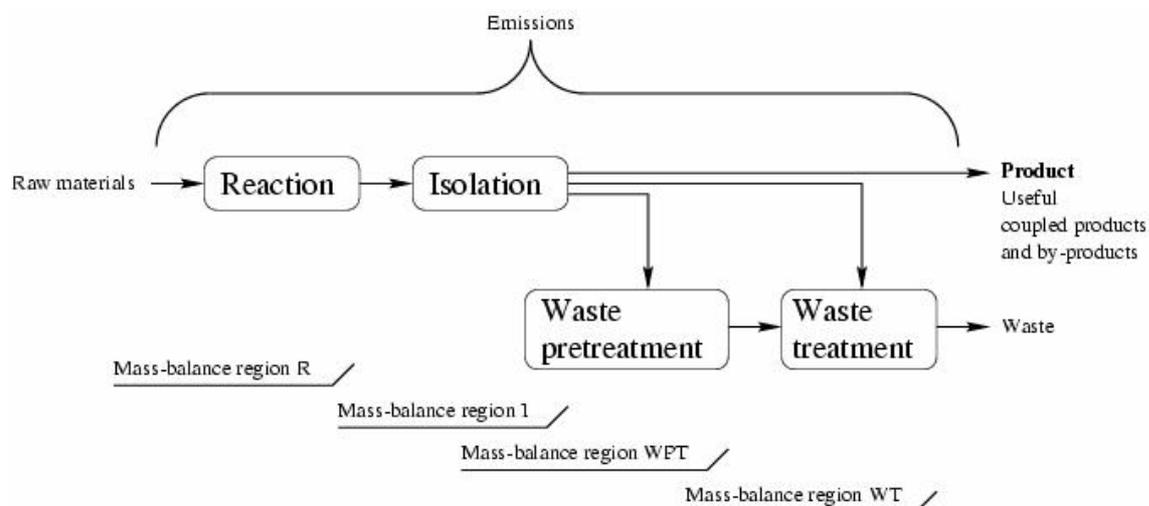
Figure 13   Mass-balance regions *REACTION*, *ISOLATION*, *WASTE PRE-TREATMENT*, and *WASTE TREATMENT*

In other respects, as well concerning the auxiliary materials, input is made analogically to the substrates (chapter 3.2.3.4, p. 18). In Figure 14 the register sheet *AUXILIARY MATERIALS* is filled out:

Figure 14   Input of auxiliary materials

In the case that own syntheses are not object of the study, but syntheses described in literature, often insufficient information on the auxiliaries is available. For this reason, for literature regulations the following assumptions were taken valid as standard:

- extraction: 300 ml solvent / liter aqueous medium
- washing water: 300 ml water / liter solvent
- washing saline solution: 100 ml electrolyte solution / liter solvent
- desiccant   20 g desiccant / liter substance to be dried

For the example of the synthesis of 4-methoxyacetophenone, you gain the following assumptions and reasonably list them in the respective register sheet under *COMMENT*: 500 g ice $\rightarrow$ 150 ml 1,2-dichloroethane (extraction), thus, totally 550 ml $\rightarrow$ a) 165 ml washing water; b) 55 ml sodium hydroxid solution(2 %); c) 11 g potassium carbonate.

3.2.3.8 Product

You input the quantity of the product obtained at the synthesis in the corresponding register sheet in [g], [m], [ml], or [%] (referring to the key substrate), i.e., for the example of the synthesis of 4-methoxyacetophenone 60%. The input in [ml] requires the indication of the density. Possibly, graschromatographical studies of the raw product

showed a higher yield than obtained after the isolation. For the input of this information, you must tick off the toolbar *YIELD (GASCHROM.) KNOWN* under *YIELD (GASCHROMATOGRAPHICALLY)*, and then, additionally, input the value in the input-line underneath, so that the yield obtained gaschromatographically makes possible a determination of the yield loss by the work-up procedure. Naturally, the gaschromatographical yield must become a higher value than the isolated yield and a lower than the *CONVERSION* input under *SUBSTRATES* (see chapter 3.2.3.4, p. 18).

Beyond it, there exists the possibility to consider the formation of possible undesired diastereoisomers or enantiomers by firstly selecting under *ISOMERIC RATIO* between *ENANTIOMERIC RATIO*, *ENANTIOMERIC EXCESS* and *DIASTEREOMERIC RATIO.*. In the input-line underneath you input the corresponding value, e.g., 90 : 10 for the indication of a relation of isomers and 80 for an enantiomeric excess. The made product always is the default-indication of the *NAME OF ISOMER* and must be changed, correspondingly, i.e., e.g., you must precede with „*S*-" or „*D*-„. The corresponding quantity from the product will be subtracted program internally and assigned to the isomer.

The functionality of the remaining toolbars corresponds to the substrates described in chapter 3.2.3.4 (p. 18).

Figure 15   Input of the product

3.2.3.9   Coupled Products

According to the stoichiometric equation of the synthesis inevitably formed coupled products are listened in the respective register sheet. Here, no specifications are necessary, because the quantities formed in the synthesis dependent on the stoichiometric equation and the yield are calculated internally. Indeed, in some cases coupled products are regarded as value product beside the product. This is the case, e.g., if they are used as raw materials in other syntheses or if they are used already as a raw material in the synthesis' run regarded, or if they are utilizable anew in the circulation system after recovery. By input of the *USEFUL QUANTITY* of the utilizable coupled products in the corresponding input-line, these coupled products can be characterized correspondingly and the quantities can be indicated later in the graphic diagram . Thereby, the percentage indication refers to the conversion of the key product and, therefore, it may not exceed the yield.

For the description of the remaining toolbars see chapter Substrates 3.2.3.4 (p. 18).

Figure 16   Register sheet coupled products

3.2.3.10   Byproducts

The yield-reducing conversion of substrates to undesirable byproducts takes places, if besides the desired synthesis there are running side reactions, which are competitive to it, or if subsequent reactions occur . As an example we mention the Friedel-Crafts-Alkylation where, by further alkylations, a reduction of the yield of the monoalkylated

product is the consequence. Another example, to pick up the synthesis of 4-methoxyacetophenone used until now, is the formation of the byproduct 2-methoxyacetophenone from the acylation of anisole at the ortho-position .

Program-internally, the quantity of these byproducts defined by stoichiometric equation and yield is determined, so that you must not make any indications in this register sheet. But if there are known single byproducts as well as the quantities of their formation, you should indicate them, to be able to consider their substance specific characteristics in the terms of the synthesis. Utilizable byproducts can be marked with a cross under *BYPRODUCT USEFUL*, so that they can be identified in the graphical diagram as value product. For demonstration, in Figure 17 we input a virtual byproduct 1, which quantity has to be input.

Figure 17   Register sheet byproducts

3.2.3.11 *Additional ingredients*

For all entered substances of the synthesis you can indicate a degree of purity. With the purity which can rely on a real impurity not known in detail as well as on further substances in a substance mixture, you can specify *ADDITIONAL INGREDIENTS* (Figure 18) – in the example synthesis those of an auxiliary (2% sodium hydroxide solution) – and allocate them under *KIND OF SUBSTANCE* to the categories *IMPURITY*, *AQUEOUS MEDIUM* or *MISCELLANEOUS* (Figure 19).
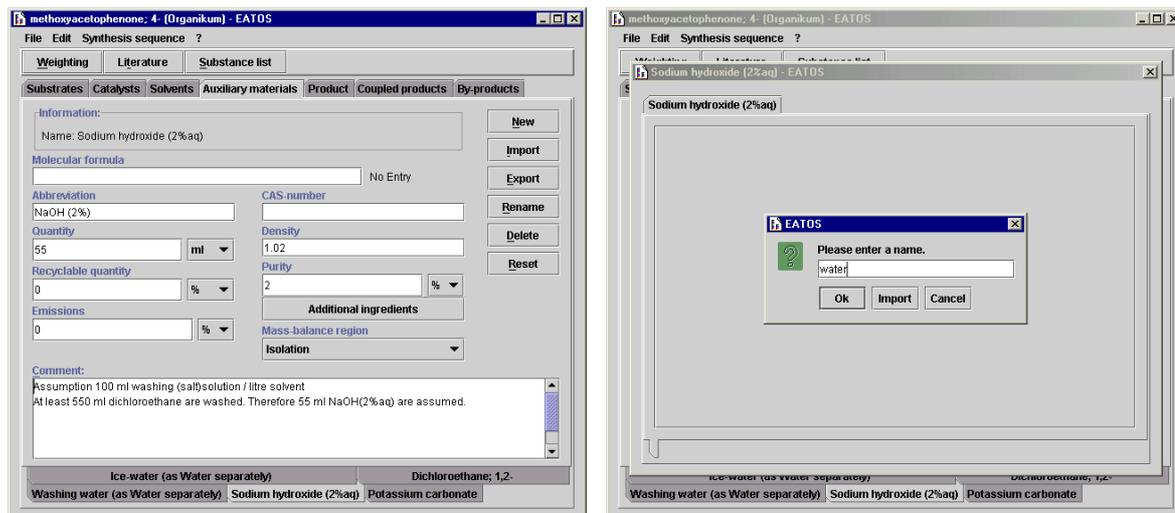
Figure 18   Input of an additional ingredient to an ‚impure' substance I
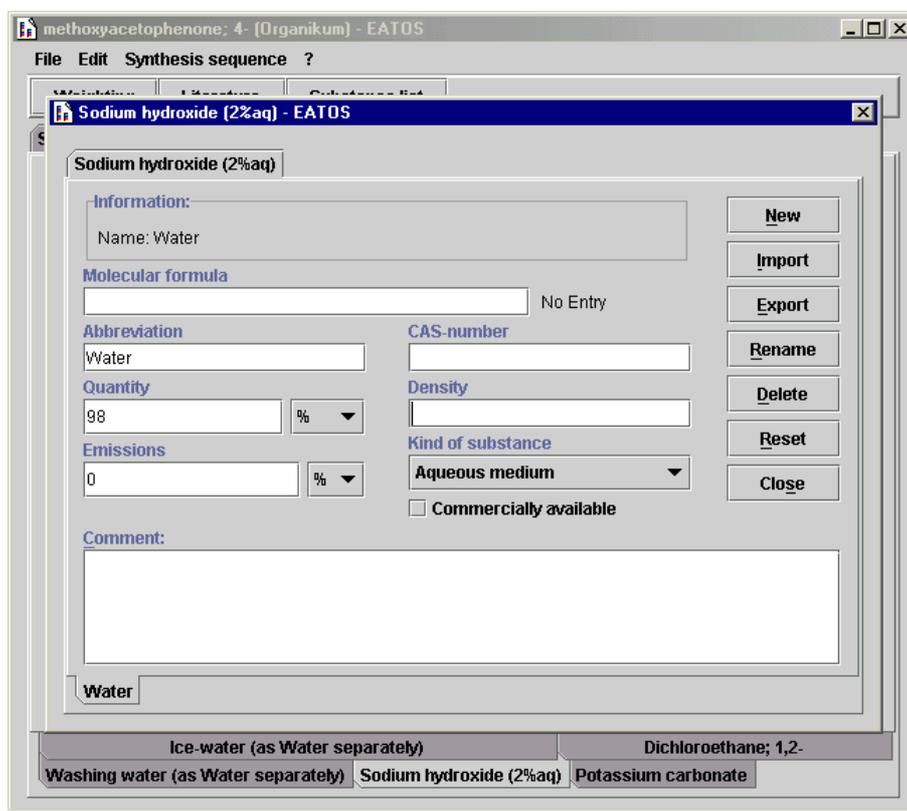
Figure 19   Input of an additional ingredient to an ‚impure' substance II

For these assignments in the graphic presentation of the results there exist own, appropriately selectable categories. Under these categories, exactly those substance quantities are specified which got the corresponding assignment as further contents material. Under ‚*SEWAGE/WATER*', e.g., ingredients appear which assignment is made under *KIND OF SUBSTANCE* to *AQUEOUS MEDIUM*. The opposite consequence is as well that only those materials can appear which were input under *AUXILIARY MATERIALS*. Thus, the SOLVENT water or the *AUXILIARY MATERIAL* water is not

listed under ‚ *SEWAGE/WATER*' but under the category solvents or auxiliary material, respectively. Only an *ADDITIONAL INGREDIENTS* can be categorized in that way. But in the matter of principle – by a short way round – it is possible to allocate water used as solvent or auxiliary to the category ‚*SEWAGE/WATER* '. For this, you must input, e.g., the solvent water with a very low purity, e.g., 0.001 %, and redefine water under *ADDITIONAL INGREDIENTS* with the remaining 99.999 %.

