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Assessment of the Integral Resource Consumption of Individual Chemical Production Processes in a Multipurpose Pharmaceutical Production Plant: A Complex Task

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Up to now, process specific integral resource consumption is barely used as criterion for the selection and improvement of fine chemical and pharmaceutical production processes. Reasons are the complexity of the supply networks in multipurpose plants and the requirement of a detailed data inventory from the production plant itself and from facilities delivering supporting utilities and treating waste streams. In this paper, a methodology is presented to set up integral mass and energy balances of specific production processes in the pharmaceutical and fine chemical industry. This methodology is based on the principle that each chemical production process is a sequence of unit operations in which basic operations at individual equipment take place. These basic operations are considered as the building blocks for all production processes. If the resource consumption of each building block can be quantified, not only at the operation itself but also at the on-site and off-site upstream and downstream processes to sustain the operation, the integral resource requirement of a whole specific production process can be quantified by the summation of the resource requirements of all building blocks involved. This methodology allows the development of a calculation tool for the quantification of the integral resource consumption with minimized data inventory. This tool will enable the selection of the most resource efficient production process and will indicate points of improvement. In this way production processes in pharmaceutical and fine chemical industries can become economically and ecologically more sustainable.

Introduction

Increased resource prices and more severe environmental legislations obligate the chemical industry to move toward more sustainable production. Developing sustainable chemical production processes for active pharmaceutical ingredients (API) involves working from an early clinical phase of development with economically and ecologically sustainable processes. However, in this phase of development much uncertainty exists about economical, ecological, and technical parameters.[1,2] Despite these uncertainties, developers have to select as early as possible the best ecological and economical process for further development. For this selection procedure, processes in the fine chemical and pharmaceutical industry are today mainly evaluated on mass balances over a narrow system boundary, for example, "reaction mass intensity (RMI)" or on qualitative evaluation methods, such as, "the Design for Environment (DfE) tool".[3] The energy requirements for the production of one mole API are usually not included in these selection criteria. The follow up of the energy consumption currently occurs only at the building level because allocation of the energy consumption to one specific production process is difficult due to complex networks of mass and energy supply in multipurpose plants.[4,5]

Next to taking into account the energy consumption as a selection criterion, the system boundaries should be enlarged for proper resource intake assessment. At present, industry looks mostly to a narrow system boundary. This is the boundary around the equipment inside the multipurpose production plant that has contact with the chemical compounds of the production process (e.g., reactor, dryer...). It is very well-known in industry what mass goes in and out this equipment to perform one process. These data can be found quite easily in batch production reports (BPRs) or production records (PRs) which are the "recipes" of a specific production process.[6] By enlarging the system boundaries, one considers also on-site resource requirements for the production of utilities, recuperation of solvents, and treatment of waste streams. Eventually all off-site resource requirements for the production of all industrial products and services to sustain the process could be considered for proper integral resource consumption.[7] However, taking into account more data means more data have to be inventoried. This data inventory is the main drawback of making an integral resource consumption evaluation of fine chemical and pharmaceutical production processes.[8] Although efforts are already made to reduce the data inventory and estimate the life cycle impact of pharmaceutical and fine chemical products and production processes, up to now no methodology is presented to set up detailed integral mass and energy balances of specific production processes in the pharmaceutical and fine chemical industry.[8–10]

The problem of extended data inventory is also known in the life cycle assessment (LCA) evaluation method as the life cycle inventory (LCI) step.[11] Similar working procedures as in LCA will also be used in this methodology. However, some differences with the integral resource consumption method used in this article have to be mentioned. First, according to the four steps of a usual LCA, the impact assessment (step 3) and interpretation (step 4) will not be discussed here.[12] Second, the focus is on the resources instead of focusing on the emissions for the LCI step. In this article, emissions are assumed to be

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treated in order to comply with legislative emission levels. In this way resource requirements for abating emissions are taken into account.

From yearly based data of the production site of Janssen Pharmaceutica Belgium, the importance of enlarging the system boundaries for the determination of mass and energy requirements can be illustrated easily; 70% of the total annual water requirement of the Janssen Pharmaceutica production site is consumed in the chemical production plant (narrow system boundary). The other 30% of the total water consumption is consumed for the production of utilities and treatment of waste. Similar numbers are available for the annual electricity consumption. If the annual electricity consumption is assessed in the narrow system boundary (production plant itself), only 65% of the electricity consumption will be taken into account and 35% is neglected. This illustration shows the impact of enlarging system boundaries from a plant level to a production site level. The resource requirements will increase even more if the system boundaries are enlarged to enclose the complete industrial network.

