Application of Indicators for Assessing Environmental Aspects of Chemical Processes to Case Studies From Pharmaceutical Production

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Abstract: As a result of legislation and increasing public awareness, environmental considerations are given more and more importance in chemical process design. Furthermore, the focus in environmental protection has shifted from end-of-pipe technologies to improvements of the chemical processes. The realization of such improvements, on one hand, requires chemical or technical innovations (new molecules, new synthesis routes, new process designs) and, on the other hand, assessment methods are needed that deliver an objective comparison of process alternatives on appropriately defined system boundaries.

Four different indicators for assessing the environmental impact of chemical processes are discussed: Mass Loss Indices (MLI), Environmental Indices (EI), a comprehensive EHS (Environment, Health, and Safety) assessment method, and Eco-Indicator 95, an evaluation method used in the Life Cycle Analysis (LCA) framework. These methods are summarized, compared, and applied to case studies from the chemical industry. Finally, the corresponding results are discussed and conclusions on the capability and limitations of the different indicators are drawn, in particular with regard to their applicability during the early phases of process development.

Keywords: Case studies · Environmental indicators · Fine chemical production · Green chemistry · Integrated process design

Introduction

As a result of legislation and increasing public awareness, safety and in particular environmental considerations are given more and more importance in chemical process design (e.g. [1][2]). Initially efforts in environmental protection concentrated on preventing or reducing emissions through the installation of end-of-pipe technologies. These measures generally reduced the economic benefit of the corresponding chemical processes. Recently, the reactive strategy to solve environmental problems changed towards proactive avoidance and reduction of pollution and resource depletion. Only this approach allows a possible ecological improvement together with an increased economic benefit.

In the proactive approach all parts of a chemical process are considered, from the reaction pathway over the separation techniques to the generation of energy and utilities. To achieve true improvements - resulting in better ecological as well as economic performance - chemical or technological innovations are needed. Such innovations might be new, easy-to-synthesize, but nevertheless effective molecules, new chemical synthesis routes, or new features of chemical process design. To verify and highlight the corresponding ecological improvements, assessment methods are needed that deliver an objective comparison of process alternatives on appropriately defined system boundaries. The proper definition of system boundaries as well as the definition of a functional unit to which both the economic profit as well as the environmental damage are related are of major importance for obtaining meaningful results. Because nowadays time to market is crucial, such methods have to be implemented in a way that they support the chemical engineer in integrated process design without slowing down the innovation process.

Here, we briefly present a general methodological framework for considering safety and environmental issues in chemical process design and discuss in more detail the concepts of four different assessments methods measuring environmental impact (Mass Loss Indices, Environmental Indices, a comprehensive EHS assessment, and Eco-Indicator 95) as well as their application to case studies from chemical industry. The results obtained and the problems associated with the application of these methods as well as their capabilities and limitations will be highlighted.
Methodology

General Framework for Integrated Process Design

A general framework for integrated process design is presented in Fig. 1. At different stages of chemical process development, design alternatives are generated. The generation of process alternatives is a crucial step because here the previously unlimited search space is restricted significantly. Because of its importance, efforts have been undertaken to develop methods that support the systematic generation of alternatives by exploiting heuristic knowledge (e.g. [3–5]). Heuristics are also used for the automatic generation of process designs [6].

Once generated, process alternatives have to be simulated to enable their assessment and comparison. At early stages of process design the corresponding models have to be rather simple while at the later stages, when more data are available, more sophisticated approaches and simulation tools can be used. This means also that in particular at early stages uncertainty should be considered in the simulation procedure. While mathematical procedures such as Monte Carlo are available for uncertainty propagation, it is generally difficult to characterize parameter uncertainty exactly because the information needed is not available.

Data availability is a major problem in the whole framework. Particularly in the early phases, property estimation methods are required to close data gaps. Improvement and extension of such estimation methods are therefore important for applying the concept of integrated process design already at the early phases. In particular reaction yields and related information are very sensitive parameters and should be known as precisely as possible. Therefore, also the corresponding experimental procedures have to be improved. In general, sensitivity analysis is an important concept to reveal the most sensitive parameters to be determined with highest precision in following design steps.