By the option *ADDITIONAL INGREDIENTS* any material mixtures can be input. In the following, we specify to examples for the input of material mixtures:

A commercially achievable 48% acetous hydrogen bromide solution has a pureness of 48% and additionally contains of the ingredient acetic acid, which you must assign to the category *MISCELLANEOUS* under *KIND OF SUBSTANCE* and is available in an amount of 52%.

A saturated aqueous sodium pyrosulfite solution (solubility of $Na_2S_2O_5$ at 20°C: 54 g / 100 g water; see Handbook of Chemistry and Physics, David R. Lide, 73rd Edition 1992 – 1993, ISBN 0-8493-0473-3, p. 4 – 101) consists of a salt share of (54 / 154 =) 35,06%, what is the reason why the proportion of water amounts to 54,94%, which is assigned to the category *AQUEOUS MEDIUM* under *KIND OF SUBSTANCE*.

3.2.3   Exchange of Syntheses

As described before, syntheses can be input in the project or as well adopted by the function *EXCHANGE* (see Figure 2, p. 13) by means of the same denominated toolbar from projects made already by shifting or copying. For the example of the synthesis of 4-methoxyacetophenone, as presented in the following figure, in this way you can also take into consideration a further project (name: anisole+4-methoxyaceto-phenone.project), where 3 additional syntheses of 4-methoxyacetophenone and two syntheses of anisole can be adopted by copying (Figure 20 and

Figure 21).
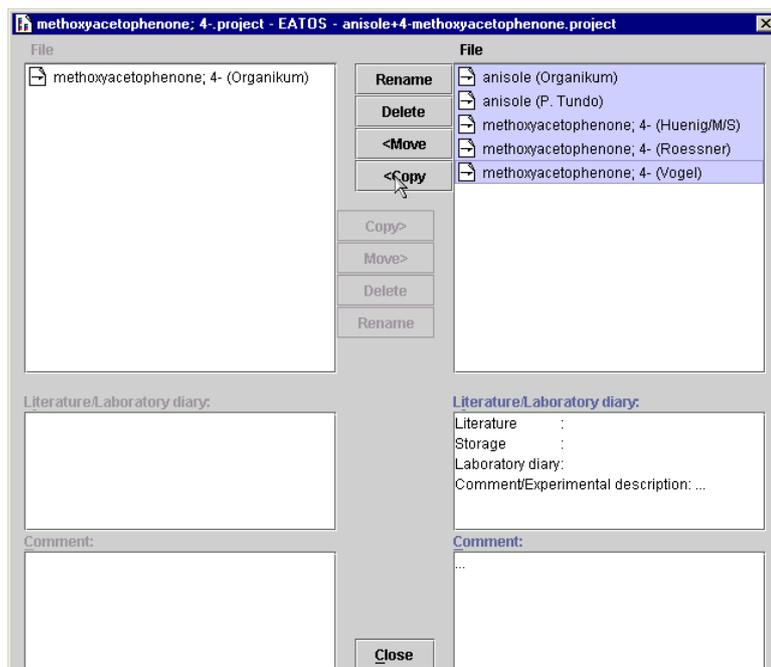
Figure 20   Copying of syntheses from project to project I
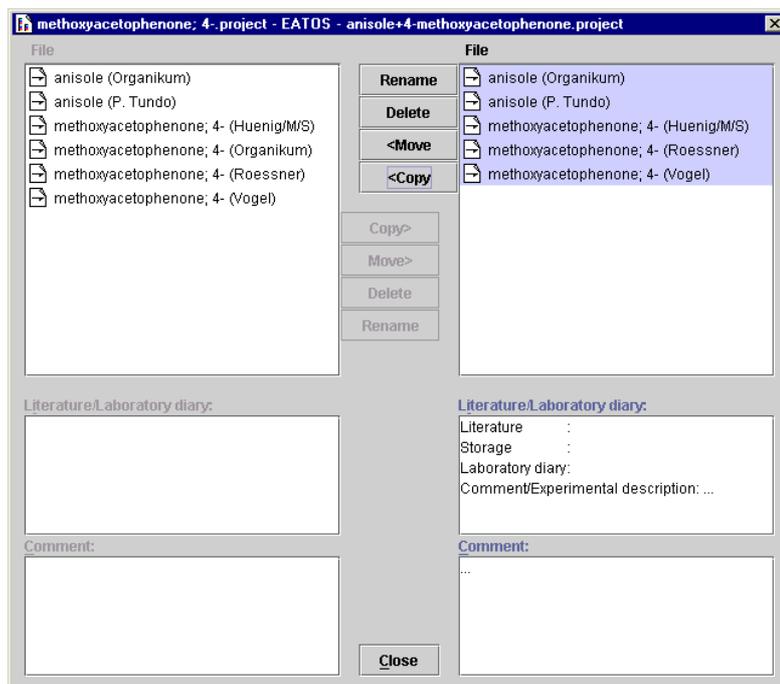
Figure 21   Copying of syntheses from project to project II

3.2.4   Project, substance list, program

Clicking the toolbar *FILE* of the project window (Figure 2, p. 13) you save the project or change to another project. Besides, you can open the substance list (chapter 3.5, p. 50) or close the program.

By means of the toolbar *LANGUAGE SETTINGS* you can change between German and English. The change of the language settings becomes operative after you start the program once again.

3.3   Weighting

An important function of the program EATOS is to identify weak points for the improvement of the quantitative material flows by revealing the claiming of resources and the arising of waste per product unit. This is possible already by the input described already: material input and environmental factor E (waste [kg] / product [kg] are indicated in the graphic result representation.

The other important function of the program is the inclusion of the used substances' quality in the evaluation of a chemical synthesis. The substance specific characteristics of the materials involved determine the potential environmental relevance and its threat to the human being. For evaluating and examining chemical syntheses as well regarding these aspects, the quantitative material flows are weighted with their qualitative characteristics according to a program-internal algorithm. The more problematic a substance is the more stronger its share in the mass balance is presented. This is made by multiplication of the substance quantity with a substance specific weighting factor , shortly indicated as „Q". This substance specific weighting factor Q can take values between 1 and 10 and, in doing so, among other things, it optionally composes of human toxicity, eco-toxicity, ozone creation potential, and so on. By clicking the toolbar *WEIGHTING* (see, e.g., Figure 5, p. 16) (or via *EDIT*), the user gains access to the weighting categories (Figure 22), which mostly correspond to those from the life cycle assessment and are represented with one or more impact categories.
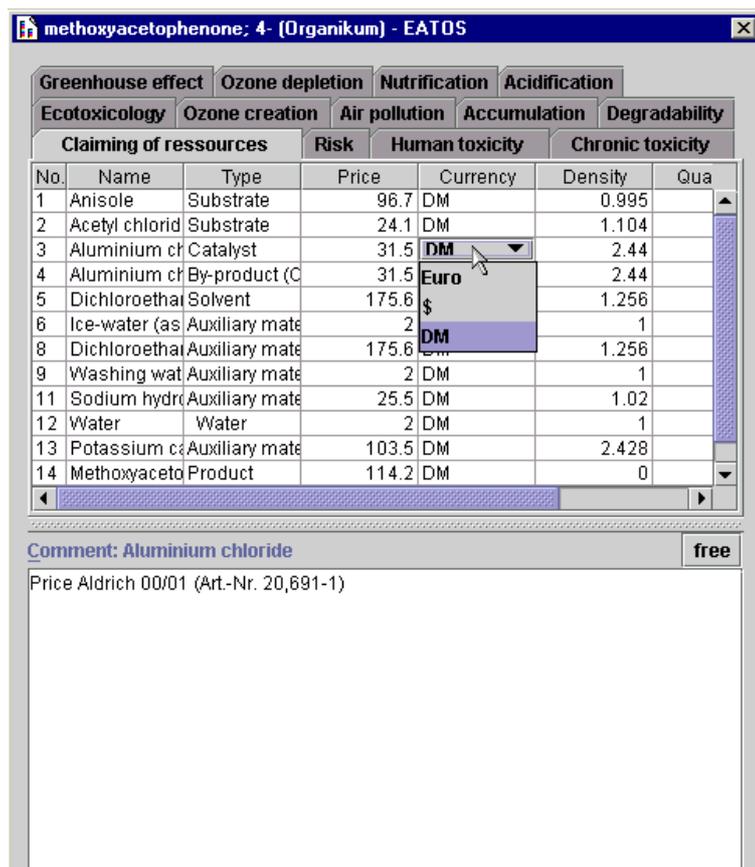
Figure 22   Weighting categories

The user selects the register sheets of the weighting categories desired, and to the substances used at the synthesis (given: no., name, type), he inputs the corresponding substance parameters, which act as impact categories for these weighting categories. Thereby, the human toxicity, e.g., is represented by the work place threshold value (MAK, Maximale Arbeitsplatzkonzentration) and the ecotoxicology by the WGK-value (Wassergefährdungsklasse). You revert to alternative substance parameters as, e.g., the hazard sign or the LC_{50}-value, if MAK-value, resp., WGK-value, do not exist.After clicking the toolbar *FREE*, you can select directly single substances and make inputs in the *COMMENT* field, to explain substance parameters in detail and/or to make indications of resources concerning the data. In doing so, the toolbar *FREE* changes into *FIXED*. Clicking this toolbar once again produces the previous status *FREE* again, so that in the comment field the specifications to the substances appear, where the cursor is situated atop . To the substances imported from the substance list with complete data set (chapter 3.6.2, p. 52), the substance parameters are available already, so that they must not be input once more. Therefore, we recommend to export newly entered substances with their complete data set into the substance list (chapter 0, p. 52), so that they will be available for later applications in other investigations and simply can be imported. In this way, by the set up of a data bank in form of a substance list, a convenient utilization of the program *EATOS* becomes possible, because the data of a substance must be input once, only!

Totally, there are 13 weighting categories: two refer to the input of the synthesis, the others refer to the output (except for the product). The material balance is represented in form of a column diagram . Therewith, the columns lean against two of the key figures defined by R. A. Sheldon (‚*Consider the environmental quotient*‘, *CHEMTECH* **1994**, 3, 38 – 47) – the selectivity ‚*S*‘ and the environmental factor ‚*E*‘. The selectivity *S* is the weight-related ratio of product and substrates, i.e., a degree for the effectiveness in converting the substrates to the product desired. In accordance to this key figure, an inverse selectivity (S^{-1}); also indicated as *mass intensity* or *mass index*, resp., is defined which, indeed, takes into consideration as well all additional input materials besides the substrates. The exponent S^{-1} indicates that, on the contrary to the selectivity S, not the relation of the product to the input materials but the reversed relation is determined:

$$\text{mass index } S^{-1} = \frac{\sum \text{substrate}[g] + \text{solvent}[g] + \text{auxiliary material}[g] + \text{cat.}[g] + ...}{\text{product}[g]}$$

Thus, the mass index S^{-1} represents the mass index per product unit – the so called input of the reaction. The analogous relation of waste to the product by R.A. Sheldon is named the ‚environmental factor‘ (*E*).

$$\text{environmental factor } E = \frac{\sum \text{waste}[g]}{\text{product}[g]}$$

The impact categories of each weighting category are allocated program-internally to the weighting factor *Q* 1 to 10. For the determination of the total weighting factor Q_{total} of a substance, a mean value from the *Q*-values and the weighting category selected is formed.By the way, this is the reason why all weighting categories are standardized to the uniform weighting factors‘-scale 1 to 10. The selection of particular weighting categories and the weighting of the weighting factors‘ importance among each other can be made in the graphical representation of the result to be able to investigate one or several synthesis in terms of one or several weighting categories (see chapter 3.7.1, p. 61).