The methodology explained in this article is designed to facilitate the set up of the integral resource requirements of one specific production process. For this methodology development, first a functional unit is defined to allocate the resource consumption of one specific production process. Second, the system boundaries over which the resource consumption can be quantified will be defined. The third step will be the inventory of data from the particular production site and the organization of all data into different databases which will enable the development of a resource consumption calculation tool based on this methodology. Finally, this methodology will be illustrated with a real case from industry.

Methods and Materials

Methods. The resource evaluation methodology explained in this article is based on two methods. First, it is based on the first two steps of the LCA methodology. Second, this methodology is based on approaches used in simulation software to split up specific production processes into recurring units. To avoid confusion some terminology will be explained. A specific production process of a chemical compound is defined here as one step, for example, conversion of A into B, B into C, or C into D in a chemical synthesis route A → B → C → D toward a final API: D. A specific production process will be indicated in this article as C→ D.

1. LCI as a Part of the LCA Methodology. The first step of the LCA methodology is the goal and scope setting. The functional unit (FU) and the system boundaries have to be defined. The FU for the allocation of the integral resource consumption to one specific production process is chosen to be "one mole of chemical produced compound", for example, one mole of D starting from C. Next to the FU, the resource consumption of many auxiliaries will be required, as there are for example different heating and cooling media produced in other buildings on the production site. For these auxiliaries, different functional units have to be identified which makes it possible to allocate the integral resource consumption of the auxiliaries to the specific utility requirements for the production of one mole of chemical compound D.

After defining the FU, the system boundaries have to be defined. In this work three system boundaries (α, β, and γ) similar to those defined in the paper of Dewulf et al.[7] will be taken into account. In the α system boundary only the inputs and outputs for the operation at the equipment in the production process C → D will be taken into account. In the β system boundary all the resource requirements for on-site utility delivery and waste treatment to sustain C → D will be included. These utilities can be separated in two groups. On the one hand, there are utilities that have to be delivered to the production plant. These are for example heating and cooling media. On the other hand, there are waste treatment installations which need resources to treat the waste produced by the specific production process. Finally, there is the γ system boundary. This boundary comprises the complete industrial network. In this system boundary all resources extracted from the natural environment and brought into the technosphere to sustain the production of one mole of the specific chemical or pharmaceutical compound D from C are taken into account.

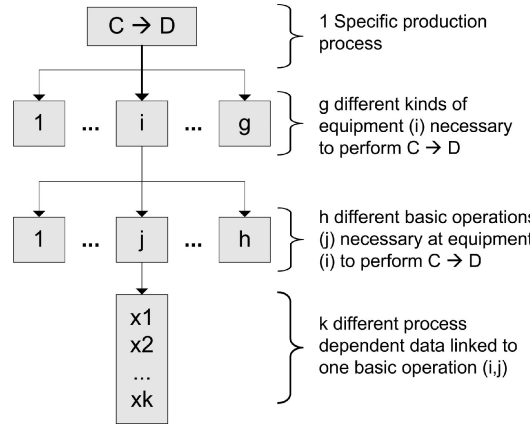

Figure 1. Split up of a specific production process in reoccurring units.

After setting the goal and scope, step 2 "the life cycle inventory" of the required data can start. This LCI step is the most time-consuming step in the assessment of the mass and energy requirements for one specific process (C → D).

2. Basic Operations As Building Blocks for a Complete Production Process. Next to the LCI method as starting point for this methodology development, another method is required to actually facilitate the previously mentioned data inventory. This method is also used in simulation software as there are, for example, "Intelligen Superpro Designer" and "Aspen Batch Plus".[13] Complete synthesis routes A → B → C → D to produce one chemical compound or API can be split up in different production processes. One such production process (C → D) requires *g* different kinds of equipment (e.g., reactor, filter, dryer, tanks, etc.). In these different kinds of equipment, *h* different kinds of basic operations (BOs) can be performed. Because different production processes will require different equipment and different BOs, the BOs are defined as the building blocks for specific production process as illustrated in Figure 1. There is however some difficulty involved in this concept. Some sequences of BOs are typically put into a cluster, such as cleaning and inerting. To fit these clusters in Figure 1, they can be placed at a sublevel between the equipment level and the BO level. However, the cleaning procedure is a cluster of different BOs and an extra cluster: inerting which again consists of different BOs. Fitting the clusters in a sublevel as previously mentioned will result in looping between levels. To avoid this looping and to simplify the eventual resource calculation tool, a cluster of BOs will again be called a BO and will be put in the same level. This will be illustrated later in this article.