The balances (mass, energy, money) generated by simulation have then to be evaluated using appropriate indicators. The definition of such indicators in the context of integrated process design is an area of intensive ongoing research activity, in particular with respect to measuring environmental impact of chemical processes. Concepts presented vary from mass indices (e.g. [7]) to the application of the life cycle assessment (LCA) methodology (e.g. [8–10]). The various methods require quite different amounts of data. Finding the balance between data requirement and conclusions to be drawn from the results is one of the challenges in defining and selecting indicators. The four indicators used in this paper are discussed below.

Because generally different indicators are used for the different objectives (economy, safety, environmental impact) either a multi-objective approach such as Pareto curves or some kind of aggregation has to be applied in decision making. The whole procedure is applied in an iterative manner until a promising/the most promising process alternative has been found. The methodology can also be used for assessing alternatives for specific problems emerging at different stages of process development.

Indicators Measuring Environmental Impact

The four types of indicators used in this paper are Mass Loss Indices (MLI), Environmental Indices (EI), an comprehensive EHS (Environment, Health, and Safety) assessment method, and Eco-Indicator 95, an evaluation method used in the Life Cycle Analysis (LCA) framework. The characteristics of these methods are summarized in the Table. The concept of Mass Loss Indices and Environmental Indices used here was originally presented in [7]. For these indices different balance regions from reaction to downstream processing and waste treatment are defined. For the different balance regions the corresponding mass balances are related to the mass of product resulting in a number of dimensionless Mass Loss Indices (MLI). The MLI highlight the nonidealties of the process in terms of mass lost due to e.g. the stoichiometry (formation of coupled products), low selectivity (by-products), or the consumption of solvents and auxiliary materials.

Through combination of the MLI with simple environmental weighing factors based on ABC analysis, a simple classification method, Environmental Indices (EI) are obtained [7]. The ABC analysis is divided into an input- and an output-oriented part. Aspects considered in the input part (EI input) are the complexity of the raw material synthesis, raw material consumption, critical materials used, and the availability of raw materials. The output part (EI output) considers the characterization of effluent streams with regard to air and water pollution as well as special problems. Further details on the MLI and EI indices are given in [7].

The third indicator considered here is a comprehensive methodology for assessing EHS (Environment, Health, and Safety) aspects recently presented in [11]. This approach is based on existing concepts of EHS and uses a corresponding set of effect categories. For each substance present in an investigated chemical process and for each effect category, the most reliable data are selected from a variety of different parameters or estimation methods. After identifying EHS
problems as dangerous properties, their magnitude is analyzed as potential of danger and can be reduced by technological measures. Further details on the EHS approach are given in [11].

The fourth index considered is Eco-Indicator 95 [12], an evaluation method used in the Life Cycle Analysis (LCA) framework. The Eco-Indicator 95 (EI 95) considers the damage to human health and the environment caused by released substances. The damage caused by substance release is usually estimated by determining the emissions of the process during normal operation, and calculating environmental concentrations in different compartments as well as the intake (dose) via different exposure pathways. Finally, the effects or the damage caused to humans and the environment are estimated. Recent reviews on the state-of-the-art in environmental impact assessment applied in LCA were presented in [13,14]. A review on the application of LCA in chemical process design was given in [15].

**Comparison of Indicators**

In the Table, a characterization of the four indicators discussed in this paper is given. Mass Loss Indices (MLI), Environmental Indices (EI), and Eco-Indicator 95 (EI'95) only assess environmental impacts while the EHS method also evaluates safety (process) and health (workplace) aspects of chemical processes. The assessment approaches with respect to the latter two safeguard subjects are not discussed in this paper. The system boundaries of the MLI, and EHS methods are expandable from considering the reaction step only to a ‘gate to gate’ approach while EI and EI'95 generally are applied to chemical processes in a ‘cradle to gate’ approach.

Major differences between the four indicators exist with regard to the assessment approach used and the degree of detail of the corresponding results. The MLI are not substance-specific and therefore major hazards cannot be identified in detail. The EI on the other hand consider single substances, but for the assessment, categories according to legal threshold values are used instead of substance-specific data. Consequently, a ranking of hazards can only be done between chemicals belonging to different classes of legal threshold values. The EHS method and the EI'95 both consider substance-specific data. The EHS method uses a simplified environmental fate model but considers different toxic effects in detail. The EI'95 assessment is based on model-based environmental impact data but considers toxic effects in less detail than the EHS method.

