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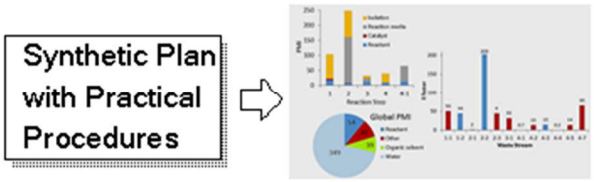
Table of Contents Entry

1. Colour Graphic:



2. A new algorithm to estimate the PMI for each contributing chemical and E factor for every component of waste effluents.

Comprehensive Mass Analysis for Chemical Processes, a Case Study with L-Dopa Manufacture

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Abstract

To evaluate the "Greenness" of chemical processes in route selection and process development, we propose a comprehensive mass analysis to inform the stakeholders from different fields. This is carried out by characterizing the mass intensity for each contributing chemical or waste component with a new algorithm. The analysis is demonstrated with the evaluation of commercial processes for L-Dopa. The plan-wide impacts on inputs are estimated for design features such as choices of starting material, the use of one-pot synthesis for multiple reactions, recycling the wrong enantiomer, methods for intermediate isolation, and volumetric productivity. The waste effluent profile is generated to project waste management needs. It has been found the current biocatalytic process (Ajinomoto) has the best process efficiency and minimal waste treatment needs. The mass efficiency has been improved by at least 6.5 folds through biocatalyst optimization, and reaction intensification employing crystallization-induced equilibrium shift.

1. Introduction

Green Chemistry principles have been widely accepted in process design to drive efficiency within the context of sustainability.[1] Adopting green chemistry in route selection and process development is challenging because it always involves stakeholders from different fields.[2] Prioritizing options for development involves consideration in many respects such as compliance for safety, health and environmental (SHE) regulations, freedom to operate (legal), quality parameter control, production throughput, and economics.[2b] Under time and resource pressure, the prioritization needs be streamlined by grouping options by key hypotheses, and ranking them with formal decision tools such as Kepner-Trego Decision analysis.[2a, 3] To equalize quantitative rigor of the performance in meeting different objectives, weight-based scores are employed as the proxy indicators. The sum of scores is used to achieve consensus by the stakeholders.[3b, 4] In

this exercise, it is desirable to use objective metrics to quantify the options so that all stakeholders can project the impact more realistically. Together, they will build better consensus to embed sustainability values from conceptual design to process development.

Mass efficiency has been the most fundamental parameters for synthetic efficiency.[1b,5] It is an appropriate driver for synthesis design and process development, because the metrics are easy to measure and the most efficient process usually has the best mass efficiency, i.e., the lowest mass intensity. For other stakeholders, mass efficiency parameter is tangible, objective, and transparent, with strong correlation to their interests because the impact of a chemical is the product of its mass and the intensive factor. Improving mass efficiency will not only drive synthetic efficiency, but also implicitly reduce the impact for all other stakeholders.

Mass efficiency is measured both in theory and in practice. Atom Economy (AE) is the theoretical efficiency, typically used to evaluate conceptual design of synthetic strategy.[6] However, it has little relevance to mass efficiency in practice due to other more intensive needs such as solvent use, product isolation, etc.[7] At practical level, mass efficiency can be measured by several metrics including Environmental factor (E factor), Process mass intensity (PMI), and Reaction mass efficiency (RME).[8] For process analysis, E factor and PMI are more intuitive than RME because they both use mass of product as the common denominator, therefore the total value can be broken down by contributions from different needs. ACS Green Chemistry Institute Pharmaceutical Round Table recommends using PMI as it measures mass efficiency from the input perspective, thereby encouraging cost reduction at the origin.[9] Still, waste issue is important in synthetic manufacture because the quantity is high and the composition is complex:[10] A recent survey shows that the median PMI is 68 in commercial manufacture, indicating that 98.5% of the input mass ends up as effluent waste.[11] To project the need for waste management and treatment, we propose to use E factor to characterize the waste effluent.

As far as we know, PMI has been a retrospective indicator for global mass cost. The Eli Lily group proposed to set global PMI targets based on its correlation with the complexity of molecule.[12] A justified PMI target can drive mass efficiency through narrowing the gap, but its impact on design is limited. This is because a retrospective, global PMI is not predictive about the outcome of changes in process design. To break this limitation, we propose to extend the use of PMI to measure mass cost of each contributing chemical in a synthetic plan (Eq. 1-5).

By the principle of mass balance, a process can be summed up in Eq. 1, where *Input* is the mass of material that goes into a process, and *Waste* is the mass of effluent other than the product. By definition, the global PMI is expressed in Eq. 2, and E factor is expressed in Eq. 3. The contributing chemical, such as $Input_1$ has a PMI expressed in Eq. 4. Similarly, $Waste_1$ has an E factor expressed in Eq. 5. To preserve mass balance in Eq. 1, water should be included in the estimation of E factor although there has been disagreement about this choice. [1b, 5, 10]

$$Input_1 + Input_2 + \cdots Input_n = Product + Waste_1 + \cdots Waste_m \qquad (1)$$

$$PMI_{global} = \frac{\sum_1^n Input}{Product} \quad (2)$$

$$E\ factor_{global} = \frac{\sum_1^m Waste}{Product} \quad (3)$$

$$PMI_1 = \frac{Input_1}{Product} \quad (4)$$

$$E\ factor_1 = \frac{Waste_1}{Product} \quad (5)$$

This analysis directly relate synthetic strategy to mass intensity. For example, when a synthetic plan involves sequential steps, the scale of a step needs to be adjusted to compensate losses in all subsequent steps. Since the *Input* and *Waste* of a step are proportional to its scale, its PMI and E factor can be reduced by moving the step closer to the final product.

The proposed PMI indicator is the *process mass property* of a contributing chemical in a synthesis plan. By tagging every chemical with its PMI value, the chemists create a realistic picture of the process. The PMI gives the exact quantity of a chemical with tractable context: the reaction in which it is to be used and the step of this reaction in the synthesis. This mass analysis enables chemists to identify productivity issues and predict the global impact of a specific improvement. For example, the chemists can estimate the plan-wide impact of reaction optimization, changing the order of coupling, or recycling of key chemicals. They can also estimate the composition and quantity of waste streams in terms of E factor by applying Eq. 1. The characteristics of waste stream inventory will help to identify hazardous streams, evaluate options for solvent and energy recovery, estimate the needs for waste management, and develop integrated treatment based on site capacity.[13] Reactions scales are critical to other stake holders as well. Scale change requires reevaluation of supply chain. Mass-intensive steps can be through-put restrictive when volumes exceed accommodation limits. Scale projection also helps other stakeholders to foresee issues in manufacturing. For example, side reactions may increase and cause quality failure in the scale-up of the reactions when physical parameters change significantly. The projected scale will guide SHE evaluation to find out the acceptable risks and the needs for compliance.[14]

We propose to determine the PMI with a three-step protocol when practical procedures are available. First, determine the sequences of isolated intermediates and their preparation reactions. Then, project the scale of the reactions with the isolated intermediates as the step references. Last, determine the need for other inputs to prepare the intermediate at the projected scale.

We use commercial production of L-Dopa as a testing case to demonstrate a two-tier approach to evaluate processes design. Four commercial processes are compared in the first tier with theoretical characteristics. Practical detail is only available for three of the four. They are evaluated with PMI and E factor as the main metrics in the second tier. The mass analysis is used to estimate the cost and benefit of design features, and estimate the potential for improvement.

Above all, we wish to demonstrate that comprehensive mass analysis offers much more realistic detail for all stakeholders to work together in route selection. This exercise serves the vision for sustainability by strengthening the collaboration early in designing stage. The prediction power enables consensus building with foresight, and resource justification to promote Green Chemistry innovations.

2. Case description

Since L-Dopa was introduced in 1967, it has been the first line treatment for Parkinson's disease, usually in combination with Carbidopa or Benzerazide.[15] It is a non-proteinogenic α-amino acid. The active pharmaceutical ingredient (API) is enantio-pure since only the (*S*)-enantiomer is bioactive (Fig. 1). The chiral product is prepared either by resolution or by asymmetric synthesis. Although many routes have been explored, only four of them have been developed and used for commercial production.