For each BO (*j*) in equipment (*i*), denoted as BO(*i*,*j*), two kinds of data can be inventoried. First, there are process depending data (x_1, x_2,..., x_k) that can be found in BPRs and these data will be different for every basic operation (*j*) in

equipment (i) for process (C → D) that has to be evaluated, for instance, the kind of solvent to use. Second, there are process independent data (e.g., characteristics of equipment) which are inherent to the basic operation in the considered equipment and will not change if other processes that make use of the same operations in the same equipment have to be evaluated. These process independent data have to be inventoried only once and can be put in separate databases. These databases can be used to develop a user-friendly tool for the calculation of process specific resource consumption. If the total resource requirement of one building block over the three system boundaries (α, β, and γ) can be determined with a minimal input of information, then the integral resource consumption of one specific production process can be easily calculated by the summation of these building blocks.

Methods to define the uncertainty of this life cycle inventory will not be discussed in this article. More information about possible methods to incorporate uncertainty calculations can be found in other publications.[14–17]

Materials. Next to the determination of the used methods, data availability has to be checked. Data availability is of primary importance when assessing the integral resource consumption of a production process. For the three previously defined system boundaries, data have to be acquired. For the data inventory of the first two system boundaries (α and β), collaboration was set up with the pharmaceutical company Janssen Pharmaceutica in Geel (Belgium), part of the Johnson & Johnson Group. Data for these two system boundaries were inventoried personally from the production site. The data inventory for the evaluation of resource requirements in the γ system boundary is performed in a different way. These data were not inventoried personally from all the suppliers of Janssen Pharmaceutica, but were retrieved from an existing LCI database: ecoinvent v2.01.[18] Using this database for the γ system boundary reduces the data inventory effort strongly. The total data inventory and corresponding data sources are summarized in table 1.

Table 1. Data Inventory for the Calculation of the Integral Resource Consumption of a Specific Production Process in the Fine Chemical or Pharmaceutical Industry and Corresponding Data Sources[a]

	data inventory	sources of data
	α system boundary	
1	list of available equipment (i) in the production plant	1, 2
2	characteristics of all equipment (i)	1, 3
3	list of all BOs (j) in each piece of equipment (i)	1, 4
4	functioning of all BOs (j) + a list with process independent data for each BO (j)	1, 4
	β system boundary	
5	list of all utility production and waste treatment installations available on site	1, 3, 5
6	technical data of all utilities and waste installations	1, 3, 6, 7
	γ system boundary	
7	list of all industrial products and services available	8
8	resource requirements of each industrial product and service	8

[a] Data sources: (1) process equipment capability overview Geel site, (2) technical data archives, (3) P&ID's, (4) functional description equipment units, (5) ground plan of the production site, (6) computer control system data, (7) technical data archives in different departments responsible for each utility of waste treatment installation, (8) Ecoinvent v2.01.

Results and Analysis

1) Methodology Setup. The first result of this article is the methodology set up for assessment of the integral resource consumption of specific production processes in the fine chemical and pharmaceutical industry. This methodology is summarized in Figure 2 and can be used for the development of a calculation tool in, for example, MS Excel that allows the quantification of the integral process specific resource consumption.

In Figure 2 four areas can be distinguished which are marked in three different background patterns (process dependent and independent input are marked in a crossed pattern, the calculation tool has a light gray background and output has a dark gray background). The two crossed pattern areas include the required input data to calculate the integral resource consumption of a specific production process. These input data can be split up in two groups, namely in process dependent and process independent data. The process dependent data will be the only remaining input that has to be introduced manually for every production process (C → D). The process independent data have to be inventoried once and are available as background information in the different databases indicated in Figure 2 as α1, α2, α3, β1, and γ1. The content of all databases is summarized in Table 2.

The third area in Figure 2 is the tool itself, indicated by the light gray shading. In this tool, databases with process independent data are implemented as well as three different operators (OPs). These OPs are MS Excel files in which different search functions and equations combine process independent and dependent data in order to deliver the resource requirements over the three previously defined system boundaries. To explain the functioning of the operators, a general input−output diagram of one BO is given in Figure 3. For the input−output diagram of a complete specific production process, diagrams as shown in Figure 3 have to be made for all BOs (i,j) and all these diagrams have to be summated.