Only the Environmental Indices (and implicitly also the MLI) consider the consumption of resources while this aspect is neglected by the other two indicators. The Eco-Indicator 95 is the only one of the considered indicators that assesses energy consumption.

**Case Studies**

**Application of Mass Loss Indices (MLI) and Environmental Indices (EI) to the Synthesis of 4-(2-Methoxyethyl)phenol**

Mass Loss Indices and Environmental Indices were calculated for different reaction routes (Scheme) for producing 4-(2-methoxyethyl)phenol, an important pharmaceutical intermediate. For the different routes, the basic reaction conditions, yields, and (where mentioned) selectivities were collected from the literature. With this information the reactor output could be estimated and MLI's for the product (P), coupled products (CP), by-products (BP), non-converted substrate (S), solvents (Solv), and other auxiliary materials (1Aux) as well as the auxiliaries required for neutralization of the reaction mixture (2Aux) were calculated.

For the environmental assessment of input and output materials (EI input and EI output, respectively) weighing factors were obtained using the ABC classification approach as explained above. If no environmental data could be found for specific compounds, data for comparable substances were used, e.g. the data for tert-butyl phenol were used instead of all substituted phenolic products and by-products. Further details on this case study are given in [16].

In Fig. 2 the results obtained for this case study are presented. This graph shows that the synthesis routes considered are quite material-intensive as all three require between 35 and 50 kg of...
raw materials for 1 kg of product. Additionally, 60–75% of lost mass is caused by solvents. The search for improvement could start by looking for solvent-free processes or solvent recycling. When the output-oriented indices are applied (EI input), coupled products (EI output) are the major contribution besides the solvents in routes A and B. About 50% of the raw materials (including dimethyl sulfate as a carcinogenic compound in stoichiometric amounts) are lost in reaction steps 2 and 3 of route A (reaction steps 4 and 5 of route B) due to the high mass of coupled products. For route C all indices are similarly dominated by the mass of solvents, which shows that simple and non-problematic raw materials are used and that comparably ‘harmless’ waste is produced. Therefore, improving this route would mean to question the need of solvents or to find ways of recovering them.

It has to be emphasized once more, that Fig. 2 only shows measures of the environmental impact due to the synthesis steps of the three processes considered. Obviously, the picture might change when the complete processes including separation and waste treatment are considered.

**Application of the EHS (Environment, Health, and Safety) Method to the Synthesis of 8a-Amino-2,6-dimethylergoline**

The EHS method was applied to a case study from Novartis Pharma AG. A six-step batch process for synthesizing 8a-amino-2,6-dimethylergoline described in [17] was assessed. Here results are presented for the 2-methylation step of 1-(tert-butyloxycarbonyl)-8a-(tert-butyloxycarbonylamino)-6-methylergoline. The reaction is performed using n-hexyl-lithium and disopropylamine in a solution of tetrahydrofuran (THF) and hexane at −60°C. After methylation with methyl iodide, the reaction is quenched using methanol and water. Product separation includes filtration, removal of THF and hexane, crystallization from methanol/water, and drying. The final product yield is 76%. Further details on the choice of parameters for assessing this case study are given in [11].

The first level of results obtained with the EHS-method is a compilation of the index values of the different substances with regard to the various effect categories without considering the actual masses used in the process. At the next level the masses are taken into account as weighing factors. For the 8a-amino-2,6-dimethylergoline case study, Fig. 3 shows that substances present only at small amounts such as amino(di)-methyl-ergoline have less influence on the safety and environmental problems and therefore are outweighed by other more important substances. The aspects of mobility and fire/explosion now are dominated by the organic solvents THF and methanol. The largest potential of energy can be released in the case of a peroxide explosion caused by THF. The toxicity, however, is still dominated by the highly
toxic compounds (methyl iodide, hexyl-lithium) although they are present at smaller amounts than the solvents. The major environmental problems of the process lie in the aquatic toxicity of hexane, in air-mediated effects caused by a number of smelly or slightly toxic volatile organics, the stoichiometric amount of (degradable) methanol, and the non-degradable THF. Finally, technological measures reducing the risk potential of a process can be taken into account within the framework of the EHS assessment. Thereby, potentials of danger might decrease significantly. For the case study presented e.g. the risks due to flammable materials or potential peroxide explosions could be reduced easily by realizing corresponding safety measures.