In the following, the several weighting categories are explained briefly.

3.3.1   Weighting category Claiming of resources

Frequently, the synthesis of a chemical substance is possible in varying ways, wherefore different substrates are reverted to. The merely comparison of the syntheses leading to the target product, without consideration of material and production expenses for the production of the maybe qualitatively very different substrates does not present the whole truth. To show that the claiming of resources is worth to be regarded as environmentally relevant, the history of the materials used in view of material and production expenses including safety and environmental engineering demands should be illustrated. Mostly, detailed information about these, like number of synthesis steps or toxicological aspects of the chemicals used thereby are not available, not existing at

all, or, normally, only investigable with efforts. It is more workable to esteem the price of the dimension of the environmental impact in the production of the substances involved. Therefore, the substance price was selected as measurement for the claiming of resources.

Because of the large range in the substance prices possible in comparison to the weighting factors Q 1 to 10 to be seized, with a logarithmic function a classification was made. The weighting factor Q of substance prices will be determined by the following equation:

$$Q = \left[\frac{\ln\left(\frac{Price}{0.0178}\right)}{0.8635} \right];$$ '[ ]' represents the integer function of Gauß, i.e., e.g.,

$$[2.3] = [2.98] = 2$$

This equation results from the conversion of the equation $price = 0.0178 \cdot e^{0.8635 \cdot Q}$ to Q, which clearly results from the pairs of value determined for this weighting category (Q = 2 / price = 0.1 Euro/g) and (Q = 10 / price = 100 Euro/g) with the basis given (here e = 2.718...). With this function (Figure 23), after changing ordinates and abscissas and application of the integer function of Gauß , which converts the resulting logarithmic function (Q = f(price)) in a step function, price ranges of Table 1 are obtained.

Table 1   Assignment of substance prices to the weighting factor $Q_{Claiming\ of\ resources}$

Q	[Euro/g]		
1	for free	to	0.10
2	0.10	to	0.24
3	0.24	to	0.56
4	0.56	to	1.34
5	1.34	to	3.17
6	3.17	to	7.51
7	7.51	to	17.80
8	17.80	to	42.22
9	42.22	to	100.13
10	100.13	to	infinite
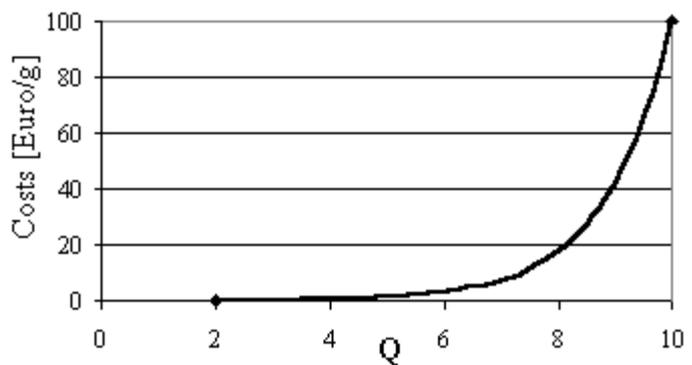
Figure 23   Exponential function for the determination of $Q_{Claiming\ of\ resources}$

By multiplication with the substance specific weighting factor $Q_{claiming\ of\ resources}$, the mass index S^{-1} is weighted under formation of the environmental index El_in, to which, besides, the category 'risk' described as follows can contribute.

3.3.2   Weighting category Risk

For the estimation of the risk potential emanating from a chemical reaction, flash point, vapor pressure, reactivity (e. g., with atomspheric oxygen and water), toxicity data, and lots of others are important parameters. However, a quick composition of information and utilization for an early evaluation of the synthesis' strategy, as well as for a comparison of various options, is not possible without expenses. Therefore, it makes sense to refer to the easily accessible R-phrases determined for the substances and, where these informations are compiled. According to the urgency of an endangerment by chemical substances, all R-phrases were assigned to the weighting factors 0.1 to 5. Normally, the R-phrase specification "very toxic" gains a higher value Q than "toxic", and this correspondingly higher than "harmful" – analogously explosiveness and inflammability, as well. The more conditions must be fulfilled in case of danger, the lower the values are for Q. Endangerment for the nature get lower values of Q, because in this category the occupational safety and health is regarded. Normally, precondition for the endangerment by swallowing is the active self-fault , and, therefore, it gets the value $Q = 0.5$, or, even if longer exposition is necessary because of danger of swallowing, only the value $Q = 0.1$. If several R-phrases are assigned to a substance, the corresponding values for Q are summed up to max. 10, to accommodate to the different effects to be conceived cumulatively.

Table 2   Assignment of the R-phrases to the weighting factor Q_{Risk}

Q	No.	R-phrase
4	R1	Explosive when dry.
4	R2	Risk of explosion by shock, friction, fire or other sources of ignition.
5	R3	Extreme risk of explosion by shock, friction, fire or other sources of ignition.
2	R4	Forms very sensitive explosive metallic compounds.
3	R5	Heating may cause an explosion.
4	R6	Explosive with or without contact with air.
3	R7	May cause fire.
4	R8	Contact with combustible material may cause fire.
3	R9	Explosive when mixed with combustible material.
1	R10	Flammable
2	R11	Highly flammable
3	R12	Extremely flammable
3	R13	Extremely flammable liquid gas
2	R14	Reacts violently with water.
3	R14/15	Reacts violently with water, liberating extremely flammable gases.
3	R15	Contact with water liberates extremely flammable gases.
3	R15/29	Contact with water liberates toxic, extremely flammable gas.
3	R16	Explosive when mixed with oxidizing substances.
4	R17	Spontaneously flammable in air.
3	R18	In use, may form flammable/explosive vapour-air mixture.
3	R19	May form explosive peroxides.
1.5	R20	Harmful by inhalation.
1.5	R20/21	Harmful by inhalation and in contact with skin.
1.5	R20/21/22	Harmful by inhalation, in contact with skin and if swallowed.
1.5	R20/22	Harmful by inhalation and if swallowed.
1.5	R21	Harmful in contact with skin.
1.5	R21/22	Harmful in contact with skin and if swallowed.
0.5	R22	Harmful if swallowed.
2.5	R23	Toxic by inhalation.
2.5	R23/24	Toxic by inhalation and in contact with skin.
2.5	R23/24/25	Toxic by inhalation, in contact with skin and if swallowed.
2.5	R23/25	Toxic by inhalation and if swallowed.
2.5	R24	Toxic in contact with skin.
2.5	R24/25	Toxic in contact with skin and if swallowed.
0.5	R25	Toxic if swallowed.
3.5	R26	Very toxic by inhalation.
3.5	R26/27	Very toxic by inhalation and in contact with skin.
3.5	R26/27/28	Very toxic by inhalation, in contact with skin and if swallowed.
3.5	R26/28	Very toxic by inhalation and if swallowed.
3.5	R27	Very toxic in contact with skin.
3.5	R27/28	Very toxic in contact with skin and if swallowed.
0.5	R28	Very toxic if swallowed.
1.5	R29	Contact with water liberates toxic gas.

1.5	R30	Can become highly flammable in use.
1.5	R31	Contact with acids liberates toxic gas.
2.5	R32	Contact with acids liberates very toxic gas.
4	R33	Danger of cumulative effects.
2	R34	Causes burns.
3	R35	Causes severe burns.
1.5	R36	Irritating to eyes.
1.5	R36/37	Irritating to eyes and respiratory system.
1.5	R36/37/38	Irritating to eyes, respiratory system and skin.
1.5	R36/38	Irritating to eyes and skin.
1.5	R37	Irritating to respiratory system.
1.5	R37/38	Irritating to respiratory system and skin.
1.5	R38	Irritating to skin.
3.5	R39	Danger of very serious irreversible effects.
3.5	R39/23	Toxic: danger of very serious irreversible effects through inhalation.
3.5	R39/23/24	Toxic: danger of very serious irreversible effects through inhalation and in contact with skin.
3.5	R39/23/24/25	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
3.5	R39/23/25	Toxic: danger of very serious irreversible effects through inhalation and if swallowed.
3.5	R39/24	Toxic: danger of very serious irreversible effects in contact with skin.
3.5	R39/24/25	Toxic: danger of very serious irreversible effects in contact with skin and if swallowed.
0.5	R39/25	Toxic: danger of very serious irreversible effects if swallowed.
4	R39/26	Very toxic: danger of very serious irreversible effects through inhalation.
4	R39/26/27	Very toxic: danger of very serious irreversible effects through inhalation and in contact with skin.
4	R39/26/27/28	Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
4	R39/26/28	Very toxic: danger of very serious irreversible effects through inhalation and if swallowed.
4	R39/27	Very toxic: danger of very serious irreversible effects in contact with skin.
4	R39/27/28	Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed.
0.5	R39/28	Very toxic: danger of very serious irreversible effects if swallowed.
3	R40	Possible risks of irreversible effects.
3	R40/20	Harmful: possible risk of irreversible effects through inhalation.
3	R40/20/21	Harmful: possible risk of irreversible effects through inhalation and in contact with skin.
3	R40/20/21/22	Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed.
3	R40/20/22	Harmful: possible risk of irreversible effects through inhalation

		and if swallowed.
3	R40/21	Harmful: possible risk of irreversible effects in contact with skin.
3	R40/21/22	Harmful: possible risk of irreversible effects in contact with skin and if swallowed.
0.5	R40/22	Harmful: possible risk of irreversible effects if swallowed.
2	R41	Risk of serious damage to eyes.
4	R42	May cause sensitization by inhalation.
4	R42/43	May cause sensitization by inhalation and skin contact.
4	R43	May cause sensitization by skin contact.
4	R44	Risk of explosion if heated under confinement.
5	R45	May cause cancer.
5	R46	May cause heritable genetic damage.
5	R47	May cause deformities.
1.5	R48	Danger of serious damage to health by prolonged exposure.
1.5	R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation.
1.5	R48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
1.5	R48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
1.5	R48/20/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
1.5	R48/21	Harmful: danger of serious damage to health by prolonged exposure in contact with skin.
1.5	R48/21/22	Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
0.1	R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed.
2.5	R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation.
2.5	R48/23/24	Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
2.5	R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
2.5	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
2.5	R48/24	Toxic: danger of serious damage to health by prolonged exposure in contact with skin.
2.5	R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
0.1	R48/25	Toxic: danger of serious damage to health by prolonged exposure if swallowed.
5	R49	May cause cancer by inhalation.
0.1	R50	Very toxic to aquatic organisms.
0.1	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
0.1	R51	Toxic to aquatic organisms.

0.1	R51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
0.1	R52	Harmful to aquatic organisms.
0.1	R52/53	Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
0.1	R53	May cause long-term adverse effects in the aquatic environment.
0.1	R54	Toxic to flora.
0.1	R55	Toxic to fauna.
0.1	R56	Toxic to soil organisms.
0.1	R57	Toxic to bees.
0.1	R58	May cause long-term adverse effects in the environment.
0.1	R59	Dangerous for the ozone layer.
5	R60	May impair fertility.
5	R61	May cause harm to the unborn child.
5	R62	Possible risk of impaired fertility.
5	R63	Possible risk of harm to the unborn child.
5	R64	May cause harm to breastfed babies.
0.5	R65	Harmful: may cause lung damage if swallowed.
0.1	R66	Repeated exposure may cause skin dryness or cracking.
0.1	R67	Vapours may cause drowsiness and dizziness.