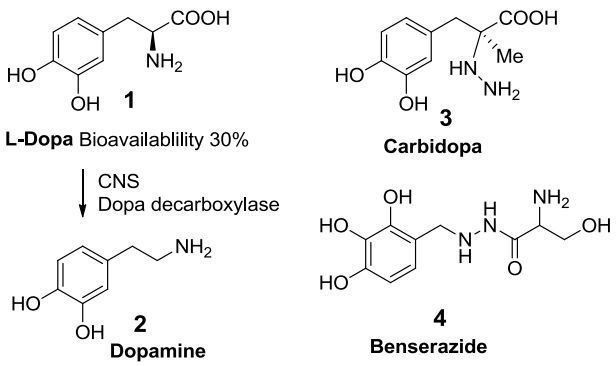
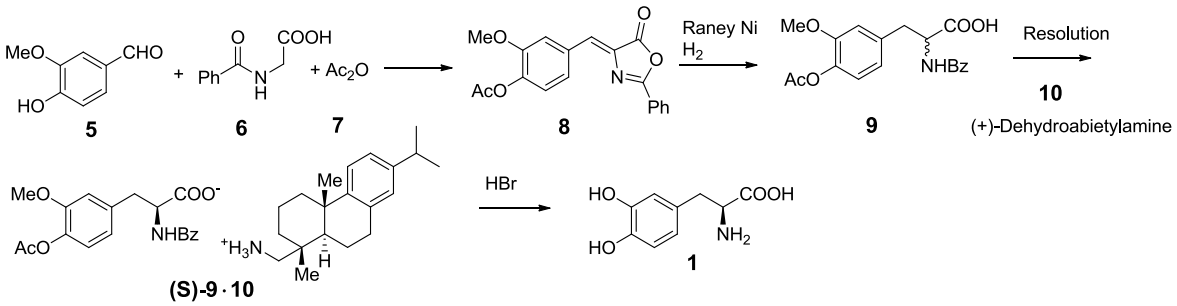


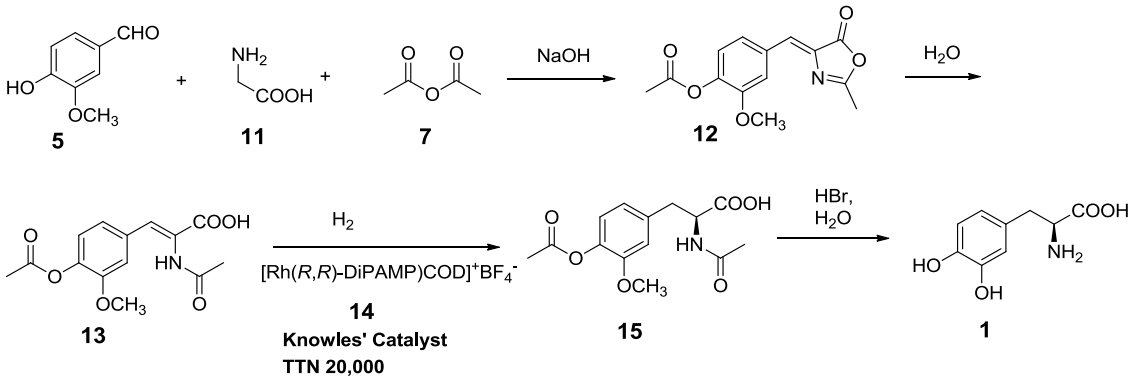
Figure 1 L-Dopa and peripheral-acting Dopa Decarboxylase Inhibitors

In late 1960's, Roche developed a resolution-based process (Scheme 1). It starts from an Erlenmeyer-Plöchl reaction with vanillin and hippuric acid (**6**). The azlactone product (**8**) is converted to the corresponding N-benzoyl amino acid **9** in one step. The desired (*S*)-**9** is isolated by classical resolution with (+)-Dehydroabietylamine. L-Dopa is obtained after deprotection by HBr in the final step.



Scheme 1 Route to prepare L-Dopa developed by Hoffmann La- Roche

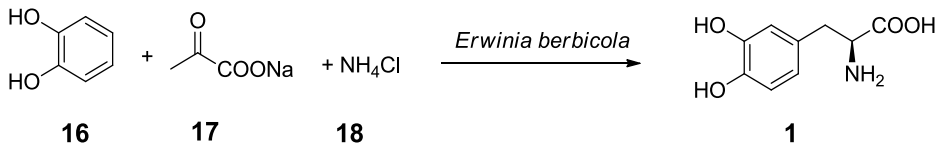
Meanwhile, a Monsanto group led by William S. Knowles focused on developing an asymmetric hydrogenation for enamide reduction in a similar process (Scheme 2). From 1970 to 1973, they discovered and optimized a series of chiral phosphine ligands, reaching DiPAMP as the final choice. The Rhodium DiPAMP catalyst exhibited spectacular efficiency: with 0.005 mol % catalyst, enamide **13** was completely reduced in 1 h, offering the desired (*S*)-**15** in 95% *ee*. The reaction was put in operation in 1974. It was the first commercial asymmetric synthesis employing chiral transition metal complex as the catalyst.[16]



Scheme 2 Monsanto Route featuring asymmetric hydrogenation

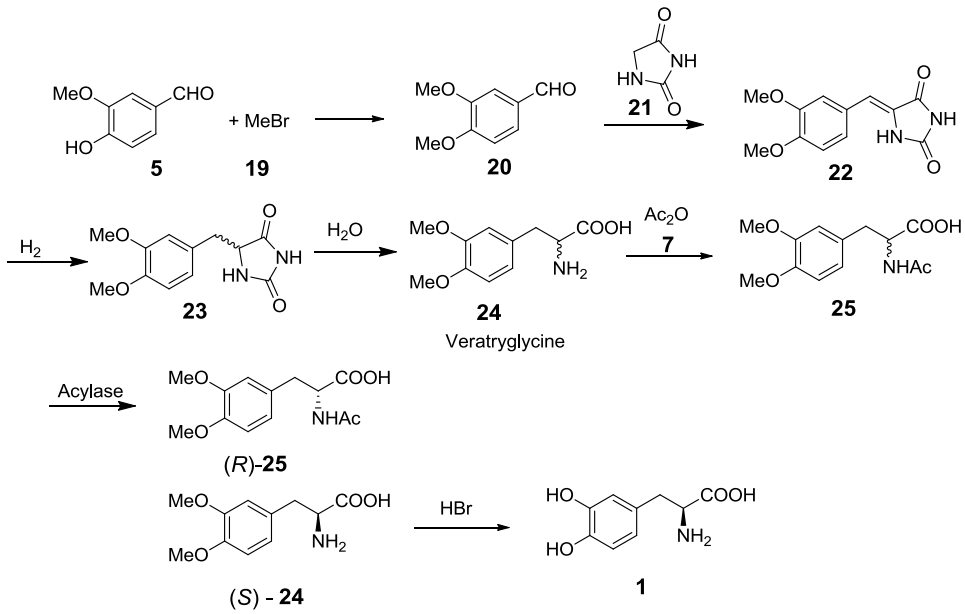
The Ajinomoto process (Scheme 3) is based on a discovery in 1960's made by Kumagai's group at Kyoto University, that Tyrosine Phenol Lyase (TPL) can synthesize L-Dopa with catechol (**16**), a non-physiological substrate.[17] This reaction holds great potential because it prepares the API from common chemicals in one step. However, the efficiency was too low (≤10 g/L) in the beginning. The long development of the Ajinomoto process marked significant improvements: in 1978, Kumagai's group reported that they had reached 55 g/L by using a fed-batch protocol.[18] Later the efficiency was further improved to 110 g/L through catalyst optimization. This process

was commercialized by Ajinomoto in 1993. The scale of production was reported to be 110 ton/year.[19]



Scheme 3 Ajinomoto Route based on biocatalysis

Interestingly, the current largest commercial producer (Xinhua Pharmaceutical, Shandong, China) uses a resolution-based process (Scheme 4) developed by Sankyo Kasei Co. in late 1990's. [20] This process features the resolution of veratraglycine (**24**) with amidase hydrolysis.[21] According to the press release, the pilot production started in 2008 and would reach full production capacity of 300 ton/year.



Scheme 4 Sankyo route featuring enzymatic resolution

3. Method

We use a two-tier approach to simplify process efficiency evaluation. Each requires inputs with different levels of detail. In the first tier, the synthetic plans are compared by theoretical performance. For Sankyo process, this is the only tier where it can be compared with others with

equitable input, because its procedure has not been disclosed except for the resolution. The second tier evaluation requires complete detail for execution.

Information extracted from the literature includes reaction schemes, conditions, yields, work up and isolation, and properties of intermediates and products. Reaction yields of certain examples in patents may be atypically low; probably resulting from the fact that the reactions had not been optimized. For these cases, yields are estimated based on the results of the same or similar reactions in the literature. When detail is missing for reaction work up or product isolation, a practical procedure is created based on popular protocols and the physical properties (solubility, boiling point, azeotropic composition, etc.) of the products or solvents. To ensure transparency, all assumptions for these gap-filling details are backed by literature or justification with relevant examples.[22] All the primary information are documented in the Supporting Information, including schemes with balanced reactions, AE determination, lab protocol with material inventory tables, process flow diagram, and waste stream composition.

3.1 The first tier evaluation (Fig. 2)

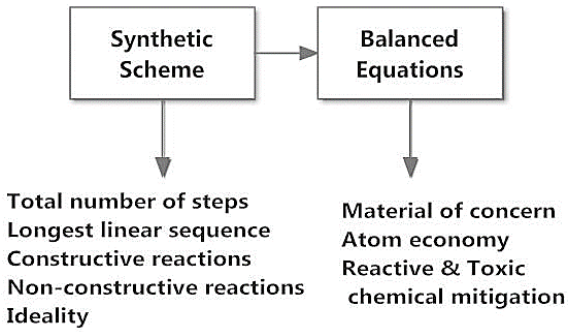


Figure 2 Plan of the first tier evaluation

In the first part, synthetic schemes are compared by total number of steps, the longest linear sequence (LLS), and Synthetic Ideality. LLS is a familiar concept with practical implications: it is directly related to production planning, and is the main sequence for PMI determination (*vide infra*). A strategy is characterized by the employed reactions: they are classified as constructive (construction reaction or strategic redox reaction), or non-constructive (functional group interchange, protection group manipulation, non-strategic redox reaction, or chiral resolution) reactions. The overall performance is represented by a value of Synthetic Ideality, which is the percentage of constructive reactions as defined Gaich and Baran.[23]

In the next part, the reactions are balanced to give a complete list of reactants and products with stoichiometry coefficients. AE is determined with balanced reactions and quantitative relationship among them, which depends on the multiplicity of products and limiting reactants. Resolution chemicals such as chiral bases are included in AE determination, because classical

resolution involves acid/base reactions in which at least half equivalent of a resolution chemical is needed. This part of evaluation also provides the first opportunity to capture chemicals of concern, including hazardous chemicals or those with supply issues.