The purpose of operator 1 (OP1) is to quantify the inputs (m) and outputs (n) over the α system boundary for each BO involved in the specific production process. This will be achieved by combining the process dependent data: equipment (i), BOs (j) and parameters (x) coming from the BPR with process independent data from databases α1, α2, and α3. Most important here are the macros from α2 that are required to calculate the inputs (m) and outputs (n) of each of the 197 BOs (i,j). The equations required for constructing these macros are similar to the equations defined by Bieler et al. (2004). After all macros have run, the inputs $m\forall(i,j)$ and outputs $n\forall(i,j)$ can be summated to assess the total input (o) and output (p) of the α system boundary (output 1). The inputs $m\forall(i,j)$ and outputs $n\forall(i,j)$ are also used as input for operator 2 (OP2). The inputs and outputs of one BO (i,j) in the α system boundary mostly involve some utility (u) or waste treatment (w) requirements which have an extra resource consumption in the β system boundary. This extra resource consumption again can be allocated to one BO (i,j). This extra or replacing input $q\forall(u,w)$ and extra output $r\forall(w)$ can be quantified for all inputs $m\forall(i,j)$ and outputs $n\forall(i,j)$ of the α system boundary. These inputs (q) are actually industrial products that have to be delivered to the production site. The outputs (r) are products that require extra resources in the overall industrial network for their treatment. Therefore, these outputs (r) can be seen as the requirement of an industrial service to treat these outputs. Combining the inputs

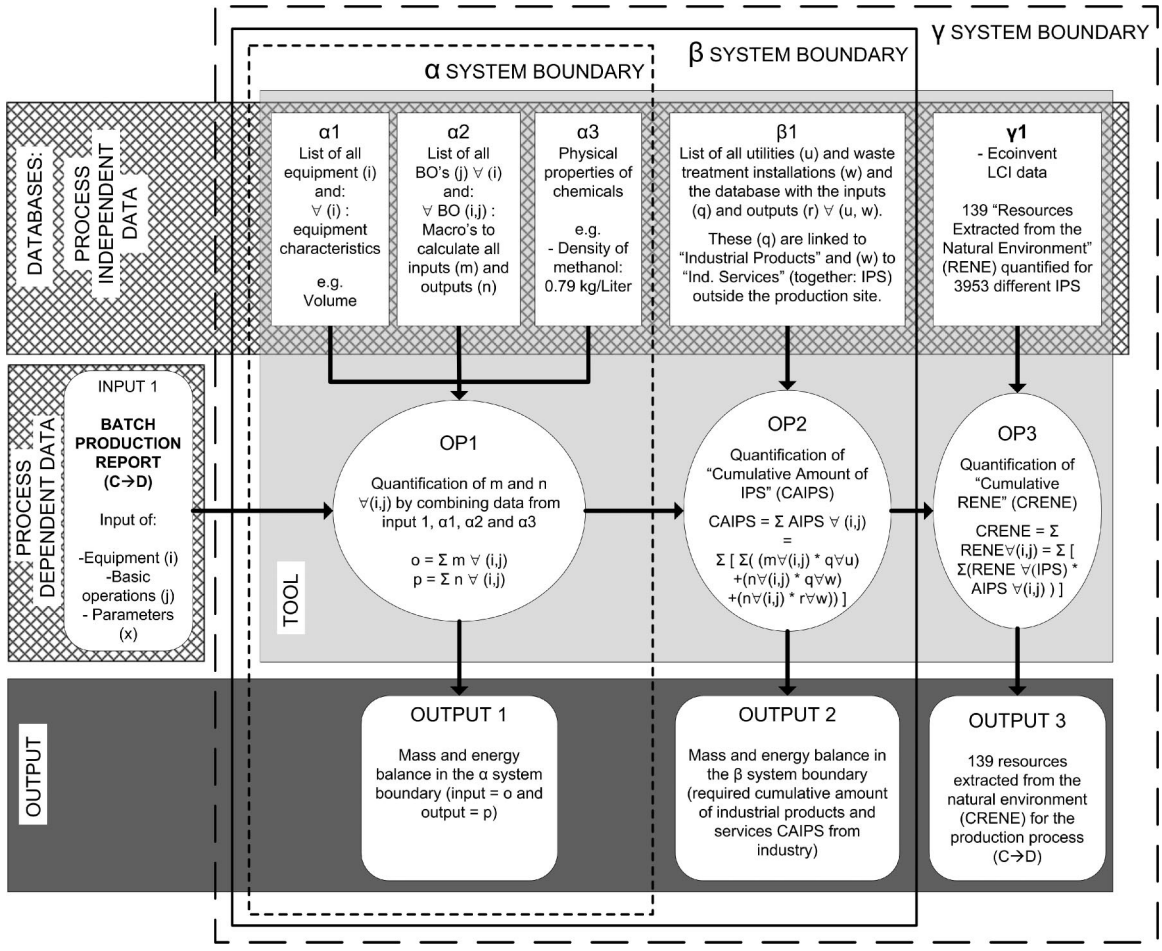

Figure 2. Resource evaluation methodology for quantifying the resource consumption of a specific production process (C → D).