To be able to estimate the risk potential for the employee with EATOS, the substances on the input-side presented under the denotation 'S^{-1}' in form of a column, are weighted with the weighting factors specified for them. Besides, the environmental index for the input 'EI_in' (Environmental Index (Input)), if desired, together with the category 'Claiming of resources', is formed.

3.3.3   Weighting category human toxicity

The acute toxicity of chemical substances can be judged by the assistance of three impact categories: MAK (workplace threshold value, Maximale Arbeitsplatzkonzentration), hazard sign, or LD_{50}-, LC_{50}-values, respectively. Using logarithmic functions, similarly to the methodology in 'claiming of resources' (impact category substance price), weighting factors Q were assigned to MAK-, LD_{50}-, LC_{50}-value-ranges, respectively, which will be produced from the pair of value indicated.

Table 3   f(MAK) and f(LX$_{50}$-value) with X = C or D and (x/y)-pairs of value 1 and 2 for the calculation of functions f(Q). ('[]' is the integer function of Gauß, i.e., e.g. [2.3] = [2.98] = 2)

f(MAK) and f(LX$_{50}$-Wert)	Pair 1 (Q / LX$_{50}$)	Pair 2 (Q / LX$_{50}$)
Q = [ln(MAK/28284)/-1.3246]	Q = 2 / MAK = 2000 mg/m^3	Q = 10 / MAK = 0.05 mg/m^3
Q = [ln(LC$_{50 \text{ inhal.}}$/68.39)/-0.6148]	(Q = 2 / 20 mg/l /4h)	(Q = 8 / 0.5 mg/l /4h)
Q = [ln(LD$_{50 \text{ oral}}$/8615)/-0.7303]	(Q = 2 / 2000 mg/kg)	(Q = 8 / 25 mg/kg)
Q = [ln(LD$_{50 \text{ dermal}}$/17230)/-0.7303]	(Q = 2 / 4000 mg/kg)	(Q = 8 / 50 mg/kg)

f(MAK) and f(LX$_{50}$-value) result from the exponential functions f(Q) = MAK = 28284 · e$^{-1.3246·Q}$ LC$_{50 \text{ inhal.}}$ = 68.39 · e$^{-0.6148·Q}$, LD$_{50 \text{ oral}}$ = 8615 · e$^{-0.7303·Q}$, and LD$_{50 \text{ dermal}}$= 17230 ·e$^{-0.7303·Q}$. The hazard sign (Xn, T, or T$^+$) were assigned to the values Q = 4, 7, and 10 (Table 4). The value-ranges for the workplace threshold value and the LD$_{50}$-, the LC$_{50}$-values, resp., are shown in Table 4 and Table 5.

Table 4   Assignment of MAK-value-ranges and symbols of danger to the weighting factor Q$_{Human}$ toxicity (acute)

Q	MAK-range [mg/m^3]			hazard sign
1	7520.98	to	1999.90	
2	1999.90	to	531.79	
3	531.79	to	141.41	
4	141.41	to	37.60	Xn
5	37.60	to	10.00	
6	10.00	to	2.66	
7	2.66	to	0.71	T
8	0.71	to	0.19	
9	0.19	to	0.05	
10	0.05	to	0.00	T$^+$

Table 5   Assignment of LD$_{50}$-, resp. LC$_{50}$-value-ranges to a weighting factor Q

Q	hazard sign	way of intake							
		LC$_{50}$ inhal. [mg/l /4h]			LD$_{50}$ oral [mg/kg]			LD$_{50}$ dermal [mg/kg]	
1		36.98	to	20.00	4150.40	to	1999.52	8300.80	to	3999.03
2	Xn ≈	20.00	to	10.81	1999.52	to	963.30	3999.03	to	1926.59
3	Xn ≈	10.81	to	5.85	963.30	to	464.08	1926.59	to	928.16
4	Xn ≈	5.85	to	3.16	464.08	to	223.58	928.16	to	447.16
5	Xn, T ≈	3.16	to	1.71	223.58	to	107.71	447.16	to	215.42
6	T ≈	1.71	to	0.92	107.71	to	51.89	215.42	to	103.78
7	T ≈	0.92	to	0.50	51.89	to	25.00	103.78	to	50.00
8	T$^+$ ≈	0.50	to	0.27	25.00	to	12.04	50.00	to	24.09
9	T$^+$ ≈	0.27	to	0.15	12.04	to	5.80	24.09	to	11.60
10	T$^+$ ≈	0.15	to	0.00	5.80	to	0.00	11.60	to	0.00

The weighting factors Q of the value-ranges presented in Table 5 fairly well agree with the assignment (made in Table 4) of the weighting factors Q to the hazard signs Xn, T,

and T^+, which were listed in the column 'hazard signs' according to the legal restraints from Table 6.

Table 6   Classification criteria and selection of hazard sign according to 67/548/EEC Appendix 6(2)

hazard sign	way of intake		
	inhal. [mg/l /4h]	oral [mg/kg]	dermal [mg/kg]
T^+	$LC_{50} < 0.5$	$LD_{50} < 25$	$LD_{50} < 50$
T	$0.5 < LC_{50} < 2$	$25 < LD_{50} < 200$	$50 < LD_{50} < 400$
Xn	$2 < LC_{50} < 20$	$200 < LD_{50} < 2000$	$400 < LD_{50} < 2000$

The sequence of priorities prefers the program-internal use of MAK-values instead of the symbols of dangers and the symbols of dangers instead of the LD_{50}-, resp. LC_{50}-values.

3.3.4   Weighting category Chronic toxicity

In the weighting category 'Chronic toxicity' you can divide teratogenic, carcinogenic, and mutagenic substances into the classes 1 – 3. However, program-internally, in view of weighting factors, we do not distinguish between the respective classes, because even in case of suspicion of, e. g., carcinogenic effects the release of the substances must be prevented. Therefore, all classes the weighting factor Q = 10 is assigned to! A compound at the same time mutagenic and carcinogenic, twice the value Q = 10 is assigned to.

3.3.5   Weighting category Ecotoxicology

Ecologically important parameters are dispersion tendency, persistence, the conversion products resulting from the decomposition, combinatorial effects with other substances and their toxicological aspects. The category 'Ecotoxicology' regarded in EATOS mainly concentrates on the last-mentioned parameters, namely the toxicology. In EATOS we used WGK (Wassergefährdungsklasse, i.e. Water Endangerment Class), LC_{50}-, EC_{50}-, and IC_{50}-values for the determination of weighting factor Q and assigned to the values 1 to 10 (Table 7). The parameters for the water endangerment class (harmless for water; 1, 2, or 3) are acute oral toxicity for mammals (LD_{50}, rat), acute toxicity for bacteria (cell reproduction-inhibition test, Pseudomonas putida, threshold of toxicity EC_0), acute toxicity for fish (LC_0 Goldorfe 48 h), and behavior of biodegradation (OECD screening test). In the case that an examination is necessary, further points of view as carcinogenicity or mutagenicity, high bio-accumulation or toxicity compared to, e.g., algae or daphnia , are considered in the assessment of value. Therefore, the WGK-value makes a more complete statement concerning the ecotoxicology of a substance as an LC_{50}-value may do it. If the WGK-value as well as another toxicity-value is indicated, EATOS prefers to use the WGK-value (1st priority). The fixing of the (x,y)-pairs (Q = / XC_{50} = 1 mg/l) and (Q = 2 / XC_{50} = 100 mg/l) (with X = L, E., or I for fish, daphnia , or alga) defines the exponential function XC_{50} =

$464.16 \cdot e^{0.7675 \cdot Q}$, which, with a value a little bit modified $- XC_{50} = 464 \cdot e^{0.7675 \cdot Q}$ is used – leads to value ranges in Table 7, so that the function, with which Q is determined by use of toxicity values, reads: $Q = \left[\ln(w/464)/0.7675 \right]$ with $w = LC_{50}$, EC_{50}, or IC_{50}.

Table 7   Assignment of WGK and LC_{50}-, EC_{50}-, or IC_{50}-value ranges to the weighting factor $Q_{Ecotoxicology}$

Q	WGK	LC_{50} (fish, 96 h), EC_{50} (daphnia, 48 h), IC_{50} (alga, 72 h) [mg/l]			R-phrase
1		215.38	to	99.97	
2		99.97	to	46.40	52
3		46.40	to	21.54	52
4	1	21.54	to	10.00	52
5		10.00	to	4.64	51
6		4.64	to	2.15	51
7	2	2.15	to	1.00	51
8		1.00	to	0.46	50
9		0.46	to	0.22	50
10	3	0.22	to	0.00	50

The modification was made for obtaining an optimal distribution of the classification limits 1 mg/l, 10 mg/l, and 100 mg/l of the so called Gefahrstoffverordnung (GefstV, German act, engl. Hazardous Materials Act)) Appendix I 1.3.2 according to Table 8 to the value range 1 to 10. As you can reconstruct as exemplified in the column 'R-phrase' in Table 7, we achieved this by assigning the R-phrases to the value ranges in accordance with Table 8.

Table 8   Classification limits of the GefstV Appendix I 1.3.2 for the assignment of R-phrases*

R 53 & [#] & [§]	acute toxicity		
#	fish (96 h) [mg/l]	daphnia (48 h) [mg/l]	alga(72 h) [mg/l]
R 50	$LC_{50} < 1$	$EC_{50} < 1$	$IC_{50} < 1$
R 51	$1 < LC_{50} < 10$	$1 < EC_{50} < 10$	$1 < IC_{50} < 10$
R 52	$10 < LC_{50} < 100$	$10 < EC_{50} < 100$	$10 < IC_{50} < 100$

* R 50 Very toxic to aquatic organisms, R 51 Toxic to aquatic organisms, R 52 Harmful to aquatic organisms; [§] and the substance is easily degradable or logKow < 3 (except for the fact, that the BCF, being experimental determined, < 100)

3.3.6   Weighting Category Ozone creation

For a weighting of, e.g., solvents in regard to potential ozone creation, in the category denominated the same you can take into consideration information on their different formation of ozone creation potential. The ozone formation potential of substances is regarded in relation to the ozone creation potential of ethylene, and the percental ratio is denominated POCP (Photochemical Ozone Creation Potential). In the program EATOS, for the weighting factors Q we determined POCP-ranges, which besides Q = 1 include ten units, resp., (Table 9) and subdivide the range between 0 and 100, because the usual POCP-values of organic substances range to approximately −10 - 150. The

corresponding function, with which Q is determined by use of POCP-values, reads:

$$Q = [POCP/10 + 0.5]$$

Table 9   Assignment of ozone creation potentials (POCP) to the weighting factor $Q_{Ozone\ creation}$

Q	POCP[ethylene := 100]		
1	0	to	15
2	15	to	25
3	25	to	35
4	35	to	45
5	45	to	55
6	55	to	55
7	55	to	75
8	75	to	85
9	85	to	95
10	95	to	>

3.3.7   Weighting category Air pollution

In the environmental protection law of Switzerland, among other things, the Luftreinhalteverordnung (LRV) (air pollution act) is positioned. In Art. 4 (LRV) and App. 1 numeral 71 LRV, for the mass stream [g/h] of organic and inorganic emissions there are determined threshold values subdivided in categories. For gaseous or vaporous inorganics there exist the categories 1 to 4, whereby a higher category means a higher threshold value.

Analogously, for gaseous, vaporous, or particle-formed organics there exist the categories 1 to 3. In EATOS, these categories are assigned to the values for Q as follows.

Table 10   Assignment of categories of Luftreinhalteverordnung (LRV) (air pollution act) of Switzerland to the weighting factor $Q_{Air\ pollution}$

Q	category
1	4
2	
3	
4	3
5	
6	
7	2
8	
9	
10	1

For carcinogenic substances, which emissions threshold values are assigned to three categories in the LRV, as well, the weighting category air pollution installed in EATOS is not provided.