**Application of the Eco-Indicator 95 to the Enantioselective Reduction of Ketoesters**

The Eco-Indicator 95 (EI95) was applied to examples of enantioselective reduction of ketoesters (Fig. 4) serving as intermediates in pharmaceutical production. Two alternatives transform the α-ketoester 2-oxo-4-phenyl butyric acid ethyl ester (OPBE) into the corresponding (R)-alcohol, while the other two reduction methods transform the β-ketoester acetyl acetic ethyl ester into the corresponding (S)-alcohol. For each transformation, a bio- and a metal-catalyzed process were investigated. For the reduction of the α-ketoester either enzymes (D-LDH from *Staphylococcus epidermis* [18] or a Pt/Al2O3 [19][20] catalyst modified by chinchonidine may be used. The β-ketoester can be reduced using baker’s yeast [21][22] or with the homogeneous catalyst Ru/BINAP [23]. All methods except the homogeneous Ru/BINAP process were developed by industry for a scale of approximately 100 kg per batch. For the Ru/BINAP process a linear scale up to a 100 kg batch process was performed based on a laboratory recipe. All mass and energy flows estimated for the application of the EI95 were derived from industrial operating instructions. Within the system boundaries also separation and waste treatment processes in addition to the reaction step are included. The different operations were compiled in different modules (see below). The inventories obtained for the different processes were assessed using SimaPro 3.1S [24]. Further details on the processes as well as on the application of the EI95 are given in [10].

The results of this case study are shown in Fig. 5. The environmental impact measured using EI95 is given for the different modules (represented as stacks) and as running sum (displayed as line). The process alternative A1 shows the negligible environmental impact of the enzyme production (Fig. 5, A1-M1) and the reducing agent formic acid (M2; less than 10% of total impact). The major contribution to the total environmental impact is due to work-up, i.e. extraction into organic solvents (about 80%). The production of ethyl acetate contributes about 90% to the module M4, whereas only 10% is due to direct solvent losses to the environment. The high environmental impact of solvent recycling can be explained by the energy intensive operations such as distillation and rectification (90% of M8).

For the process alternative A2, the catalyst losses contribute about 30% to the total environmental score although an overall platinum-recycling yield of 90% was assumed. The comparably low enantioselectivity of 82% causes another significant contribution to the total environmental score of about 35% (Fig. 5, A2-M7). Only small amounts of solvent are used in this process and hence modules M2, M3, M5&6, and M8 are less important.

The enantioselective reduction using yeast (B1) shows a broad distribution of environmental scores to almost all modules. The production of yeast (B1-M1) contributes about 10% to the total environmental score as large amounts of yeast are needed for optimal reaction conditions. The reduction step (B1-M2) contributes about 15% which can be explained by the sugar fed to the yeast and the energy required to aerate the yeast. The solvent-intensive extraction from the dilute aqueous phase (20%, B1-M4) and the solvent recycling (25%, B1-M8) contribute the most to the total environmental score. Again, this is due to the production of the solvent itself and to the steam consumption during the recycling by distillation.

An outstandingly low cumulative environmental impact, which is about one

| Substrate | Biocatalyst | Metal catalyst | Products (Intermediates) |
|-----------|-------------|----------------|--------------------------|
| α-ketoester | A1 enzyme | Pt 5%/Al2O3, dihydrochin-chonidine (heterogeneous) |  |
| β-ketoester | B1 yeast | Ru/BINAP (homogeneous) |  |

![Fig. 4. Summary of the four synthesis alternatives for enantioselective reduction of ketoesters.](image-url)
For both cases, A and B, the metal-catalyzed process shows a better performance, but while for case B the difference is significant, in case A both technologies result in an environmental impact of the same order of magnitude. The work-up procedures are usually the same for both technologies (distillation, rectification, and solvent recycling) and contribute 94% (A1), 53% (A2), 71% (B1), and 62% (B2) to the total environmental impact. This fact shows that independent of the order of magnitude of the total environmental impact obtained for one process, the work-up procedures in all cases represent a significant contribution. For the heterogeneous reduction (A2), the environmental impact is almost equally influenced by the production of the catalyst (recycling included) and the comparatively low enantioselectivity.