3.2 The second tier evaluation

Comprehensive mass analysis is conducted in the second tier (Fig. 3). Based on lab protocol, a material inventory table is created for each step, in which mass information is organized for PMI evaluation. In addition, a process diagram is created for waste stream evaluation. The reaction mass balance is checked in the material inventory table, and step mass balance (work up and isolation included) is checked in the process diagram.

Special treatments are incorporated to mitigate byproducts with high reactivity or toxicity. Additional reactions are included to prepare chemicals or catalysts that are not commercially available.

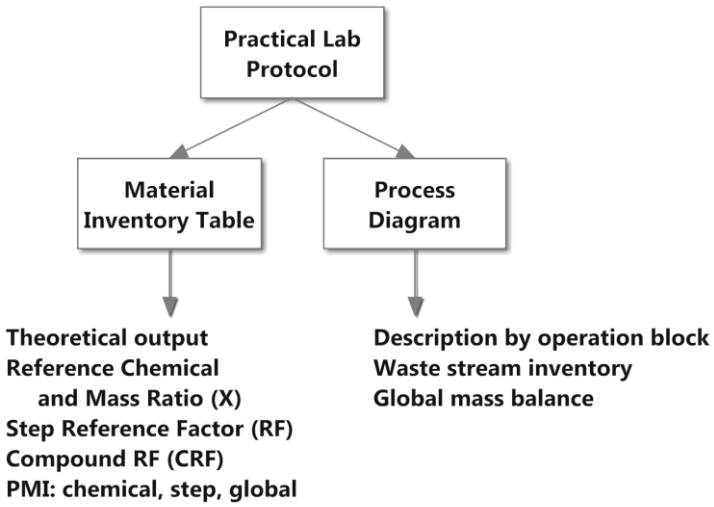


Figure 3 Plan of the second tier evaluation

3.2.1 Material inventory table and PMI determination

The lab protocol is prepared based on the disclosed examples. The procedures are streamlined, and the quantities of chemicals are directly quoted for convenient verification. A material inventory table is generated for each step by organizing the inputs into four groups: inputs to carry out the reaction, theoretical output, input for work up and isolation, and actual yield of the product. Theoretical output is estimated based on the balanced reaction. The role of each chemical is annotated for PMI assessment. The limiting reactant (typically the intermediate from the prior step) is designated as the step reference.

The method starts from the determination of key variables, including mass ratio for all inputs versus step reference, and reference factor for each reaction.

Assume a reaction is represented by a general equation (Eq. 6), where, $A_i$is the reference reactant, P_i is the desired product.

$$aA_i + bB_i = cP_i + dQ_i \quad (6)$$

X is the mass ratio of input chemicals with the respect of the step reference (Eq. 7).

$$X_{Bi} = \frac{Mass\ of B_i}{Mass\ of\ A_i} \quad (7)$$

For the reference chemical, X_{Ai}= 1

RF_i is the Reference Factor for Step *i*. This is the mass ratio of the step reference vs. the step product (Eq. 8). The expression (Eq. 9) to determine RF_i is derived from the definition of molar yield. If A_i is prepared by parallel routes, the *Yield* in Eq. 9 is the sum of the yields.

$$Mass\ of\ A_i = RF_i \cdot Mass\ of\ P_i \quad (8)$$

Where, $$RF_i = \frac{1}{Yield} \frac{Molecular\ Weight\ of\ A_i}{Molecular\ Weight\ of\ P_i} \quad (9)$$

Apparently, a small *RF* is desirable because it is a factor for PMI of all inputs in the step. This requires high reaction yield and product P_i bigger than reactant A_i – both are critical for synthetic reactions.

In the simplest case where P*i* (Eq. 6) is the final product, the PMIs of the two reactants are estimated by the following equations because no scale adjustment is involved:

$$PMI_{Ai} = X_{Ai} \cdot RF_i = RF_i \quad (10)$$

$$PMI_{Bi} = X_{Bi} \cdot RF_i \quad (11)$$

In general, reaction in Eq. 6 is Step *i* in a synthetic plan as described in Fig. 4. The scale will be adjusted by the need in subsequent steps. The LLS in this plan has *n* steps, and the shorter branch with *m* steps (*m* < *n*) gives compound B_i for Step *i*. The reference reactant in Step *i* is Compound A_i. Each step has its *RF* as determined by Eq. 9, and the estimation of PMI requires factoring in the *RF* values of all subsequent steps. The product of *RF* of the steps is termed as Compound

Reference Factor (*CRF*). The *CRF* of a step is the *PMI* of the reference compound (i.e., $CRF_i = PMI_{Ai}$).

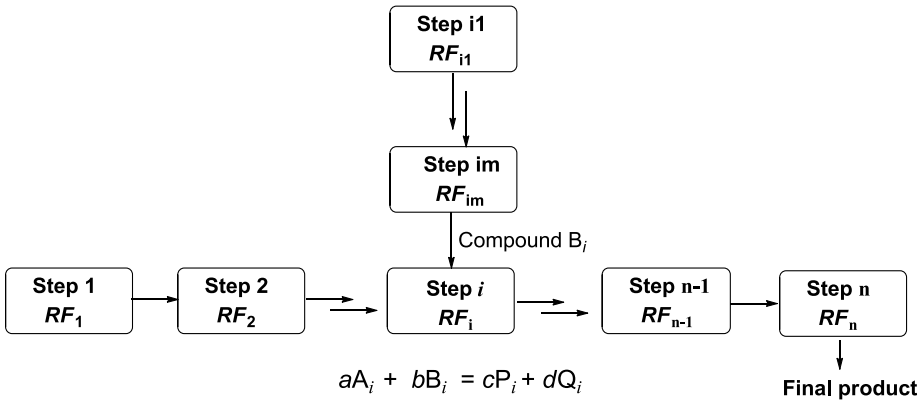


Figure 4 A convergent synthesis with a m-step branch to give Compound B at Step *i*

In practice, the *CRF* for each step is determined by starting from Step *n*, and work backwards to the beginning of the sequence. For LLS in Fig. 4, the steps *CRF*s are compiled in Table 1.

Table 1 The *RF* and *CRF* for the Sequence from Step 1 to Step n (Figure 4)

Step	***RF***	***CRF***
n	RF_n	RF_n
n-1	RF_{n-1}	$RF_n \cdot RF_{n-1}$
…	…	….
i	RF_i	$RF_n \cdot RF_{n-1} \cdots RF_i$
…	…	…
2	RF_2	$RF_n \cdot RF_{n-1} \cdots RF_i \cdots RF_2$
1	RF_1	$RF_n \cdot RF_{n-1} \cdots RF_i \cdots RF_2 \cdot RF_1$

The general formula for *CRF* in this sequence is Eq. 12.

$$CRF_i = \prod_{j=i}^{n} RF_j \qquad (12)$$

The PMI of input chemical in the LLS is the product of Mass Ratio *X* and the corresponding *CRF*. For example, the PMI for B_i is determined by Eq. 13.

$$PMI_{Bi} = X_{Bi} \cdot CRF_i = X_{Bi} \cdot \prod_{j=i}^{n} RF_j \qquad (13)$$

For the branch to prepare compound B_i (from Step *i*1 to Step *im*), the *CRF* for Step *im* will be:

$$CRF_{im} = PMI_{Bi} \cdot RF_{im} \qquad (14)$$

The general formula for *CRF* of Step *il* in this branch is:

$$CRF_{il} = PMI_{Bi} \prod_{ik=il}^{im} RF_{ik} \qquad (15)$$

With the algorithm described above, the PMI value is determined for each input chemical in the plan.

3.2.2 Process flow diagram and waste stream inventory

The process flow diagrams are created with the excel template downloadable at www.pprbook.com. [24] The process diagram is built by working backwards from the last step, in which the quantity of L-Dopa product is set at 100 kg. In a step block, the input chemicals are organized by unit operation. The Step *RF* is determined by Eq. 9. The quantity of the reference chemical is determined by Eq.10. The mass of other reactants are determined by Eq. 11, where the mass ratio *X* is from the corresponding material inventory table. To connect consecutive steps, the scale is matched by equating the mass of the reference chemical to the product of the prior step (i.e., $A_i = P_{i-1}$). This exercise is repeated until the flow diagram reaches the first step of the sequence.

For each isolation, the composition and quantity of the rejected waste stream are estimated by balanced equations. The waste streams are characterized by their point of generation, composition, and quantity. In preparing the flow diagram, the mass balance of each step is checked to meet Eq. 1.

The quantity of waste component is expressed as an E factor. A stream is evaluated in terms of composition, total quantity, regulatory concerns, pretreatment requirements, and recyclability.

The calculation equations are embedded in the spreadsheet therefore scales can be adjusted consistently. An example of the flow diagram is in Fig. 5.