Table 2. Content of Databases α1, α2, α3, β1, and γ1

	α System Boundary
α1	list of 26 different kinds of equipment (*i*) available to perform a specific production process (C → D), e.g., 4000 L SS reactor
	list with all characteristics of each kind of equipment (*i*) (21 for a 4000 L SS reactor), e.g., inerting volume = 5236 L
α2	list of all BOs (*j*) available in each kind of equipment (*i*) (15 for a 4000 L SS reactor; 197 for all (*i*)), e.g., inerting, cleaning, pumping in solvent, pulling vacuuum,...,
	macros to calculate the resource consumption of each BO (*i*,*j*) in the α system boundary
α3	physical data of all chemicals that can be used in a specific production process, e.g., density of methanol = 0.79 kg/L
	β System Boundary
β1	list of 18 utilities (*u*) available on the production site and required for (C → D), e.g., steam production (175 °C, 8 bar)
	list of 6 waste treatment installations (*w*) available on the production site and required for (C → D), e.g., waste water treatment facility
	matrix with energy and mass balance (*q*,*r*) per FU ($m\forall(i,j)$ and $n\forall(i,j)$) of the 24 ($u + w$), e.g., *q* equals 0.0283 Nm^3 natural gas/MJ heat from steam (175 °C, 8 bar) and 3.723 kJ electricity /MJ heat from steam (175 °C, 8 bar)
	γ System Boundary
γ1	ecoinvent v2.01 database
	matrix with 139 resources extracted from the natural environment (RENE) for 3953 industrial products and services (IPS), an example of an IPS is 1 Nm^3 natural gas, at plant

and outputs of one BO (*i*,*j*) over the β system boundary will give the required amount of industrial products and services for one BO (*i*,*j*) (AIPS ∀(*i*,*j*)), the overall industrial network has to deliver to the production site under consideration. Again, the AIPS ∀(*i*,*j*) of all BOs required to perform one specific production process can be summated to get the cumulative amount of industrial products and services (CAIPS) to perform the production process (C → D). This result will be in output 2 of the β system boundary and includes all the industrial products

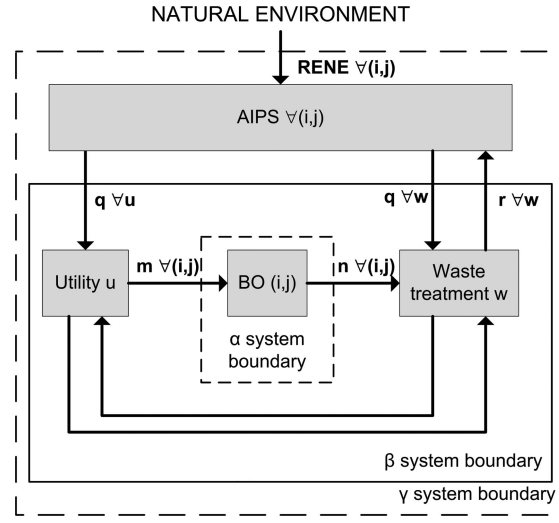

Figure 3. Input−output diagram of one BO over the three system boundaries (α, β, and γ) (AIPS = amount of industrial products and services, RENE = resources extracted from the natural environment, *q* and *m* = input, *r* and *n* = output).

that are bought and all the products that are sent outside the production site for further treatment.

Similar methods as in OP2 are used in OP3 to calculate the integral resource consumption of one specific production process (C → D) in the γ system boundary. In this system boundary RENE are quantified for all IPS required in the β system boundary to perform each BO (*i*,*j*) of the whole production process (C → D). RENE values for 3953 industrial products

Table 3. Cleaning Operation Information on a BPR for a 4000 L SS Reactor (WWTF = Waste Water Treatment Facility, NRS = Nonrecyclable Solvent)

	required equipment (i) = 1 4000 L SS reactor, 5 flexible connections	
	basic operations (j)	process dependent information (x)
1	rinse for x1 min with x2 and send to x3	x1 = 3, x2 = water, x3 = WWTF
2	stir for x4 min at x5 tpm	x4 = 20, x5 = 15
3	rinse for x1 min with x2 and send to x3	x1 = 10, x2 = water, x3 = WWTF
4	rinse with x6 L x7 and send to x3	x6 = 25, x7 = acetone, x3 = NRS
5	inert	
6	pump in x6 L x7	x6 = 500, x7 = methanol
7	stir for x4 min at x5 tpm	x4 = 140, x5 = 70
8	heat to reflux	
9	reflux for x8 min	x8 = 50
10	cool until x9 °C	x9 = 25
11	empty toward x3	x3 = NRS
12	rinse with x6 L x7 and send to x3	x6 = 30, x7 = acetone, x3 = NRS
13	rinse for x1 min with x2 and send to x3	x1 = 10, x2 = water, x3 = WWTF
14	inert	
15	rinse with x6 L x7 and send to x3	x6 = 50, x7 = acetone, x3 = NRS
16	inert	