**Conclusions**

Mass Loss Indices and Environmental Indices can easily be applied to characterize the environmental performance of whole chemical processes or single steps even at the early design stage because only few data are needed. The application to the corresponding case study showed that Mass Loss Indices can identify the most promising starting points for improving a process (i.e., raw material and solvent consumption). The Environmental Indices have an only slightly higher data requirement than Mass Loss Indices but they can reveal single, problematic substances and allow an estimate of the hazards involved. Because toxicity is considered in a basic approach, chemicals present in a process only at small amounts might be identified by the EI as greater hazards than non-toxic compounds present at large amounts.

This latter aspect is considered in a much more refined approach in the EHS method discussed. While again highly toxic substances might signify high potentials of danger even when present in rather small amounts, this method, on the other hand, assigns mass independent index values to carcinogenic compounds.

An advantage of the EHS methods is that the most reliable data are selected and that possible data gaps might be closed (e.g., using Quantitative Structure Activity Relationships (QSAR)). These features are enabled by implementing the method as a software tool. Furthermore, the automation of the procedure guarantees that the assessment can be done quickly and can be carried out by non-EHS experts.

The Eco-Indicator 95 considers the broadest range of environmentally relevant aspects of chemical processes. In particular energy consumption is considered, which is not the case for the other three methods investigated. At least in fine chemical and pharmaceutical production energy is generally a minor factor from the economic point of view. In contrast, in the environmental impact assessment, and in particular when applying the EI'95, energy consumption might dominate all other aspects. In the corresponding case study, energy consumption (solvent production, separation tasks) together with direct air pollution (solvent losses) and acid rain (catalyst production) were identified as the major problems. Here the appropriate weighting between energy consumption and other effects is a problem to be solved by research. The fundamental complexity of the approach (e.g., the complete inventory of the upstream processes has to be known, resulting in high and very specific data requirements) renders a quick application by non-experts during chemical process design difficult, in particular during early development phases.

In summary, a detailed but at the same time automated tool such as the EHS method seems to be the most appropriate environmental assessment approach for the important stage of early process design. Nevertheless, extensions of this method such as the consideration of energy consumption would be desirable. Finally, it can be supposed that the process-inherent avoidance or reduction of environmental problems, such as those identified by the four indicators when applied to the case studies presented, will also result in an increased economic benefit. Therefore, the proactive consideration of environmental issues in an integrated approach during early process design generally leads to processes that show a better performance with regard to several objectives.

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Reduction of Chemical Waste Means Sustainable Development

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Abstract: The implementation of sustainable development activities is a key success factor in the chemical industry. The development and the results of a waste minimization program for a chemical production site is explained. Within three years an impressive improvement of 26% was achieved. The obvious ecological benefit is in line with considerable financial savings. Hence it is a case study for eco-efficiency.

Keywords: Chemical waste · Eco-efficiency · Green chemistry · Management cycle · Sustainable development.

1. Introduction

In the last twenty years aspects of environmental protection have become increasingly important in chemical production. The 1980's were characterized by so-called 'end-of-pipe' solutions, the technical driven treatment of polluted water and air. In the early 90's the International Chamber of Commerce launched the Business Charter for Sustainable Development [1], the chemical industry committed to Responsible Care Programs [2] and the Earth Summit in Rio de Janeiro resulted in the Rio Declaration, Agenda 21 [3]. These events triggered many efforts to improve eco-efficiency in industry. Knowing that financial, environmental and social needs are interdependent, the chemical and pharmaceutical industries endeavor to put the demands of Rio into practice. Nowadays all important globally acting companies work according to a well-defined Safety Health and Environmental protection (SHE) policy and publish their SHE reports.

The Sisseln site of Roche Holding Ltd. produces vitamins, carotenoids and formulations as well as active ingredients for pharmaceuticals. SHE aspects have a long tradition. In 1996 efforts for sustainable development were strengthened and among other projects, a waste minimization program was started.

2. Development and Implementation of a Waste Minimization Program

The waste minimization program was set up according to the management cycle of ISO 14000 (Fig. 1). Briefly some keywords to the steps in the management cycle will be commented on.

2.1. Commitment and Policy

Roche signed the Responsible Care Program. Beside other goals, a commitment for waste reduction was signed by the site management. To generate ideas, to work out and to run a project a cross-