		Roche Process Flow Diagram Step 1					Yield	0.80		
Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**	**Stream 1-1**	Weight (kg)	kMol	
Vanillin	402.3	→	Erlenmeyer reaction				Acetic acid	476.4	7.94	From rxn
Hippuric acid	470.6					20	NaOAc	398.2	4.86	
NaOAc	398.2						DMF	124.7		
Ac_2O	856.8		↓				(Ac_2O)	316.9	3.11	excess
DMF	124.7		↓				HOAc	372.9	6.21	from Ac_2O
							Water	3664.4		
			Crystallization, isolation	**1-1**						
Water	3673	→		→	5036.5	4				
			↓				**Stream 1-2**			
			↓				Water	4264.0		
			Rinse, dry	**1-2**			Organic	175.3		Un-isolated product
Water	4264	→		→	4439.3					
			↓							
Reaction input	2253		↓							
Isolation input	7937		**Step 1 product**	**1-3**	Est. Total waste	Total waste				
Total input	10189		713		9476	9476				

Figure 5 Process flow diagram for Step 1 in Roche process, scaled to give 100 kg L-Dopa in the last step

4 Results & discussion

For Sankyo process, the supporting information includes a complete list of reactions, and a summary table for AE determination. The other three have additional information including lab protocols, material inventory tables, and a process flow diagram with the scale set to give 100 kg L-Dopa. For waste evaluation, we prepared a summary of waste streams for the three processes.

4.1 The first tier evaluation

The three chemical processes are all linear syntheses starting from vanillin (**5**). The side chain skeleton is constructed by a condensation of the aldehyde with a protected glycine. The resulting C=C bond is reduced by hydrogenation to give the amino acid side chain. To carry out these two constructive reactions, the phenol in vanillin and the amino group in glycine need to be protected. When hydrogenation is not selective, chiral resolution is used to obtain the (*S*)-enantiomer.

Roche process reaches 50% in Synthetic Ideality by integrating multiple reactions in three of the four Steps (Scheme 1). The first step involves condensation of vanillin with hippuric acid (**6**) and phenol acetylation. In the next step, compound **8** is hydrolyzed to enamide, and then reduced by hydrogenation to give *rac*-**9**. The desired (*S*)-**9** is isolated by resolution with half equivalent of (+)-dehydroabietylamine (**10**). In the last step, the salt (*S*)-**9**·**10** is decomposed and deprotected to give L-Dopa.

The first step in Monsanto process (Scheme 2) fulfills the protection of amine and phenol in addition to the condensation to build the side chain. The azlactone (**12**) is hydrolyzed to give the enamide **13**, which is reduced by asymmetric hydrogenation to give the desired (*S*)-**15**. In the last step, (*S*)-**15** is treated with HBr to deprotect the phenols and the amide to give L-Dopa. The asymmetric feature of Monsanto process greatly improves theoretical efficiency, placing it higher than the other two chemical processes in AE (Table 2). Potentially, the azlactone hydrolysis (from **12** to **13**) and hydrogenation can be carried out in one pot, thereby reducing the total number of steps to three.

Sankyo process has the longest LLS because it has no One-pot reactions (Scheme 4). The phenol group is protected by methylation. The aldehyde **20** is condensed with hydantoin **21** to give the benzylidene hydantoin **22**, which is reduced by hydrogenation to give *rac*-**23**. Three additional steps are employed to resolve the racemic mixture by amidase hydrolysis to give (*S*)-**24**. The two methoxy groups are deprotected with HBr.

Table 2 Characteristics of commercial routes to prepare L-Dopa

Characteristics	Sankyo	Roche	Monsanto	Ajinomoto
Total number of Steps	7	4	4	1
PG manipulation	3	1	1	0
FG inter-conversion	1	0	1	0
Resolution	1	1	0	0
Constructive reaction	2	2	2	1
LLS	7	4	4	1
% Ideality	29	50	50	100
AE	0.158	0.123	0.294	0.719

The AE for Roche process is lower than that for Sankyo process, showing that shorter synthesis does not always result in higher AE. This is the consequence of larger input chemicals in Roche process: hippuric acid (**6**) is larger than hydantoin (**21**) in condensation; and half equivalent of (+)-dehydroabietylamine (**10**) is used for resolution, while enzymatic resolution is catalytic. Nevertheless, synthetic plan efficiency as indicated in Ideality is closer to practice, since reaction auxiliaries such as solvents contribute most PMI.[25] Comparing with Sankyo process, Monsanto and Roche processes are highly integrated. They should offer better throughput and mass efficiency in practice.

In chemical processes, demethylation causes safety concern as it requires harsh condition and generates MeBr, a volatile organic compound (VOC) that has multiple hazards. This byproduct is difficult to manage, and needs to be captured and decomposed for disposal. The mass cost for MeBr mitigation should be included in the evaluation. In this consideration, Monsanto and Roche processes are better than Sankyo process, since the latter gives two equivalents of MeBr in deprotection.

The Ajinomoto process is a three component, one step synthesis (Scheme 3). Starting from catechol (**16**), TPL installed the side chain and the amino group in one step by forming C-C bond and C-N bond simultaneously. There is no functional group manipulation or protection. It offers the highest theoretical efficiency both in AE and in Ideality. There is no material of concern in this plan.

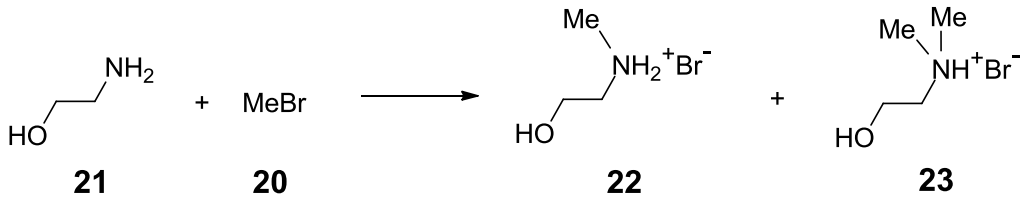
In the first tier analysis, Ajinomoto process stands out as the best option. Among the three chemical processes, Monsanto process is better than the other two, and Roche process is more efficient than Sankyo process.

4.2 MeBr byproduct and its mitigation

MeBr is an odorless, colorless gas (boiling point 4 ˚C) with occupational and environmental hazards. In work place, it has a permissible exposure limit (PEL) of 20 ppm due to neurotoxicity.[26] MeBr also has environmental hazard because it is an ozone depleting chemical.[27]

Thermal decomposition is a main option for VOC pollution control. MeBr pyrolysis gives HBr as the main product, but the product profile is dependent on temperature, residence time, and other components in the gas mixture.[28] The variability of gas composition and flow rate in a batch process makes it difficult to decompose MeBr with pyrolysis.

There are very few reports on MeBr decomposition with a scrubber. Several nucleophilic reactions have been tested, but only the reaction with aqueous ethanolamine (Scheme 5) has been comprehensively described for pilot demonstration.[29] For PMI evaluation, we add this reaction to the deprotection step for MeBr mitigation.



Scheme 5 Methyl bromide decomposition with ethanolamine

4.3 Process mass intensity evaluation

For Step PMI evaluation, the inputs are grouped into reactant, catalyst (including co-catalyst), reaction media, and isolation. Each group of chemicals accomplishes a specific goal, and can be optimized separately. Custom catalyst preparation (such as enzyme) can be mass intensive so it is in a separate group.

The handling of water in mass analysis depends on the use of the metrics. Water is included in PMI because pure water for manufacture has significant environmental impact and aqueous waste effluents require treatment. For E factor estimation, some authors choose to exclude water for more meaningful comparison. This is because water usually has high mass intensity as the medium for reaction or isolation; other inputs, while more important, may appear to be less significant.[1b, 5, 10] In our PMI analysis, water is counted by its role as a reactant, and a reaction or isolation medium. Correspondingly, water is included in E factor to characterize the composition of waste effluents.

We also estimated the global impact of the step efficiency improvement as well as strategy modification. A well-integrated process featuring efficient one-pot reactions should have low PMI for reaction media and isolation. Additionally, a convergent process with high Synthetic Ideality should decrease the PMI for reactants. For Ajinomoto process, we determined the impact of biocatalyst optimization and volumetric productivity improvement. For Roche process, we evaluated the cost and benefit of recycling the wrong enantiomer (*R*)-**9**.

For global PMI profile, we classify the chemicals by the suggestion of ACS Green Chemistry Institute Pharmaceutical Round Table, in which water is counted as a separate group.[9]

4.3.1. Hoffmann La- Roche process

The low overall yield of 19.2% is largely caused by the resolution step (Step 3, Table 3). Step 4 is a non-constructive reaction in which (*S*)-**9**·**10** (Scheme 1) is decomposed and deprotected to give **1**. The low mass efficiency is reflected in the high value of RF_4 (4.12, Table 3). This value is factored in the *CRF* values of all the preceding steps, resulting in high PMI for every input. Step 1 and Step 2 have the highest PMI values (Fig. 6). For Step 1, most PMI is from isolation (80.3, Table 3). Step 2 is a one-pot reaction involving hydrolysis and hydrogenation in aqueous

medium. The concentration of **8** is only around 5%, making the medium the largest PMI contributor (152.9, Table 3) of the step. Apparently, this reaction is throughput-limiting. Scale increase is difficult because hydrogenation requires special equipment. MeBr scrubbing reaction in Step 4-1 has a PMI of 64.5 (Table 3) when Step 4 yield is 74%.