and services (RENE ∀(IPS)) are available in the γ1 database. This γ1 database is actually a part of the ecoinvent v2.01 database where for all the 3953 IPS, 139 resources extracted from the natural are quantified. These RENE ∀(IPS) values can be multiplied with the AIPS ∀(i,j) which results in the resources extracted from the natural environment for each BO (i,j) (RENE ∀(i,j)). Summating all the RENE∀(i,j) values for all BOs (i,j) will result in the cumulative RENE (CRENE) value, being the integral amount of resources extracted from the natural environment to perform the one specific production process (C → D). The output of OP3 is thus a list with 139 resources quantified to perform the whole production process (C → D).

2. Case Study: Cleaning a 4000 L SS Reactor. This methodology will be illustrated by a specific BO at a specific piece of equipment that is one BO in a set of typically around 30 BOs required to convert C into D. This BO under consideration is the cleaning of a 4000 L stainless steel (SS) reactor and as mentioned before is a cluster of different other BOs. A cleaning operation normally takes place after the production of several moles of compound D. This means that the results shown in this example have to be divided by the amount of moles produced in a production campaign. The more moles of D produced in a campaign, the lower the impact of a cleaning operation on the resource consumption related to the production of one mole D.

When the resource consumption of this cleaning operation in the three different system boundaries is calculated, this data can be stored in the database α2 of Figure 3 as a new BO and from this moment on, the BO "cleaning of a 4000 L SS reactor" and the corresponding resource requirements can be fixed in the calculation tool as process independent data. In this way, the 16 BOs of the cleaning cluster will never need to be added again into the tool for the calculation of the resource consumption related to this tool. This is an illustration on how this calculation tool and corresponding databases can evolve during time to fulfill the users' final expectations of this calculation tool.

The cleaning operation is available in the format of a BPR. A short version of this BPR is given in Table 3. The information in Table 3 will be the 16 different BOs being part of the cleaning cluster and other process dependent input (input 1) for the resource consumption calculation tool as illustrated in Figure 3.

From the BPR input (Table 3) it is known that the required equipment (i) for the cleaning of the SS reactor 4000 L is of course the reactor (i = R1) itself and 5 flexible connections. These two kinds of equipment can be picked out from the α1 database thanks to the search functions in OP1. If the equipment is chosen, the search functions of OP1 will also find the corresponding characteristics of the equipment required to calculate resource consumption in the α system boundary. The second step is reading in the 16 different BOs (j) of the cleaning cluster into the tool. These BOs (j) are performed into the reactor R1 and are also given in the BPR, numbered from 1 to 16. The flexible connections have no BOs and just serve for liquid and gas transport. The only resource consumption related to these flexible connections is their cleaning in the mobile cleaning installation. No further emphasis is thus put on these flexible connections. The required BOs (R1,j) can be picked out of database α2 which contains all possible BOs in a SS reactor of 4000 L. The macros related to each BO (R1,j) are linked in OP1 to calculate the resource consumption at the α system boundary. The last step is now to read in the remaining process dependent data specific for each BO (R1,j). For example for the BO (R1,6) "pump in", this extra process dependent information will be x6 = the volume: "500 L" and x7 = the solvent: "methanol". In this way, all the information can be inserted into the tool. The third database α3 contains physical properties of chemicals and will for example be used to change the unit of the input "500 L methanol" into "395 kg methanol". The reason for this will become clear later in this example. Once the input from the BPR is completed, calculations are performed by the macros in OP1 and this will result in the input m∀(R1,j) and output n∀(R1,j) over the α system boundary. As an example, the input m of BO (R1,6) over the α system boundary is 395 kg methanol and 1650 kJ of electricity for the pumping. There is however no output n for this BO (R1,6). If the input m∀(R1,j) and output n∀(R1,j) are quantified for all 16 BOs, they can be summated. These results are presented in Table 4. To simplify this illustration, residues inside the reactor from previous production processes (which are the reason to clean the reactor) are not taken into account in the outgoing waste streams. Also the volatility of the organic solvents is not taken into account and 100% of the used organic solvents are recuperated in this case.