3.3.8 Weighting category Accumulation

The enrichment of chemical products in particular environmental compartments is termed accumulation. Organisms assimilate substances by their nourishment (bio-magnification), by the surrounding medium (bio-concentration), or by both ways (bio-accumulation). Ecological magnification, i.e., a substance' concentration increase in an ecological system or a food chain at transition from a lower to the next higher trophic level, can result in consequence and, especially, jeopardize the human being situated at the end of the food chain, who mostly himself is the initiator of the immissions of problematic substances.

At the bio-accumulation we do not regard absolute concentrations but the relation of the concentration in the organism to that of its environment. The accumulation of substances in the organism depends on the environmental concentration, the level of the internal assimilation, and the passive (diffusion processes) or active (enzymatical detoxification) segregation. By the help of freely accessible software, logKow-values (octanol/water-distribution coefficients) of substances can be determined simply after input of their structure and used for the estimation of the accumulation instead of BCF-values to be gained expensively in an experimental way. According to the international convention, a substance is classified as accumulating if the logKow > 3 (national logKow > 2.7 in Germany). Therefore, the assignment of logKow-ranges to weighting factors Q in the EATOS program is made starting from the lowKow-value 3 (Table 11) with the function $Q = [(w + 1/3 - 3) \cdot 3]$ with $w := \log(BCF/0.048)$ or logKow. The program-internal assignment of the substance-specific weighting factor Q concerning the accumulation is made primarily according to the BCF-value and – if this does not exist – according to the Kow-value. Table 11 represents this assignment.

Table 11   Assignment of $\log(BCF/0.048)$, resp. logKow-ranges to the weighting factor $Q_{Accumulation}$

Q	log(BCF/0.048)- resp. logKow-range		
1	3.00	to	3.33
2	3.33	to	3.67
3	3.67	to	4.00
4	4.00	to	4.33
5	4.33	to	4.67
6	4.67	to	5.00
7	5.00	to	5.33
8	5.33	to	5.67
9	5.67	to	6.00
10	6.00	to	<

3.3.9 Weighting category Degradability

Substances brought into nature, there, by photolysis, hydrolysis, or metabolic activity of organisms, are degraded to inorganic materials, which again enter the materials' metabolism, e.g., the carbon or nitrogen cycle. The nature's intake capacity for substances of, especially anthropogenic origin, and the ability to degrade them, is

restricted. Substances that accumulate in nature and are degraded poorly are called 'persistent'. For example, we indicate the plant protective agents Aldrin, Chlordan, and the industry-chemical hexachlorobenzene, which production even was forbidden, recently, counted among the persistent semi-volatile substances (POPs, Persistent Organic Pollutants). A measurement for the degradability is the half-life period. Substances are classified as to be degradable quickly if the half-life period (HLP) comes up to one week and as resistant if it comes up to one year. Therefore, in EATOS the period of one week the weighting factor Q = 2 was assigned to, and the period of one year the value 10. A linear split of the value ranges for Q is shown in Table 12.

Table 12   Assignment of half-life periods to the weighting factor $Q_{Degradability}$

Q	half-life [h]						
1	0	to	168	≈	7	days	fast (1 - 7 days)
2	168	to	1242	≈	52	days	moderate (1 - 4 weeks)
3	1242	to	2316	≈	97	days	
4	2316	to	3390	≈	141	days	
5	3390	to	4464	≈	186	days	slow (1 - 6 months)
6	4464	to	5538	≈	231	days	
7	5538	to	6612	≈	276	days	
8	6612	to	7686	≈	320	days	
9	7686	to	8760	≈	365	days	resistant (6 - 12 months)
10	8760	to	<				

From the coordinates (Q = 2 / HLP = 186 h) and (Q = 10 /HLP = 8760 h) the function HLP = 1074 · Q - 1980 results, wherefrom - at HLP given - the weighting factor Q = [(HLP + 1980) / 1074] arises.

The degradation of chemicals takes place in different compartments. The kind of reduction can be indicated in EATOS to be able to assign the data-affiliation, but no diversely distinguished assignment of the weighting factor Q is made.

3.3.10   Weighing category Greenhouse effect

Greenhouse-effective gases contribute to the heating of the earth and to the climate change. The largest part of the greenhouse effect is formed by the natural greenhouse gases carbon dioxide and water vapor. But methane and other trace gases like nitrogen oxides and fluorinated hydrocarbons with, among other things, anthropogenic origin, are greenhouse-effective on their parts. The global warming potential (GWP) is expressed in carbon dioxide-equivalents; $GWP_{CO_2} := 1$. In Table 13, the specific weighting factors Q concerning the greenhouse effect are compiled.

Table 13   Assignment of global warming potentials (GWP) to the weighting factor $Q_{Greenhouse\ effect}$

Q	GWP [CO_2 := 1]		
1	0.00	to	1.00
2	1.00	to	2.96
3	2.96	to	8.77
4	8.77	to	25.98
5	25.98	to	76.96
6	76.96	to	227.93
7	227.93	to	675.09
8	675.09	to	1999.48
9	1999.48	to	5922.08
10	5922.08	to	<

The coordinates (Q = 2 / GWP = 1 (CO_2-equivalent) and (Q = 9 / GWP = 2000 (CO_2-equivalents) yield the exponential function GWP = $0.114 \cdot e^{1.0858 \cdot Q}$, wherefrom the weighting factor Q at a given GWP is calculated: Q = $[\ln(GWP / 0.114) / 1.0858)]$.

Essentially, greenhouse gases produced for the energy supply make an impact on the greenhouse effect of a process. Possibly liberated CO_2 or N_2O from a synthesis itself substantially is of less importance. Therefore, the weighting category is provided especially for data from the energy supply.

3.3.11   Weighting category Ozone depletion

In the stratosphere, ozone is enriched with a maximal volume percent of 10^{-5} (ozone layer) and absorbs UVA- and UVB-irradiance of the sun which, among other things, can cause cancer to human beings. The ozone layer especially is depleted by chlorofluorocarbons (CFC), which are produced as aerosol blowing agent or emerged from the use of solvents (e.g., carbon tetrachloride). The ozone depletion potential (ODP) of substances is regarded in relation to CCl_3F (CFC 11), which potential is defined with 1. For the program EATOS, the ozone depletion potential of CF_2BrCl (Halon 1211) (ODP = 4) was used for the assignment of a higher value Q.

The coordinates (Q = 1 / ODP = 0.01 (CFC 11-equivalent) and (Q = 9 / ODP = 4 (CFC 11-equivalent)) yield the exponential function ODP = $0.0047 \cdot e^{0.7489 \cdot Q}$, which the weighting factor Q at a given ODP is calculated from as Q = $\ln[(ODP / 0.0047) / 0.7489)]$.

Table 14   Assignment of ozone depletion potentials (ODP) to the weighting factor $Q_{Ozone\ depletion}$

Q	ODP [CFC 11 := 1]		
1	0.00	to	0.02
2	0.02	to	0.04
3	0.04	to	0.09
4	0.09	to	0.20
5	0.20	to	0.42
6	0.42	to	0.89
7	0.89	to	1.88
8	1.88	to	3.97
9	3.97	to	8.40
10	8.40	<	

3.3.12   Weighting category Nutrification

The entry of mostly inorganic (often nitrogen- or phosphorus -) compounds into the environment by industrial waste water or gaseous emissions of, e.g., nitrogen oxides, can lead to an disturbance of the biological equilibrium, which causes the nutrification of waters, and this has to be avoided. The nutrification potential (NP) of substances is expressed in relation to the nutrification potential of phosphate (PO_4), which potential is defined by the value 1. In EATOS, this value 1 the highest weighting factor Q = 10 is assigned to, and the remaining weighting factors Q equally spaced ranges up to 0.2 for Q = 1 are assigned to. Q is determined from the nutrification potential following the expression: Q = [NP · 10]. The assignment is presented in Table 15.

Table 15   Assignment of nutrification potentials (NP) to the weighting factor $Q_{Nutrification}$

Q	NP [PO_4^- := 1]		
1	<		0.2
2	0.2	to	0.3
3	0.3	to	0.4
4	0.4	to	0.5
5	0.5	to	0.6
6	0.6	to	0.7
7	0.7	to	0.8
8	0.8	to	0.9
9	0.9	to	1
10	1		<

3.3.13   Weighting category Acidification

Acid rain (pH-value < 5.6) results from the formation of acid in the atmosphere caused by sulfur- and nitrogen oxide emissions. Damage to the vegetation (e.g., damage to forests) and by corrosion at buildings are the result. The acidification potential (AP) of sulfur dioxide is defined with the value 1, and other gases are regarded in its acidification potential in accordance with sulfur dioxide. In EATOS for the value Q = 10 the AP-value 1.9 was fixed, because the highest AP-value amounts to 1.88

(ammonia). The classification of the remaining Q-values can be seen in Table 16, where Q is calculated from an AP-value according to $Q = [AP \cdot 5 + 0.5]$.

Table 16   Assignment of acidification potentials (AP) to the weighting factor $Q_{Acidification}$

Q	AP [$SO_2 := 1$]		
1	<		0.3
2	0.3	to	0.5
3	0.5	to	0.7
4	0.7	to	0.9
5	0.9	to	1.1
6	1.1	to	1.3
7	1.3	to	1.5
8	1.5	to	1.7
9	1.7	to	1.9
10	1.9		<

3.4   Indication of reference and/or experimental procedure

To each entry of a synthesis belongs the literature source where it is based on and/or an experimental procedure, which can be input by clicking the toolbar *LITERATURE* (see, e.g., Figure 5, p. 16). (or click *EDIT*). Firstly, in this way this guarantees an explicit, comprehensible assignment to references, and secondly, informations concerning the experimental procedure and reference will be available in the graphical results' presentation. Additionally, by rendering the literature when clicking single syntheses in the project window (compare Figure 2, p. 13), the overview of the syntheses included in the resources-references will be preserved. This is needed, especially if several syntheses are named similarly, because there the same product derives from, which was obtained in different ways described in literature .

Figure 24 Input of reference and/or experimental procedure.

3.5   Substance List

The substance list includes all substances exported (see chapter 3.6, p. 51) or compiled herein, and in this way it represents a data bank. You can call it up with the toolbar *SUBSTANCE LIST* (compare   Figure 26) (or *EDIT*), so you directly can input substances, as well.
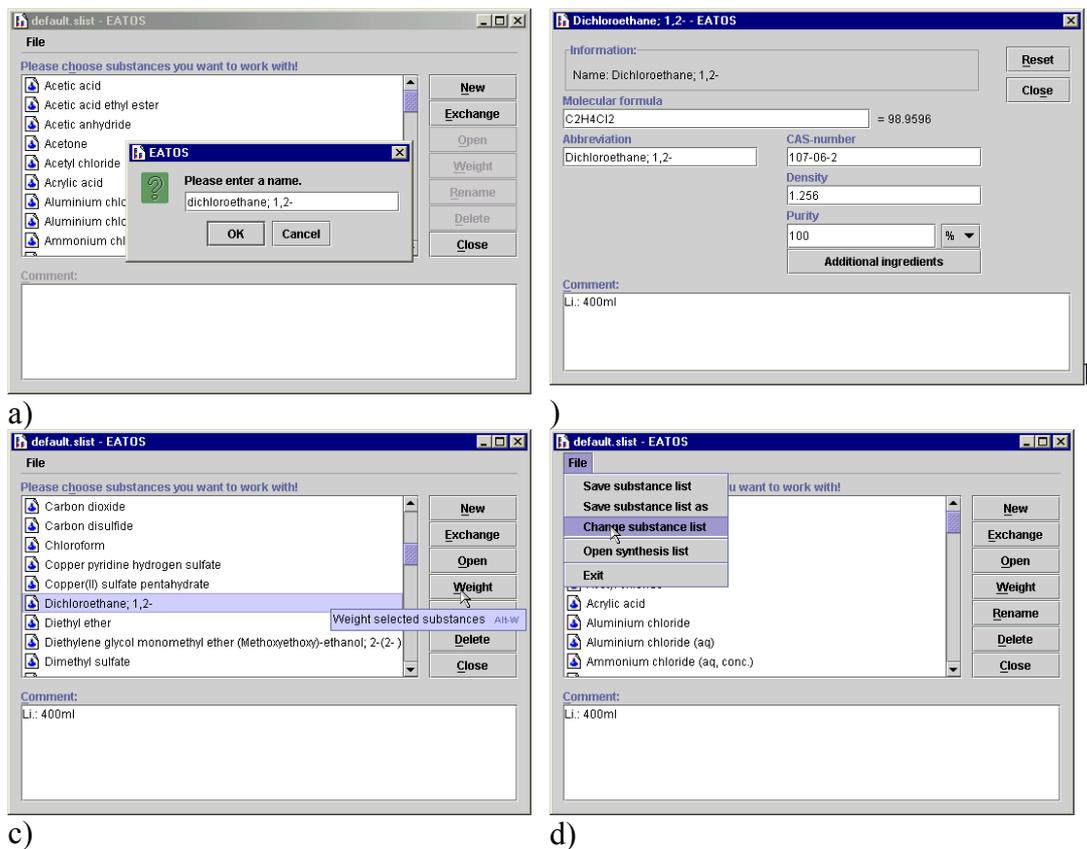
Figure 25   Input of substances into the substance list

Clicking the toolbar *NEW* (Figure 25a) you can input a new compound and specify it by clicking the toolbar *OPEN* (Figure 25b), including toxicological and other weighting-relevant data (compare chapter 3.3, p. 32), which can be enlisted after clicking the toolbar *WEIGHTING* (Figure 25c) as described (see Figure 22, p. 33). Generally, you can issue different substance lists (e. g., solely substance lists of solvents or catalysts), which you can access from by the *FILE* and *CHANGE SUBSTANCE LIST* (Figure 25d).