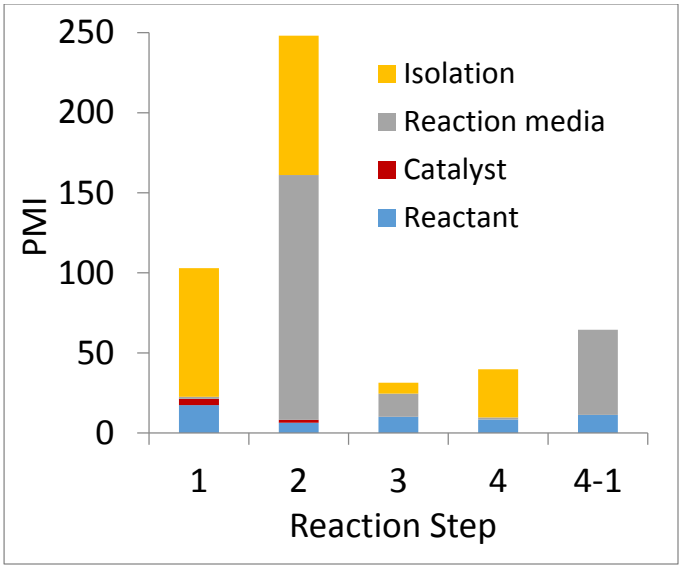


Figure 6 PMI profile for steps in Roche process (Scheme 1)

Table 3 Mass intensity of Roche process by step

Step	Yield %	RF	CRF	PMI Reactant	PMI Catalyst	PMI Media	PMI Isolation	PMI Step
1	80	0.564	4.02	17.3	4.0	1.3	80.3	102.9
2	72	1.49	7.13	6.4	1.8	152.9	87	248.1
3	45	1.17	4.80	10.1	0	14.5	6.8	31.3
4	74	4.12	4.12	8.4	0	1.3	30.1	39.8
4-1				11.3	0	53.2	0	64.5
Total	19.2			53.6	5.8	223.2	204.2	487

The global PMI is evaluated by organizing the input chemicals into groups including Reactant, Organic Solvent, Water, and Other.[9] By the classification, the PMI of Solvent or Water is from both reaction media and the need for isolation, and catalyst PMI is put into the Other group. The evaluation is expedited at the higher level by removing specific need from the consideration.

Overall the Roche process has low volumetric efficiency (Fig. 7): reactant only contributes 11% (PMI = 54) of the total PMI, while water and organic solvent contributions are 72% (PMI = 349) and 8% (PMI = 39), respectively. Other inputs (PMI = 45, or 9.2%) are relatively small.

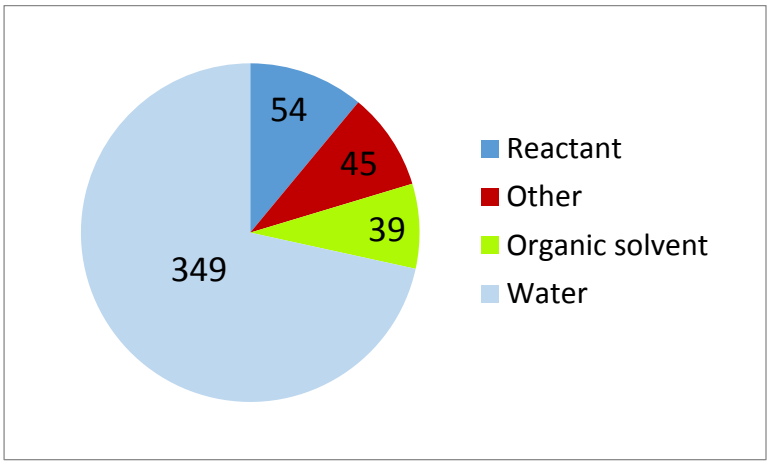
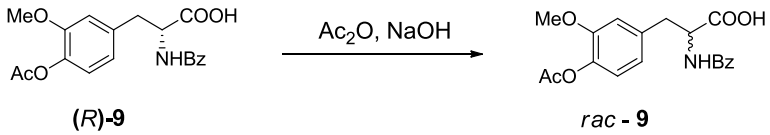


Figure 7 PMI contributor profile for Roche process

4.3.2. Hoffmann La- Roche route with racemization of (*R*)-**9**

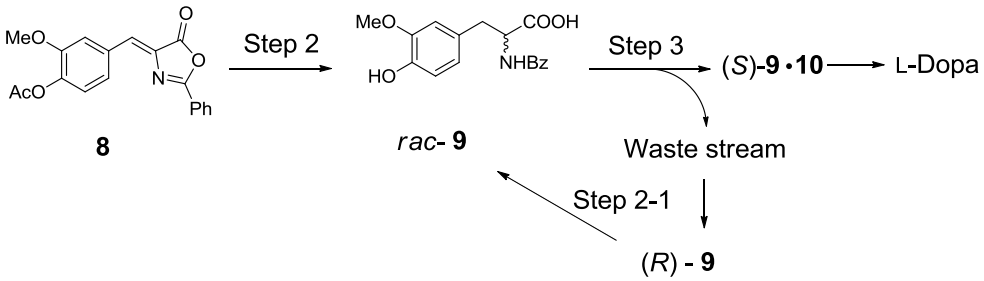
Roche also reported an option to recycle the undesired (*R*)-**9** (Scheme 6).[30] In the protocol, (*R*)-**9** is extracted from the waste stream of Step 3, then racemized in a mixture of acetic anhydride and NaOH. The isolated product is *rac*-**9** in 75% yield.



(*R*)-**9** *rac* - **9**

Scheme 6 Racemization of the wrong enantiomer

To evaluate this option with mass efficiency, we need to find out if the PMI of the racemization can be offset by the PMI reduction in Step 1 and 2. As a parallel source to produce *rac*-**9**, racemization step is designated as Step 2-1(Scheme 7).



Scheme 7 Two pathways to prepare *rac*-**9**

The yield of *rac*-**9** through Step 2-1 (racemization, $Yield_{\text{rac}}$) based on **8** is the product of the yields of the three sequential steps:

$$Yield_{rac} = Yield_{Step\,2} \cdot (1 - Yield_{Step\,3}) \cdot Yield_{Step\,2-1} \qquad (16)$$

The effective yield of *rac*-**9** is the sum of the two parallel sources:

$$Yield_{Step\,2+rac} = Yield_{Step\,2} + Yield_{rac} \qquad (17)$$

Eq. 17 gives the effective yield of 101.7% for *rac*-**9**. As the result, the overall yield for L-Dopa is improved to 27.1% (Table 4). The higher yield of *rac*-**9** also reduces the RF_2 to 1.05 by Eq. 9. With the recycling, the PMI reduction in Step 1 and 2 is 102.6, a value higher than the PMI of Step 2-1 by 48.3. Overall, the process PMI is reduced from 487 to 438 by adopting racemization.

Table 4 Mass intensity by step for Roche process with racemization of (*R*)-**9**

Step	Yield %	RF	CRF	PMI Reactant	PMI Catalyst	PMI Media	PMI Isolation	PMI Total
1	80	0.564	2.85	12.4	2.8	0.9	56.7	72.7
2	72	1.05	5.05	4.55	1.3	108.3	61.5	175.7
2-1	75*	1.05	5.05	0	11.5	0	42.8	54.3
3	45	1.17	4.80	10.1	0	14.5	6.8	31.4
4	74	4.12	4.12	8.4	0	1.3	30.1	39.8
4-1				11.3	0	53.2	0	64.5
Total	27.1**			46.7	15.6	178.2	197.9	438

* The yield of *rac*-**9** from (*R*)-**9** by Scheme 6. **The combined yield of *rac*-**9** Step 2 and 2-1based on **8** is 101.7%.

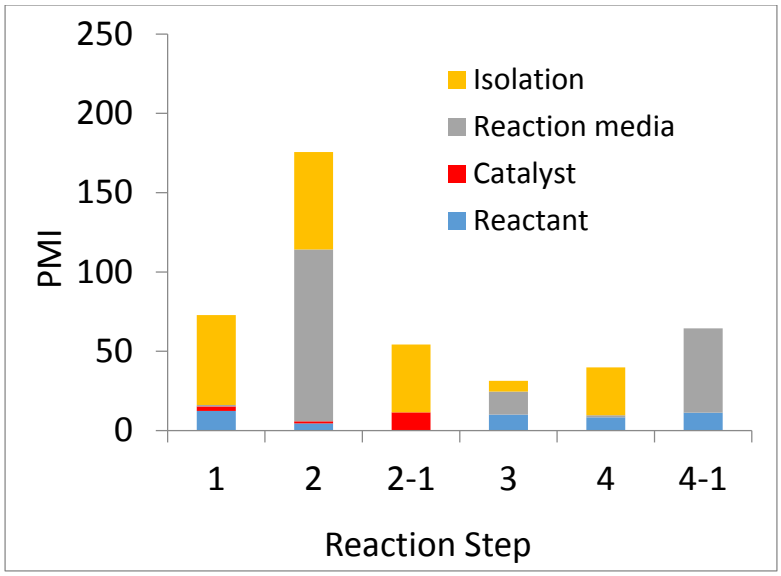


Figure 8 PMI profile for steps in Roche process with racemization (Scheme 1 and 7)

The step profile shows that the PMI for both Step 1 and 2 are reduced significantly (Fig. 8). Importantly, the PMI of Step 2 is reduced from 248.1 to 175.7, representing a 29 % reduction in the throughput-limiting step. Based on mass analysis, racemization is desirable not only for PMI reduction, but also for throughput improvement.

In overall profile (Fig. 9), The reactant PMI is reduced from 54 to 47, due to improved yield by recycling (*R*)-**9**. However, the racemization increases the organic solvent PMI from 39 to 65, and other inputs from 45 to 55. Most of the saving comes from the reduction of water, down from 349 to 271.