Table 4. Mass and Energy Balance in the α System Boundary for the Cleaning of a 4000 L SS Reactor (IBW1 = Industrial Water, ING1 = Nitrogen Gas 8 bar)

value	unit	name
	Input	
2300	L	IBW1
82.95	kg	acetone
395	kg	methanol
18.53	kg	ING1
358368.2	kJ	electricity
212233.3	kJ	heating medium
166996	kJ	cooling medium
	Output	
2300	L	IBW1
82.95	kg	acetone
395	kg	methanol
18.53	kg	ING1

The next step is the quantification of the resource requirements in the β system boundary. As example the BO (R1,6) will be used again. From the α system boundary, it is known that the input (m) of this BO equals 395 kg methanol and 1650 kJ electricity. This means these inputs have to pass the β system boundary before entering the α system boundary. For the electricity consumption, no extra resources are required in the β system boundary. The 395 kg (500 L) methanol however is stored in a resource tank park (RTP) before entering the production plant and the reactor. This RTP can be classified as a utility (u) and requires an extra input q(RTP) being 0.91Y kJ electricity for pumping per Y liter solvent stored and 18.6 +

Table 5. Total Amount of Resources Passing the β System Boundary for the Cleaning of a 4000 L SS Reactor (ETP = Environmental Tank Park, WWTF = Waste Water Treatment Facility)

value	unit	name
	Input	
2702.913	L	tap water
57.11424	kg	liquid N_2
8.314415	Nm^3	natural gas
627671.7	kJ	electricity
0.014331	L	sulfuric acid 20%
0.032428	L	sodium hypochlorite 15%
0.240421	kg	NaCl
0.5	L	detergent A
0.5	L	detergent B
102.7	kg	acetone
395	kg	methanol
0.252506	kg	$FeCl_3$ 40%
1.018639	kg	lime
0.492678	kg	NaOH 50%
1.94679	kg	liquid CO_2
0.296249	kg	H_2SO_4 96%
0.062748	kg	phosporic acid 75%
0.099557	kg	active carbon
	Output	
8.30	kg	sludge to incineration
102.7	kg	acetone to NRS (ETP)
395	kg	methanol to NRS (ETP)
2621.87	L	water to municipal WWTF

$0.00114Y$ kg liquid nitrogen for blowing out pipelines after each solvent transport and inerting the storage tanks. Storing 500 L methanol and pumping it to the production plant under consideration will thus cost an extra 19.172 kg liquid nitrogen for an inert atmosphere and 455 kJ electricity for the pumping ($m\forall$(R1,6) $\times$ q(RTP)). The resource consumption of the β system boundary then becomes: 395 kg methanol, 19.172 kg liquid nitrogen, and 455 + 1650 = 2105 kJ electricity. These three requirements are industrial products that have to be bought and introduced in the production site to perform BO(R1,6). Similar calculations for all 16 BOs in reactor R1 result in Table 5. In this table, all the resources that enter the physical boundary of the production site are listed. Next to the required inputs, some products will leave the production plant. The outputs that will require some resources for treatment (e.g., water toward municipal wastewater treatment plant) in the γ system boundary are listed as output in Table 5. Emissions to the atmosphere which do not require extra resource consumption, e.g., inert gas, water evaporation, etc., are not listed in Table 5 because they are of no importance anymore in a resource consumption evaluation tool.

From the results of the α and β system boundaries, it can already be indicated that enlarging the system boundaries is important. Compared with the α system boundary, 402.9 L extra water is required in the β system boundary. The extra electricity consumption in the β system boundary amounts to 269.3 MJ. This means a total of approximately 627.7 MJ electricity and 2702.9 L tap water have to be bought by Janssen Pharmaceutica for the cleaning of one 4000 L SS reactor.

From this case, it can be concluded that 85% of the water consumption and 57% of the electricity consumption related to the cleaning procedure is required in the α system boundary and, respectively, 15% and 43% is required for the production of utilities and treatment of waste. These numbers can be compared with the annual average numbers given in the introduction. This comparison indicates the difference in resource requirement ratios over the two system boundaries between a specific case and the annual averages. It illustrates the consequences of process selection for resource consumption when comparing alternative processes. Some processes will score better in the α system boundary but other at the β system boundary. Only when both system boundaries are taken into account for a resource consumption evaluation, can correct interpretation be made.