3.6   Import and Export

A most important function in EATOS is the import and export of substances and the import of products of other syntheses. In this way, it becomes possible to export substances with all substance-specific data into the substance list which, thus, with complete data set is available for other applications without having to input data for these, again.

In the case that a product of a synthesis is converted in a subsequent synthesis then it can be called synthesis sequence or synthesis chain. The substrate in the subsequent synthesis therefore represents the product of the precedent synthesis that using the toolbar *IMPORT* can be imported with all synthetic data. This linkage option enables the construction of complex synthesis sequences. This linkage can be carried out for

both substrates and catalysts. Therefore the efforts to synthesize the catalyst can be considered as well.

3.6.1   Export of substances into the substance list

By clicking the toolbar *EXPORT*, substances can be exported into the substance list (default.slist) with all data.
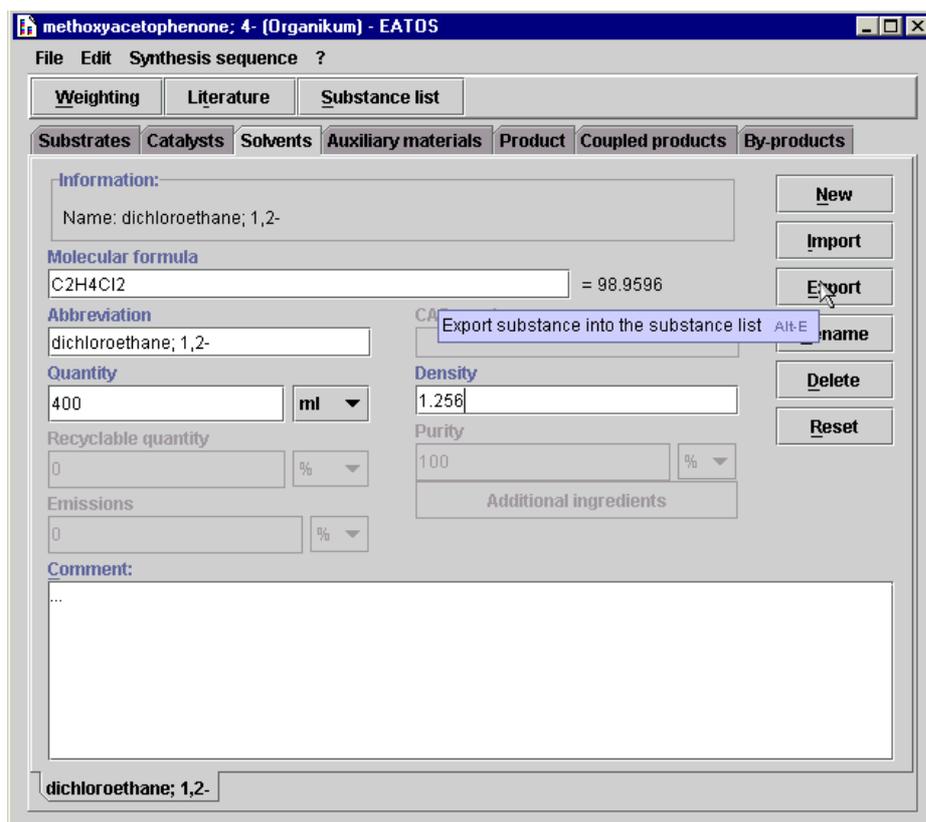

Figure 26   Export of substances into the substance list

3.6.2   Import of substances from the substance list and of products

The input of substances and belonging data into the input line of the program can be made manually or by import from the substance list, in the case that the substance was input once already and exported into the substance list or enlisted there directly. The toolbar *IMPORT* can be selected at every opportunity that offers to enter a substance. Thereby, you open a window which can have different screens. If you open the substance list after clicking the toolbar *NEW* (except for the register sheet *CATALYSTS*) via *IMPORT* (see, e. g., Figure 7, p. 20), only this appears with all substances enlisted (Figure 27a). After selecting a substance this can be imported. The same modus operandi in the register sheet *CATALYSTS* opens the possibility to import products of syntheses with all data enlisted in the project opened. In the example discussed up to now, this is the project methoxyacetophenone; 4-.project (Figure 27b). The same is

valid for the import of substances when inputting the stoichiometric equation (compare Figure 3, p. 14), if a synthesis sequence shall be created.


a)

b)
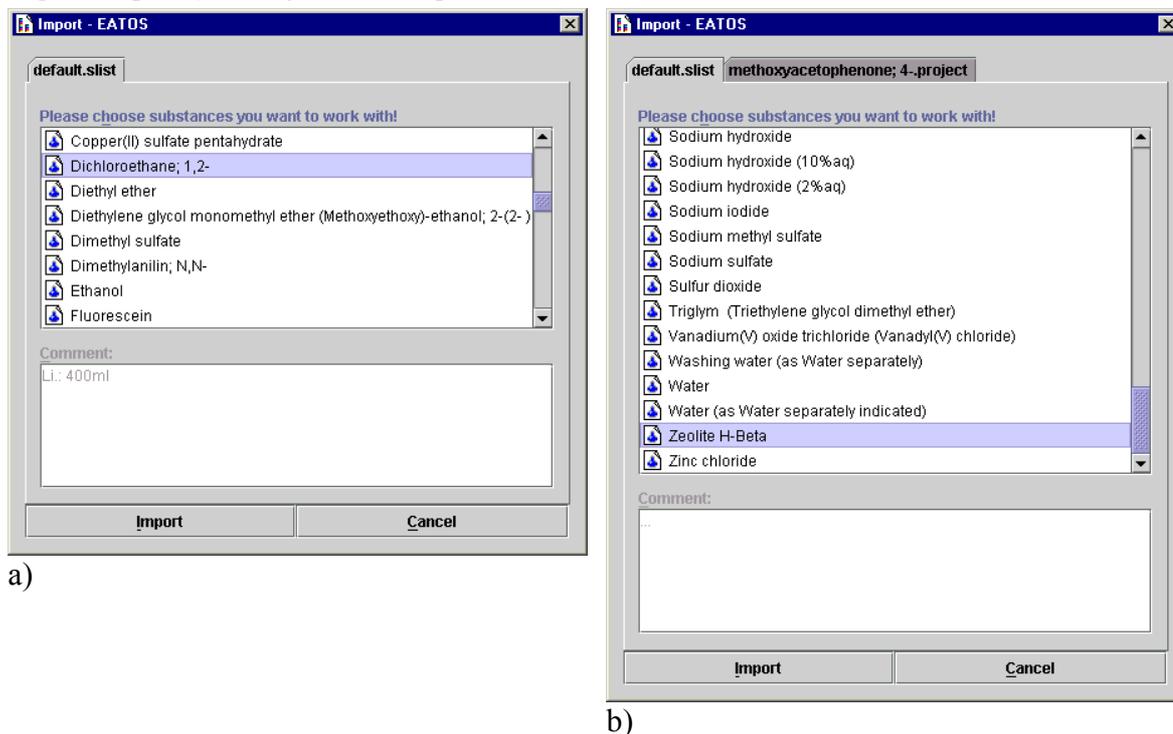
Figure 27   Import of substances from the substance list

IMPORT can be selected as well if a substance already is enlisted. In this case, all data input already, except for the comment field in the register sheet, will be transcribed with those from the substance list. This function allows to replace substances with few data enlisted by new inputs made into the substance list in the meantime being more data-rich Furthermore substrates or catalysts can be exchanged with *their* syntheses enlisted in the opened project. Sequences can be built by this procedure. But in the register sheets *SUBSTRATES* and *CATALYSTS* only substances with the identical formula, resp. with the identical molecular weight, can be selected; others will not be indicated (compare Figure 28, p. 54).

3.6.3   Syntheses Sequences

If syntheses produce products, which enter as substrates in others again, these can be linked to each other, provided that the syntheses regarded are situated in the very same project. For example, already syntheses enlisted in other projects can be copied into the project opened by the function *EXCHANGE*. Syntheses are linked with each other by not entering them manually but integrating them form the project via the toolbar *IMPORT*(see previous chapter 3.6.2, p. 52). Substances enlisted already can be transcribed (except for the comment field). Figure 28 shows how, e.g., the substrate anisole as product is imported from another synthesis called '*ANISOLE (ORGANIKUM)*' .
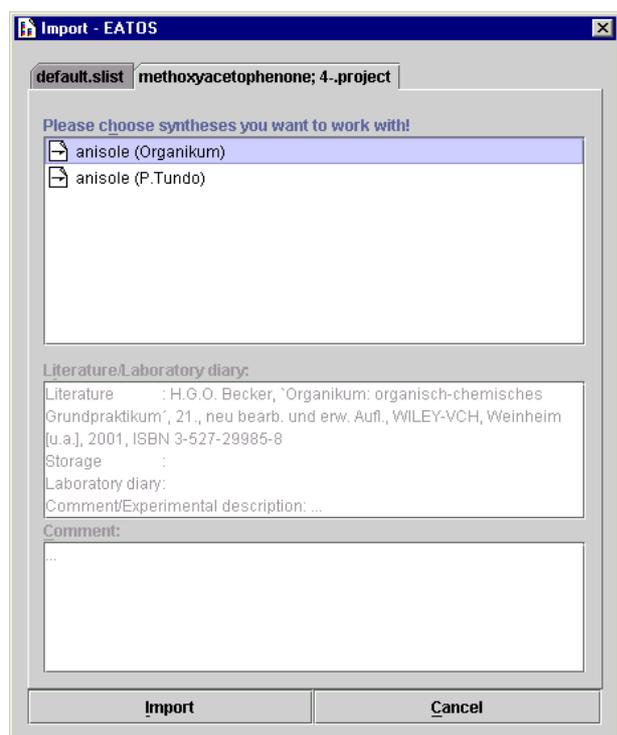
Figure 28 Import of a product of another synthesis of the project

It is about the synthesis of anisole; i.e. the methylation of phenol with dimethyl sulfate described in the Organikum (20. Ed., Deutscher Verlag der Wissenschaften, Berlin, 1996, ISBN 3-335-00492-2) is considered to be imported as precedent synthesis.
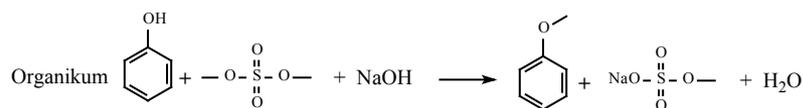
Scheme 3 Synthesis of anisole

In the register sheet anisole of the synthesis 'methoxyacetophenone; 4- (Organikum)', where the synthesis of anisole was imported into, appears (Figure 30, p. 56) next to the substance name the appendix 'imported from "anisole (Organikum)"' in the information field.