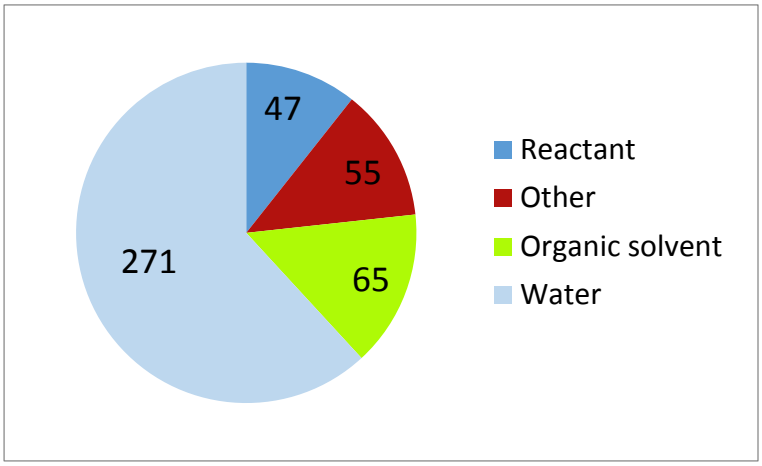


Figure 9 PMI contributor profile for Roche process with racemization of (*R*)-**9**

4.3.3. Monsanto Process

In the Monsanto process, the overall yield is increased to 47.2% by eliminating the chiral resolution (Table 5). In Step 1, all reactants are dissolved in acetic anhydride, making the step solvent-free. The product is crystallized directly from the reaction mixture after cooling. Azlactone (**12**) is hydrolyzed in a separate step to offer highly purified enamide **13**. This should stabilize the catalytic asymmetric hydrogenation in the next step. The concentration of **14** in hydrogenation is 110 g/L in a mixture of iPrOH and water. The catalyst (**15**) loading is only 0.005 mol %. The PMI to prepare the ligand of **15** is not included because it is available from STREM Chemicals (Newburyport, MA, USA). The deprotection in Step 4 is similar to that of Roche process, but no salt decomposition is involved.

Table 5 Mass intensity by step for Monsanto process

Step	Yield %	RF	CRF	PMI Reactant	PMI Catalyst	PMI Media	PMI Isolation	PMI Total
1	69	0.80	1.64	6.8	0.11	0	2.2	9.02
2	95	0.99	2.04	2.0	0	6.1	0	8.2
3	90	1.104	2.06	0.02	0.76	15.5	0.95	17.2
4	80	1.872	1.87	5.3	0	0	4.8	10.1
4-1				10.5	0	49.2	0	59.7
Total	47.2			24.5	0.88	70.8	7.9	104

The PMI for Step 1 to 4 are all significantly lower than those in Roche process (Fig. 10). Step 1 is a solvent free reaction. Step 2 has no isolation input. The product **13** is isolated by crystallization as the co-solvent acetone is removed by distillation. Most remarkably, the PMI for Step 3 (hydrogenation) is 17.2, only 7% of that for the hydrogenation in Roche process (Table 3 Step 2). It involves a slurry-to-slurry transformation, and the product crystallization is completed by distilling off the co-solvent iPrOH. Step 4-1 has the highest PMI, therefore the deprotection should be the throughput-limiting step. The RF_4 (deprotection) is 1.872 (Table 5), a value much smaller than that for Roche process. As a result, the *CRF* of all the preceding steps are between 1.64 and 2.06, much smaller than those in Roche process (Table 4).

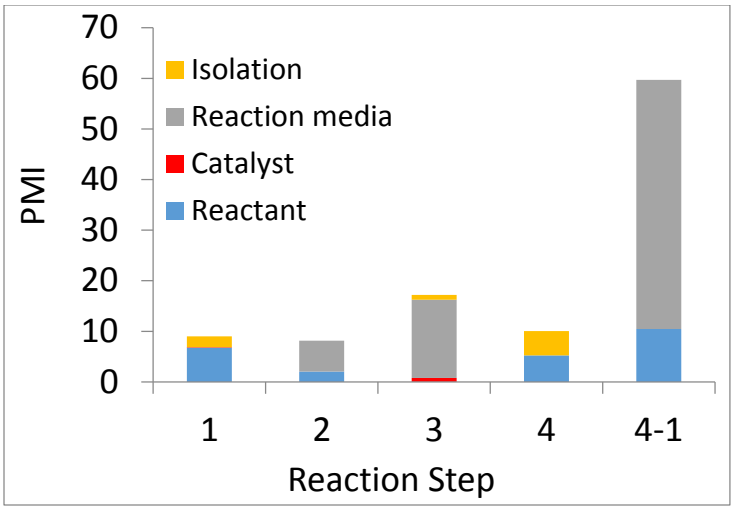


Figure 10 PMI profile for steps in Monsanto process (Scheme 2)

The total PMI for Monsanto process is 104, or 21% of that for Roche process (Fig. 11). The PMI of reactant is 20% of the total. As an enantioselective synthesis, this process reduces PMI of all contributors: the reactant PMI is 22, or 41% of that for Roche process; and the solvent PMI is 22, which is 56% of that for Roche process. The water PMI is reduced to 57 by multiple improvements, including volumetric efficiency increase in hydrogenation and direct intermediate isolation in all steps.

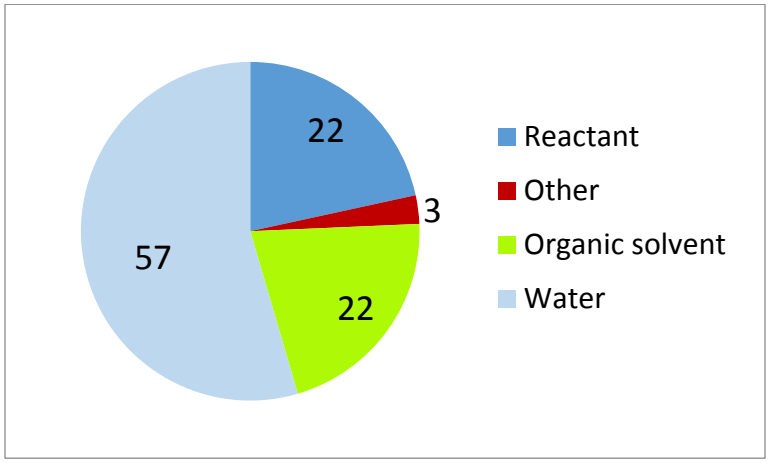


Figure 11 PMI contributor profile for Monsanto process

4.3.4. Ajinomoto process

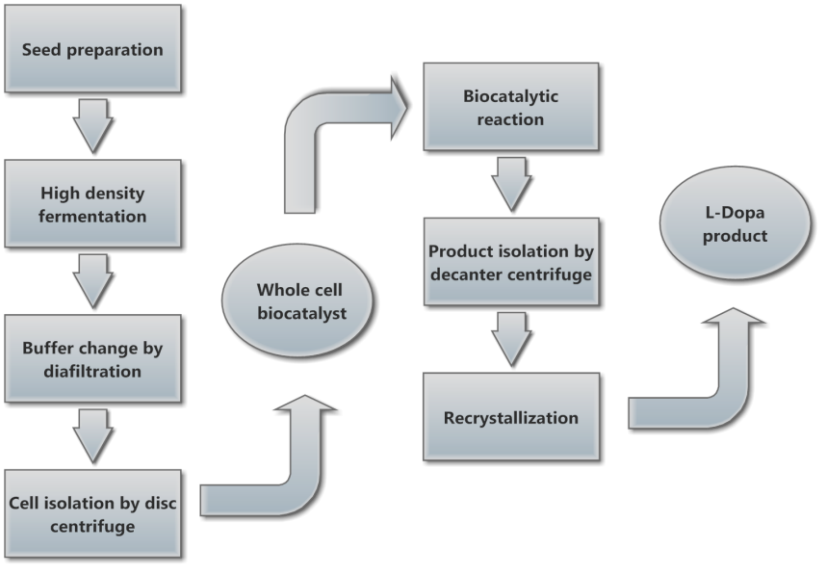


Figure 12 A flow diagram for Ajinomoto process

A streamlined plan (Fig. 12) is created for Ajinomoto process based on the literature. The enzyme is custom produced by fermentation and used directly for the biocatalytic reaction. Ajinomoto process uses a strain of *Erwinia herbicola* with deregulated expression of TPL, but the detail of fermentation and cell isolation is unclear.[18, 19] Since prokaryote enzyme production technology is transparent in *E. coli* system, we assume TPL is produced by the standard protocol. For enzyme overexpression, a TPL gene has been cloned in an expression system under the regulation of *lac* promoter. In industrial scale production, the enzyme is prepared by high-density fermentation with a fed-batch protocol. The enzyme expression is induced by adding IPTG (Isopropyl β-D-1-thiogalactopyranoside) when dry cell weight reaches 20 g/L. The fermentation is continued by adding feed medium over 8 hrs. In the end, the cell density reaches 50 g dry cell weight/L, with 15% of the soluble protein as the desired TPL (Supporting Information).

TPL catalyzes the reversible formation of L-Dopa from the three substrates in one step (Scheme 3). For practical synthesis, a concurrent product crystallization is employed to shift the equilibrium. The reaction begins with a solution with low concentration of catechol (**16**, 0.091 M) and sodium pyruvate (**17**, 0.136 M). When product concentration reaches > 10 g/L, L-Dopa crystallization is induced by seeding. Additional substrates are fed over 12 h. In the end, the product concentration reaches 110 g/L when almost all the L-Dopa is crystallized. After cell removal and re-crystallization, L-Dopa is isolated in 80% yield. The *RF* for this step is 0.70.