The last step of this methodology is the determination of the resource consumption in the γ system boundary. A similar method is used as for the β system boundary as presented in Figure 2. The result for the γ system boundary is the quantification of 139 resources extracted from the natural environment for each BO (R1,j). RENE data for the industrial products, listed in Table 5, are available in the ecoinvent database v2.01. These 139 resources extracted from the natural environment can be summated for all the BOs resulting in a list of 139 RENE for the cleaning procedure of a 4000 L SS reactor. Because a list of 139 resources is excessive information without added value in the perspective of this article, this will not be presented here. As a brief illustration of the impact of enlarging the system boundaries, some numbers are presented here. For the extraction of natural gas from ground ores, this counts up to 509.3 Nm^3 for the cleaning of a 4000 L SS reactor. For the water extraction from the natural environment, this is 8.6 m^3, and at last 13.3 MJ of wind energy is extracted.

From this case, the impact of enlarging system boundaries on the LCI can be illustrated by the amount of different resources entering the system boundaries. For the α system boundary this number is limited to six different kinds of resources. For the β system boundary the number increased up to 18. Finally for the γ system boundary, the number mounts up to 139 different kind of resources required. This is also the reason why for the γ system boundary data are taken from an existing database: ecoinvent v2.01.

For this case, it is clear that the LCI of a specific operation at a specific piece of equipment within a production process can be performed and it is hence the basis for the calculation of the total amount of resources necessary for one specific production process (C $\rightarrow$ D). At this stage, the importance of the life cycle impact assessment (LCIA) step of the LCA methodology becomes clear. Giving a list of 139 different RENE is not the ideal method to compare and evaluate different production processes or search for points to improve processes over the three different system boundaries. Therefore this LCI inventory method for the fine chemical and pharmaceutical industry has to be extended with an appropriate resource oriented LCIA method. This will however not be discussed here.

Discussion and Conclusion

This article describes the methodology to build up a detailed resource consumption evaluation tool for fine chemical and pharmaceutical processes and illustrates this with a specific case. From this case it can be concluded that this methodology is applicable for the determination of the integral resource consumption of specific processes in the pharmaceutical industry. It can be concluded that taking into account the resource requirement over different system boundaries gives a more complete and more reliable view on the resource consumption than an approach with even more accurate and complete calculations in the narrow system boundary.

It also becomes clear that a proper evaluation of the resource consumption and the proper comparison of different processes require a coherent indicator for resource evaluation. Having knowledge of the integral mass and energy input of a specific production process makes it possible to combine them with evaluation indicators (economical or ecological) allowing a coherent and user-friendly quantitative process evaluation.

The following step in this research is the development of the calculation tool based on this methodology. This tool development requires an intensive data inventory to make the databases with process independent data. For this data inventory, already the characteristics of 26 different kinds of equipment, the functioning of 197 basic operations and the mass and energy requirements of 24 utilities and waste treatment installations were inventoried from an existing pharmaceutical production site. This inventory data can be fixed in the calculation tool and the only remaining input for the determination of the process specific resource consumption is the data from a BPR.

Once this calculation tool is set up it can be extended in a way that uncertainty can be taken into account and sensitivity analysis can be performed to enhance the resource consumption evaluations. In this way, specific pharmaceutical production processes can be evaluated on the basis of their integral resource consumption in a fast and accurate way.

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Nomenclature

Acronyms

AIPS = amount of industrial products and services
API = active pharmaceutical ingredient
BO = basic operation
BPR = batch production report
CAIPS = cumulative amount of industrial products and services
CRENE = cumulative resources extracted from the natural environment
DfE = design for the environment
ETP = environmental tank park
FU = function unit
IPS = industrial products and services
LCA = life cycle assessment
LCI = life cycle inventory
LCIA = life cycle impact assessment
NRS = nonrecyclable solvent
OP = operator
P&ID = process and instrumentation diagram
PR = production record
RENE = resources extracted from the natural environment
RMI = reaction mass intensity (kg raw materials/kg product)
RTP = resource tank park
SS = stainless steel
WWTF = waste water treatment facility

Symbols

α, β, and γ = three system boundaries
$\alpha 1$,$\alpha 2$, $\alpha 3$, $\beta 1$, and γ = fifteen databases with process independent data
g = number of different equipment in a production process
h = number of different basic operations in a piece of equipment
i = equipment in a production process
IAG1 = natural gas, 1 barg
IBW1 = industrial company water
IST1 = industrial steam, 8 barg, 175 °C
j = basic operation in a piece of equipment
k = number of different process dependent parameters of a basic operation
m = different inputs of a BO(i,j)
n = different outputs of a BO(i,j)
o = total input of the α system boundary for one production process
p = total output of the α system boundary for one production process
q = different inputs of a utility or waste treatment installation
r = different outputs of waste treatment installations
R1 = 4000 L SS reactor in the cleaning operation
u = different utilities
w = different waste treatment installations
x = process dependent parameter
STW1 = tap water

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