To the synthesis' name – in our example 'methoxyacetophenone; p-(Organikum)' – a modified symbol is prefixed, that should indicate that this is a synthesis sequence:
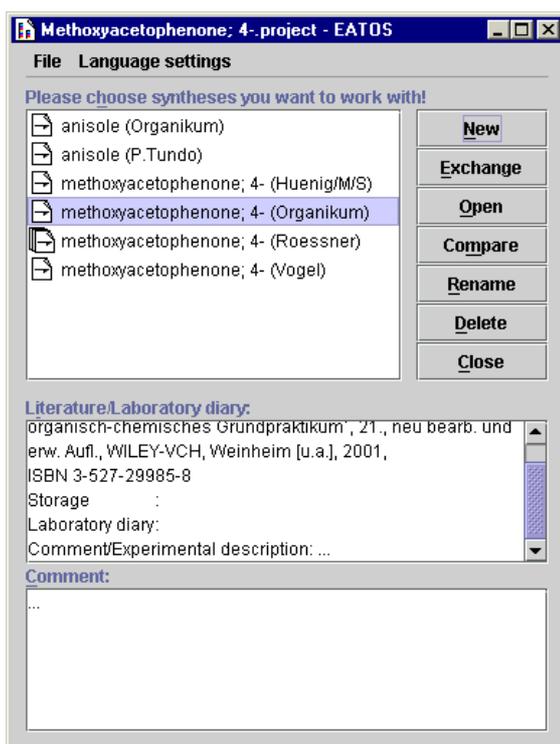
Figure 29 Project with syntheses and a synthesis sequence (marked)

By the way, we would like to mention that, despite the creation of synthesis sequences, catalysts as products of other syntheses can be imported, as well.

After creating synthesis sequences, now as before you got the possibility to change data in every single synthesis, with the corresponding consequences for the whole synthesis sequence, respectively, the chain. But the change has no direct consequences for the calculation. You update via *SYNTHESIS SEQUENCE* in the command line:
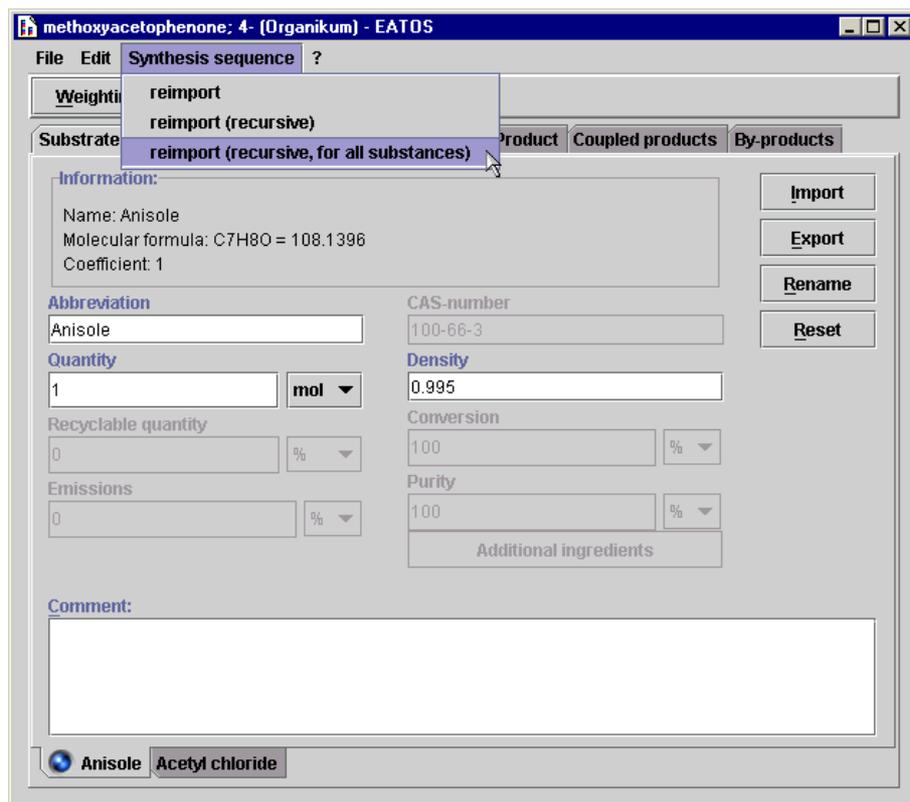
Figure 30   Reimport of syntheses of preceding synthesis steps

REIMPORT means that the synthesis step for the substance production of the register sheet opened imports again and that, in this way, its data set is updated. If the complete synthesis sequence should be updated for the substance production, you select *REIMPORT* (*RECURSIVE*). If all other substances, which register sheets are not opened, should be updated thereby, as well, you select *REIMPORT* (*RECURSIVE, FOR ALL SUBSTANCES*).

3.7   **Presentation of the results**

The graphical presentation of the materials flows by interactive column diagrams can be made either emanating from a synthesis opened (see, e.g., Figure 4, p. 15) via *EDIT* and *CALCULATE* or emanating from the project window (see Figure 31) via *COMPARE*. In the first case, exclusively data of the synthesis opened are presented graphicly, whereas, in the second case, several syntheses can be selected and represented graphically in common. In the example presented here, four different syntheses of 4-methoxyacetophenone shown in Scheme 4 should be compared to each other.
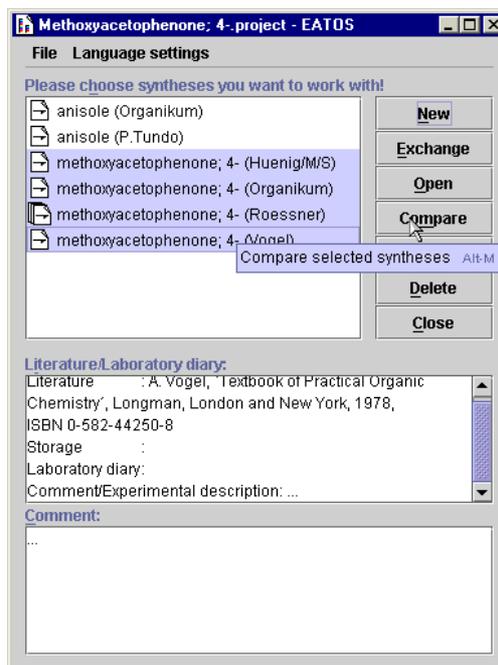
Figure 31 Comparison of syntheses
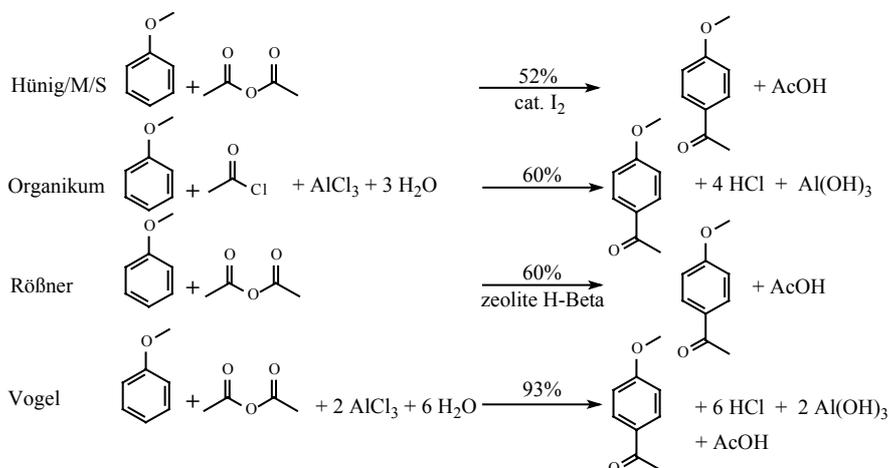
Scheme 4   Synthesis of 4-methoxyacetophenone according to a) S. Hünig, G. Märkl, J. Sauer, Integriertes organisches Praktikum, Verl. Chemie, Weinheim [u.a.], **1979**, ISBN 3-527-25473-0; b) Organikum: organisch-chemisches Grundpraktikum, 21., neu bearb. und erw. Aufl., (Hrsg.: H.G.O. Becker), WILEY-VCH, Weinheim [u.a.], **2001**, ISBN 3-527-29985-8; c) 10 g anisole (92.5 mmol), 10.39 g acetic acid anhydride (101.7 mmol) and 1.33 g Zeolite H-Beta (Südchemie, Munich) were stirred for 24 h and heated under reflux. The catalyst was filtered off, washed with 5 ml ethanol and the product was distilled fractionally in vacuum. The yield of 4-methoxyacetophenone was 8.34 g $\cong$ 60%, compare [e,f]; d) Vogel's textbook of practical organic chemistry : including qualitative organic analysis, 4. ed. / rev. by B. S. Furniss, (Hrsg.: A.I. Vogel), Longman, London [u.a.], **1978,** ISBN 0-582-44250-8; e) U. Freese, F. Heinrich, F. Rößner, Acylation of aromatic compounds on H-Beta zeolites, Catalysis Today **1999**, 49, 237–244; f) S. Ratton, Heterogeneous catalysis in the fine chemicals industry: From dream to reality, Chimica Oggi-Chemistry Today **1998**, 16(3-4), 33–37

In the graphic comparison, to all syntheses selected the metrics S^{-1} (Input [kg] / kg product), environmental factor E (waste [kg] / kg product), environmental index EI_in

(S^{-1} weighted with weighting factors) and EI_out (E weighted with weighting factors) are presented (Figure 32). The space for the presentation of the synthesis name is limited. This is the reason why a short specification such as, e.g., a), b), and so on, is recommendable. Figure 32 (p. 58) shows the order of the syntheses indicated in Scheme 4. The differently colored column segments, among other things, represent the categories substrates, coupled products, byproducts, and so on. Under *COLUMNS* you can select the metric to be presented. Besides the 4 metrics named, you can determine as well the expenses by the economic index (Cost Index, *CI*). By clicking *?* in the corresponding Figure 33 (p. 59), you can call up *HELP*, a schematic overview of the *MASS-BALANCE REGIONS* (Figure 13, p. 24), and information on the program E*ATOS*.
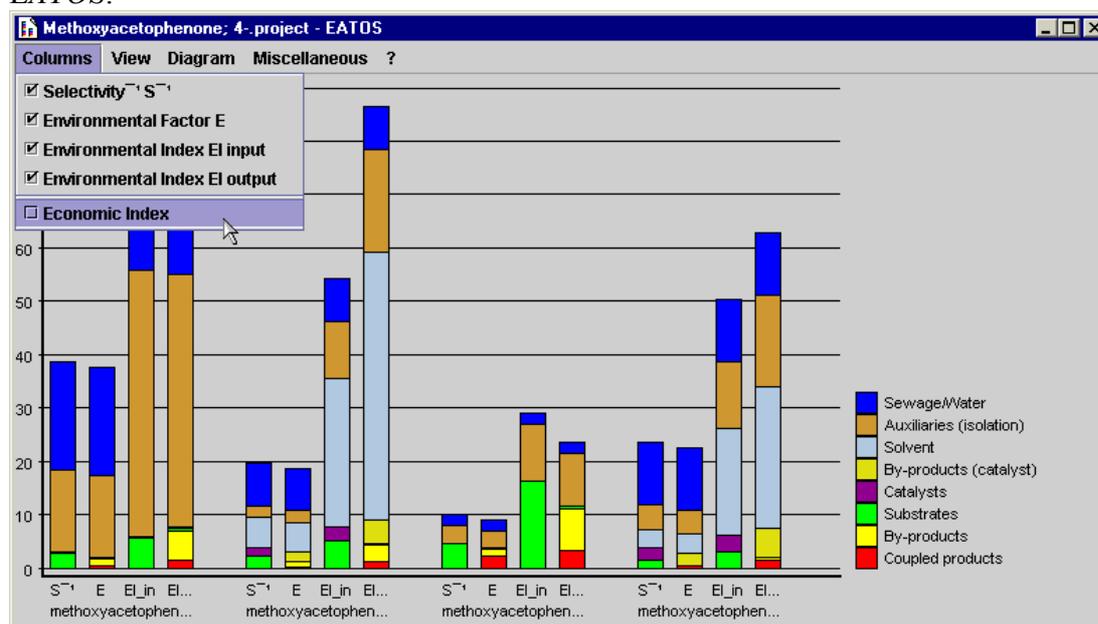