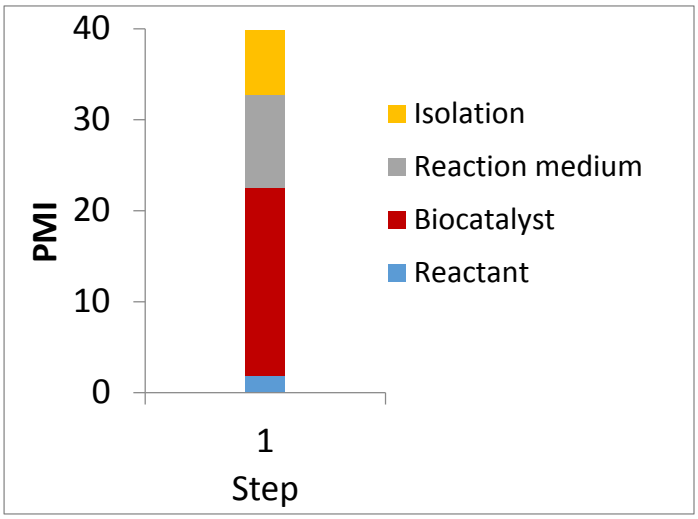


Figure 13 PMI profile for the reaction step in Ajinomoto Process (Scheme 3)

Ajinomoto process is a protection-free, one step reaction with total PMI of 39.8 (Fig. 13). The reactant PMI is as low as 1.9. The isolation PMI is 7.1, all from product re-crystallization. Preparation of the biocatalyst (TPL) is the largest contributor, costing a PMI of 20.6. This process uses water for all the operations. For the reaction itself, the PMI of water is 14.3 (Fig. 14). Although catalyst preparation is in the Other group, water is the main contributor with a combined PMI of 19.8 (Supporting Information).

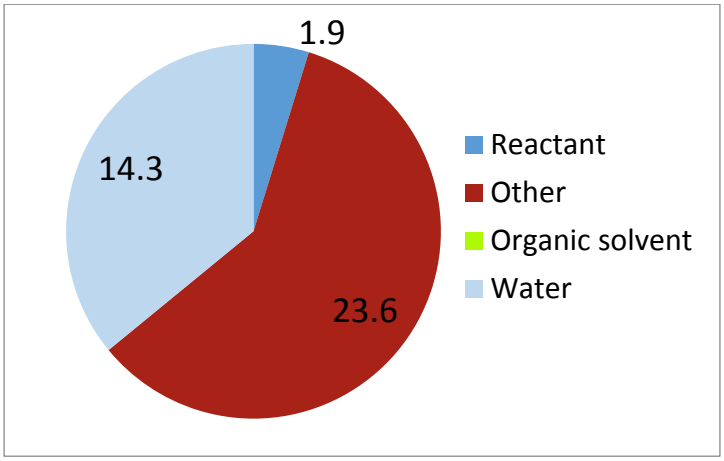


Figure 14 PMI contributor profile for Ajinomoto process

At current level of productivity, Ajinomoto process is clearly the most efficient one among all the four options. However, it was not the obvious winner in the beginning since biocatalytic

reaction was inefficient. Product concentration was limited to ≤ 10 g/L by the fact that TPL reaction is reversible. Additionally, wild type *Erwinia herbicola* has low catalytic efficiency; therefore, large quantity of cells was required. In process development, the two issues have been addressed with innovative solutions. Crystallization-induced equilibrium shift has improved the volumetric productivity in the biocatalytic reaction. As L-Dopa concentration reaches 110 g/L in biocatalytic reaction, not only the need for buffer is reduced, but also the productivity is improved. Genetic modifications of the expression system has improved TPL activity by at least 6.7 folds,[19] corresponding to an increase in total turnover number from 1.275 to at least 8.5 mol L-Dopa kg^{-1} wet cells. This improvement has reduced the mass cost in fermentation and cell isolation. To simplify the analysis, we assume the yield does not change, therefore the reactant PMI remains the same. The isolation PMI should not change because re-crystallization is dependent on the solubility behavior of L-Dopa. Substituting the variables in Eq. 18 with the PMI numbers in current state, we get Eq. 19 to estimate PMI value for Ajinomoto process within the range of improvement.

$$PMI_{total} = PMI_{reactant} + PMI_{medium} + PMI_{catalyst} + PMI_{isolation} \quad (18)$$

$$PMI_{total} = 1.9 + 10.2 \cdot \frac{110}{c} + 20.6 \cdot \frac{8.5}{TTN} + 7.1 \quad (19)$$

In Eq. 19, *c* is the concentration of L-Dopa in the range from 10 g to 110 g/L, and *TTN* is total turnover number of TPL in the range from 1.275 to 8.5 mol product kg^{-1} wet cells. Plotting Eq. 19 gives a graphical description of PMI (Fig. 15) as the function of the two variables. The PMI for Ajinomoto process in the beginning is estimated to be 259, or 6.5 folds of its current value. Correspondingly, the PMI of water is estimated to be 254, or 6.9 folds of the current value.

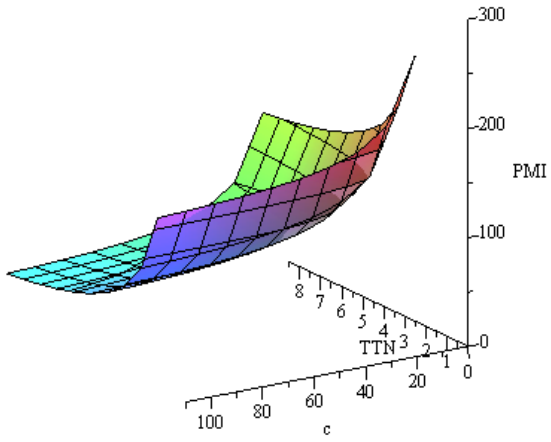


Figure 15 The PMI impact of product concentration and Total Turnover Number of TPL in Ajinomoto process

Although many biocatalytic reactions have superb theoretical efficiency, they frequently suffer from low volumetric productivity and poor catalytic efficiency for preparative synthesis. As such, many biocatalytic reactions are not options for process design because reactions with poor efficiency are generally excluded. However, if the potential of efficiency improvement can be projected, the estimation would help to justify technological investment and set expectations for innovative solutions. As demonstrated by the Ajinomoto case, the mass analysis with PMI is a suitable tool for such purpose.

4.4 Waste stream inventory

Although process waste is not typically included in Green Chemistry evaluation, the importance of waste treatment and disposal is well recognized. According to Mulholland, et al, "The funds required to move, store, and treat waste ranges from 10-35% of the total plant investment".[13b] To reduce project cost, it is desirable to address environmental issues concurrently in early stages.[2b] The waste inventory is needed when a new process is introduced, thereby the waste streams can be evaluated for decisions including segregation, reuse, recycle, energy recovery, treatment, and safe disposal.[13]

Process flow diagram is a highly useful tool for communication in production planning.[24] It provides a concise platform to evaluate material throughput, potential hazards, equipment need (type, volume, heat transfer), and waste generation.

For waste generation projection, a flow diagram enables identifying the point sources with characterizations including quantity, composition, and physical state. The waste from organic synthesis needs to be rendered harmless before discharging to the environment. In the US, this activity is regulated by the legal framework based on the Resource Conservation and Recovery Act (RCRA), the Clean Water Act (CWA), and the Clean Air Act (CAA). The regulatory burden can be tremendously high if a waste stream contains a listed hazardous waste in RCRA. The waste stream information will help the generator to evaluate resource requirement and legal burden for waste management and treatment, generate and prioritize options, and select options for further study in early stage.

In this work, a waste stream is created at its point of generation (e.g. Stream 1-1 in Fig. 5), and the composition is characterized by the components with E factors and mass percentages. Aqueous mixture of organic solvents raise special concerns because the solvents need to be removed or reduced so that waste water is treatable by biosludge. Regulatory concerns are highlighted for hazardous solvents.

Waste estimation is not precise when the remaining reactants or byproducts are not characterized. However, the amount of unaccounted-for chemicals is usually small, and should not change the conclusion of the evaluation. For example, the total E factor for Monsanto process is 103, but the E factor is only 1.5 for unaccounted-for waste (Supporting Information).

4.4.1 Waste streams from Roche process (Without (*R*)-9 recycling)

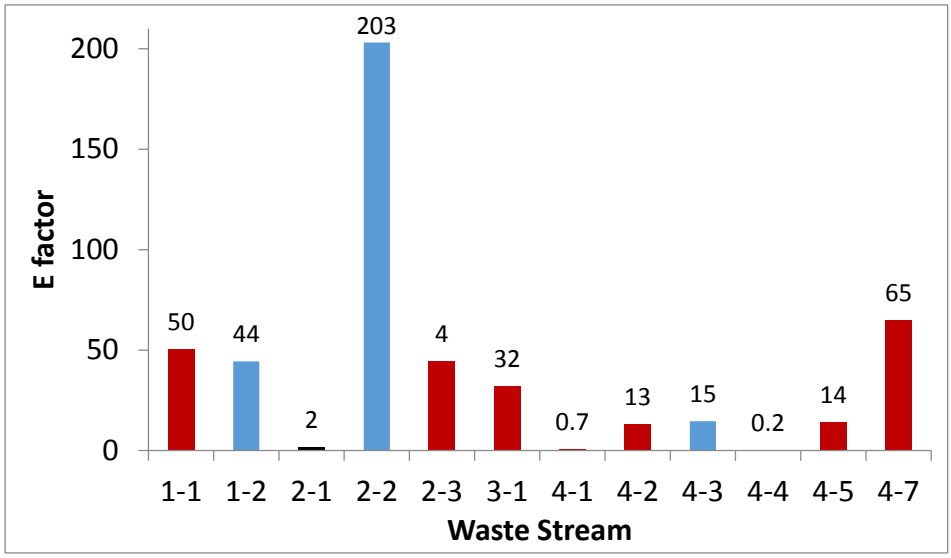


Figure 16 Waste stream profile for Roche process. Waste solvents or organic-laden streams are in red, solvent-free aqueous streams are in blue, and solid streams are in black.

Roche process has twelve waste streams, with three solvent-free aqueous streams, seven organic or solvent-contaminated aqueous streams, and two solid waste streams (Fig. 16). The largest waste stream is 2-2 from hydrogenation. It contains 95% water, 4% NaCl, and about 1% NaOAc. This stream should be treatable by biosludge after pH adjustment. The other two smaller aqueous streams (1-2 and 4-3) can be treated similarly. The two solid streams (Stream 2-1, Nickel, Stream 4-4 activated carbon) are recyclable. In organic streams, Stream 4-1 is MeBr from deprotection reaction. It is decomposed by scrubbing to give Stream 4-7, the largest stream in the organic group. It comprises of 81.6 % of water, 16.7% of ethanolamine, and 1.7 % of methylated products. Although ethanolamine is biodegradable, the concentration needs to be reduced from this stream by a pretreatment to improve biotreatability.[31] For similar reasons, pretreatment is needed for Stream 1-1 (DMF 2.5 %, HOAc 16.9%, NaOAc 7.9% , water 72.8%), 2-3 (MeOH 18%, water 77.8%, by products 4.2%), and 3-1 ((*R*)-**9** 8.2%, Compound **10** 0.6%, MeOH 54.4%, water 35.7%). In these streams, DMF raises the concern of toxicity and MeOH is regulated by CWA and CAA. Stream 4-5 contains 14% of (+)-Dehydroabietylamine (**10**), the chiral base for classical resolution. It needs to be recycled for cost saving. Stream 4-2 contains 94% toluene and 6.3% of benzoic acid. Although recycling is technically easy, this stream has to be segregated and handled as hazardous waste as required by RCRA (40CFR 261.31, F005).

4.4.2 Waste streams from Monsanto Process

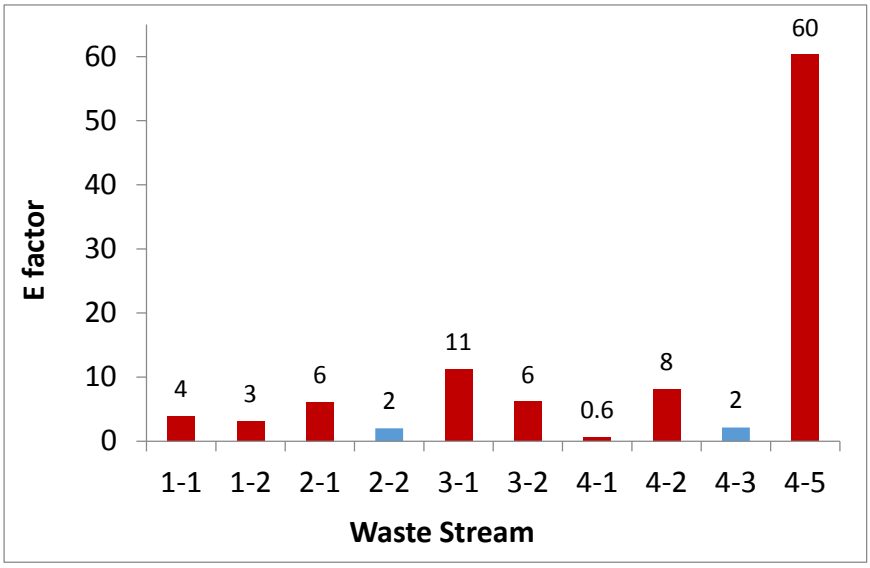


Figure 17 Waste stream profile for Monsanto process. Waste solvents or organic-laden streams are in red, and solvent-free aqueous streams are in blue.

There are ten waste streams from Monsanto process, including two solvent-free aqueous streams, and nine organic or organic-laden streams. The two aqueous streams (2-2 and 4-3) can be directly treated with biosludge. Stream 2-1 (100% Acetone) and 3-1 (88% iPrOH and 12% water) have organic components that are regulated by CWA. They should be recyclable for solvents or used in energy recovery since the stream compositions are simple. Three organic-laden aqueous streams (1-1, 1-2, and 4-2) all have acetic acid as the only organic component. Sodium acetate has been used as the external carbon source for biosludge,[32] these streams can be used similarly for waste water treatment. The MeBr in Stream 4-1 is decomposed in scrubbing reaction to give Stream 4-5 with a composition similar to the equivalent stream in Roche process. As the largest stream that requires pretreatment, Stream 4-5 will dominate the capital and operational cost of treatment for Monsanto process.

4.4.3 Waste streams from Ajinomoto process

Ajinomoto process generates five waste streams, including one solid stream and four aqueous streams (Fig. 18). The solid stream (1-2, activated carbon) can be recycled. There is no concern for hazardous components in the aqueous streams. All the four streams can be directly treated with biological methods. The focus of waste treatment plan will be on efficient oxidation of organic substances from spent media to meet general discharge standards such as Chemical Oxygen Demand (COD) and Biochemical Oxygen Demand (BOD).

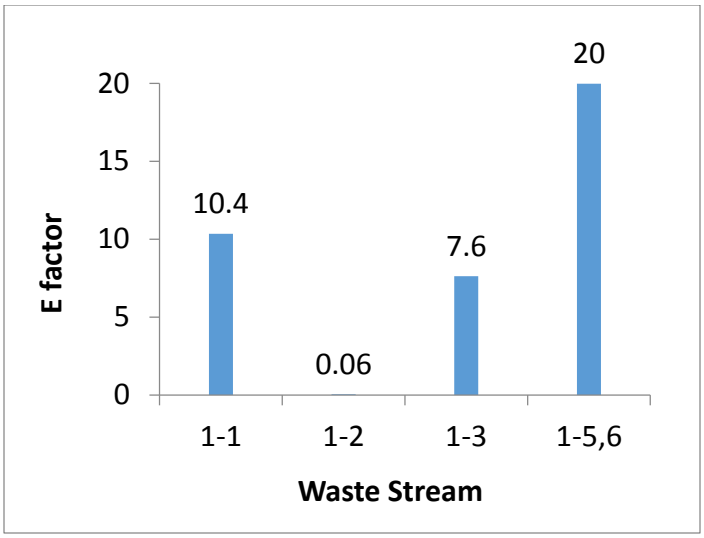


Figure 18 Waste stream profile for Monsanto process. Aqueous streams are in blue, the solid phase waste is in black.

4.4.4 Additional concerns with MeBr

MeBr is a common waste of the last step from the three chemical processes. The decomposition of one equivalent of MeBr from the last step has a PMI value around 60. In addition to the cost for waste treatment, handling MeBr has occupational risk and environmental risk. In the US, the occupational exposure of MeBr is regulated by OSHA.[26] It is in the List of Highly Hazardous Chemicals, Toxics and Reactives with a threshold quantity of 2500 lb (1.13 ton) by OSHA's code.[33] Despite of work safety measures, exposure has been found in routine activities such as equipment maintenance, and cleaning or filling canisters in MeBr manufacture.[34] For industrial applications, the manufacture, import/export, and disposition of MeBr are regulated. In the US, these activities need to be reported to EPA on quarterly basis.[35] Globally, industrial activity with MeBr is reported to the United Nations Environmental Programme.[36] In process design, this chemical should be avoided altogether.

Sankyo process involves the handling of three equivalents of MeBr (Scheme 4). One equivalent is used in the first step to protect the phenol, and two equivalents are generated in the deprotection at the last step. The burden from related operation and regulatory issues is higher than that for Roche or Monsanto processes.

5 Summary and Conclusion

As long as practical procedures are available, it is feasible to estimate the PMI for each contributing chemical and the composition of all waste effluents for detailed mass analysis of a chemical process. This exercise helps all the stakeholders to evaluate the practical impact of

process design, find problems, identify opportunities for improvements, and change the priorities in route selection and process development.

Out of the three fully evaluated commercial process for L-Dopa, Roche process is least efficient, due to high mass intensity in hydrogenation, chiral resolution, and isolation of intermediates. Recycling of the wrong enantiomer not only reduces the overall PMI from 487 to 438, but also improves the throughput by reducing the PMI of the hydrogenation step from 248 to 176.

Monsanto process has an overall PMI of 104. It features a highly efficient asymmetric hydrogenation with PMI of 17.2, as well as low mass intensity for isolation. The least efficient step is MeBr decomposition by scrubbing, which has a PMI of 60.

Ajinomoto process is most efficient. The important PMI contributors are biocatalyst preparation, and reaction buffer in biotransformation. Performance improvement in both contributors reduced the total PMI from 259 at the beginning to 39.8 in current process.

All chemical processes have waste streams that require pre-treatment. The largest organic-laden stream is from MeBr decomposition. The MeBr byproduct also entails occupational and environmental risks. Sankyo process is the worst in this respect because it involves the handling of three equivalents of MeBr. For Ajinomoto process, all streams are aqueous solutions that are directly treatable with biological methods.

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