Figure 32 Graphic presentation of four metrics to four syntheses of 4-methoxyacetophenone
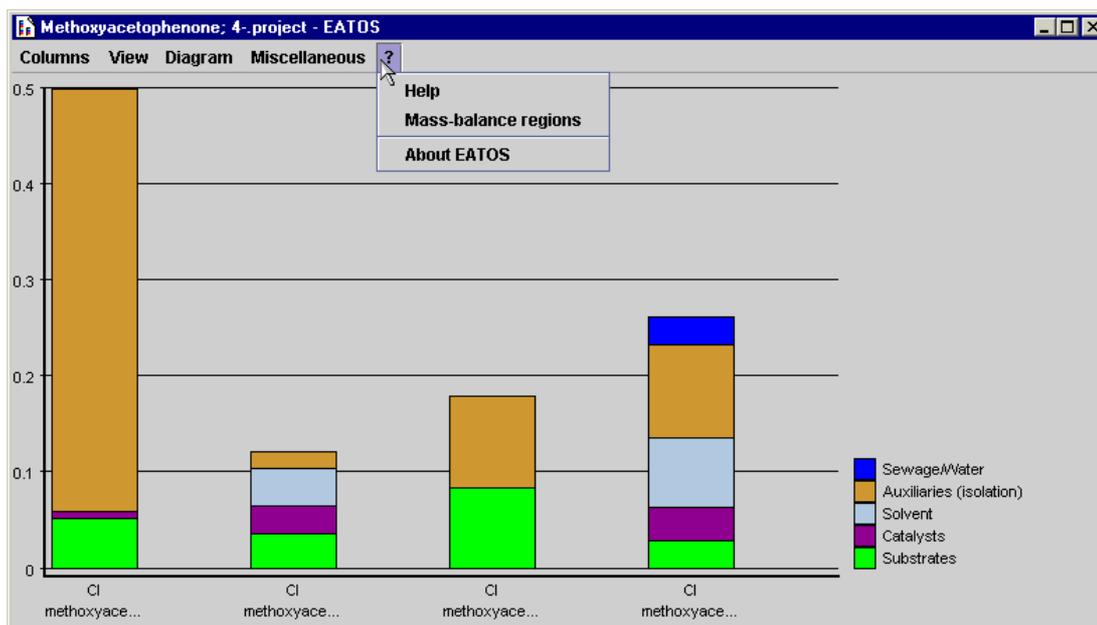
Figure 33 Economic index (*CI*) of four syntheses of 4-methoxyacetophenone

Regarded from the economic aspect, substance prices are interesting in view of the determination of the material costs per production unit. In this way, *EATOS* makes possible the calculation and distinguished presentation of the different entry items, such as substrates, solvents, and so on by the so called economic index, i.e. Cost Index (*CI*).

Under *VIEW* you make the adjustment of the presentation of the data calculated in the bar chart. In this way, it is possible to blind out, e.g., auxiliary materials via *MASS-BALANCE REGIONS*, to blend in the possibly different information level of syntheses to be compared. If there is available to a synthesis only data concerning the auxiliary materials of the reaction itself, while the necessary auxiliary materials for the isolation of another synthesis are known, these can be blinded out by calling up *REACTION* to make possible a comparison on the same information level. Default-adjustment, however, is 'Waste treatment', wherefore, firstly, all auxiliary materials will be indicated.

Substances, to which recyclable quantities were entered, can, under *VIEW*, *RECYCLE*, either be *SEPERATELY INDICATED or INTEGRATED INDICATED*; the option of *NOT INDICATED* exists as well representing the default-adjustment. In case of the separate presentation, these substances appear in a category given for them above the remaining categories, to be able to measure their portion of the whole material volume.

As a rule, the substances used in the conversion are standardized regarding the product quantity produced (i.e., their mass is divided by the product mass) to receive a term substance [kg] / kg product, which only makes possible the comparison of different syntheses, at all. However, this default-adjustment can be changed under *STANDARDIZATION*. In the register sheet *COUPLED PRODUCTS* (compare Figure

16, p. 27) you can indicate utilizable quantities, and in the register sheet *BYPRODUCTS* (compare Figure 17, p. 28) you can mark these as utilizable. These quantities can be considered in different ways. If you regard them as products, under *STANDARDIZATION* you either can assign them to the category (*STANDARDIZATION) ON PRODUCT) (DISPLAY USEFUL COUPLED PRODUCTS* or *DISPLAY USEFUL COUPLED AND BYPRODUCTS*) or even include them in the process of standardization (*STANDARDIZATION ON PRODUCT AND USEFUL COUPLED PRODUCTS*, resp. *AND BYPRODUCTS*). In the last case, all substance quantities not only are divided by the product quantity but also by the quantity of the useful coupled and, if required, by the useful byproducts. In this way, the presentation resulting from this imparts the relation of spend input and of produced waste to the produced quantity of the products. Product and, if necessary, produced useful coupled- and byproducts can be shown under *PRODUCT*. In this case, a further category with this specification appears.

Analogously to the *RECYCLE* explained before, *EMISSIONS* as well can *NOT, INTEGRATED* or *SEPERATELY* be *INDICATED*. Additionally, there exists the possibility to indicate emissions *EXCLUSIVELY* if the corresponding data material is available and should be regarded isolated from other mass transactions.

The optical presentation of the data calculated can be changed via *DIAGRAM*. The *LEGEND* either can appear in German or English (either written in short or full form). This is necessary for the export of English diagrams into other applications.

Firstly, the output data are configured according to the syntheses regarded. The column arrangement can be changed via GROUP . By clicking *ACCORDING TO INDEX* the different types of columns (S^{-1}, E, EI_in, and EI_out) are sorted so that different syntheses can be compared in consideration of these types of columns.

In the space of a column, via ORDER you can organize according to categories (substrate, solvent, and so on) or synthesis steps. In the second case, a synthesis sequence is presented subdivided in its synthesis steps, whereby especially syntheses of high quota can be identified. The differentiation of the order according to categories in consideration of *SYNTHESIS SEQUENCE*, resp. *LAST SYNTHESIS STEP* is made possible, so that the syntheses forming the target product can be compared independently from syntheses sequences, where these are based on.

Often, of synthesis sequences only the main synthesis chain, starting at a key substrate, is of importance. Additional syntheses (synthesis chains) entering into the main synthesis sequence, from which non-key substrates result, are understood under *FURTHER SYNTHESES. Under DIAGRAM* and, subsequently, under *FURTHER SYNTHESES* they either can *INTEGRATED*, *SEPARATELY*, or *NOT* be *INDICATED*.

The scaling of the diagram internally is effected according to the highest column. Therefore, markedly high columns can complicate the interactive usage of the graphical presentation when, thereby, smaller segments can not be called up with the cursor,

anymore. For this reason, via *SCALE*, *ACCORDING TO HIGHEST COLUMN* maximal *THE 5TH HIGHEST COLUMN* less distinct diagram segments can be shown enlarged in their representation. The comparison of the relative influence of categories among each other is simplified by *ALL COLUMNS ON 100 %*.

Via *STYLE* the columns either can be rendered monochrome or colored in different ways. By *FLIP* the columns are justified not upwards but downwards.

The graphic is changed and saved into a .bmp-file via *EXPORT GRAPHIC*. This means, the graphic is exported from the application to be available for other applications, where it can be inserted.

Among other things, in the command line *MISCELLANEOUS* serves to indicate the *LITERATURE* the syntheses base on, whose presentation can be preset via *CONFIGURATE LITERATURE*, before. In the same way, the stoichiometric equations can be visualized. Therein also appear the atom selectivities with the abbreviation AS. And here you will always find two indications: Firstly, the AS of the syntheses represented in the following line, secondly, the AS including the synthesis sequence, where this synthesis is based on. If you selected *STANDARDIZATION ON PRODUCT AND USEFUL COUPLED PRODUCTS* under *VIEW*, coupled products specified as useful are integrated in the determination of the atom selectivity. Then, the AS no longer is determined according to AS = MW product / Σ MW substrates, but to AS = (MW product + MW useful coupled product) / Σ MW substrates. The exactness of the specifications represented can be changed via DECIMAL PLACES , as well as the default-adjustment of the (DISPLAY) WEIGHTING OF THE WEIGHTINGS via the correspondent toolbar (compare chapter 3.7.1, p. 61).

3.7.1   Weighting of the weighting

In chapter 3.3 (p. 32) the 13 weighting categories are described, which can be used for the valuation of the material flows. Their appropriate influence can be changed in the graphic presentation, which can be called up via *EDIT CALCULATE* or via *COMPARE*, via *MISCELLANEOUS DISPLAY WEIGHTING OF THE WEIGHTINGS*.

The weighting of the input is made in equal shares via the category *CLAIMING OF RESOURCES* and *RISK*, and that of the waste *via HUMAN TOXICITY (ACUTE)*, *CHRONIC TOXICITY, ECOTOXICOLOGY*, and *OZONE CREATION*.

On the one hand, the price is the impact category for the claiming of the resources, on the other, it is useful for the specification of the economic index (cost index, CI), which can be called up under *COLUMNS*.

Figure 34   Weighting of the weighting

Among the weighting categories those can be ticked off, which should contribute to the formation of the weighting factor. In the input fields, you can change the influence rate of the selected weighting categories specified as 'k' in the term Q_{total}; the appropriate percental amount is represented on the right. In the example of Figure 34, for the determination of the output categories shares of appropriately 25 % are represented, i.e., $k_1 = k_2 = k_3 = k_4 = 0.25$.

$$Q_{total} = k_1 \cdot Q_{Human\ toxicity} + k_2 \cdot Q_{Chronic\ toxicity} + k_3 \cdot Q_{Ecotoxicology} + k_4 \cdot Q_{Ozone\ creation} \text{ with } \sum_{i=1}^{4} k_i = 1$$

Impact categories of substances showing non-problematic values are weighted with a weighting factor Q = 1 so that the dimension of the mass always maintains. But in the case that all substances, which do not contribute anything to the categories selected, shall to be blinded out, the weighting factor Q = 0 can be assigned to by clicking *ALLOW Q = 0*. Clicking *UPDATE* or CLOSE, the changes have effects on the bar chart presented.

3.8   Error Messages

The software EATOS has been developed to execute complex calculations on the base of a low information level, resp. a low data set of the user. The central point of all calculations is the stoichiometric equation input by the user and the yield. After input of the substance quantities used, e.g., the resulting amounts of coupled products or byproducts are determined therefrom. Thereby, the condition corresponding to the reality is fulfilled that the input mass always is of the same size as the output. If inputs of the users do not meet these criteria, an error message points out the cause of the problem. In this manual in the respective chapters corresponding hints to the calculations have been given, so that a solution of the problem becomes comprehensible.

In only a few cases, before calculation the program does not prove completeness of the data. In this way, e.g., a specification of the economic index (CI) is made without error message (or even not made at all), whenever to several substances namely the prices are indicated, but not the amount it is based on. In these cases, the category price will not be considered for the appropriate substances.

*****

Translated by: Elke Frenzel, Universität Oldenburg