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Inclusion of Environmental Impact Parameters in Radial Pentagon Material Efficiency Metrics Analysis: Using Benign Indices as a Step Towards a Complete Assessment of "Greenness" for Chemical Reactions and Synthesis Plans

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Ⓢ *Supporting Information*

ABSTRACT: A new benign index (BI) parameter is developed and applied to assess the overall "greenness" of chemical reactions and synthesis plans. Previously described radial pentagon green metrics based solely on material efficiency are extended to include BI which takes into account the following potentials for environmental harm: acidification−basification (ABP), ozone depletion (ODP), global warming (GWP), smog formation (SFP), inhalation toxicity (INHTP), ingestion toxicity (INGTP), inhalation carcinogenicity (INHCP), ingestion carcinogenicity (INGCP), bioconcentration (BCP), abiotic resource depletion (ARDP), cancer potency (CPP), persistence (PER), and endocrine disruption (EDP). As with other material efficiency metrics, the benign index is defined as a fraction between 0 and 1 so that it may be added as another radial axis to produce an overall radial hexagon diagram that can be used to evaluate the "green" merits of any given chemical reaction. The utility of the method is demonstrated for industrial chemical reactions producing diphenyl carbonate (DPC) and phenyl isocyanate (PI) using both phosgene-based and nonphosgene-based chemistries, and for synthesis plans for the industrial production of aniline, phenol, and aspirin. A critical discussion is presented on the limitations of the method with respect to proper decision making in route selection, particularly the availability and reliability of key parameters, and the importance of obtaining experimental data for key parameters rather than relying solely on computational methods.

■ INTRODUCTION

The application of a universal set of green metrics to assess material efficiencies of chemical reactions and synthesis plans is well described.[1−5] Various groups have successfully used such metrics to assess relative performances of multiple routes to specific target molecules[6−19] and to make choices about selecting "greenest" routes based on such assessments. Recently, the pharmaceutical industry has adopted the process mass intensity (PMI) metric as a useful and general tool to evaluate the greenness of synthesis plans.[20,21] The definition of this metric is identical to that of the inverse of global reaction mass efficiency (RME) defined earlier by Andraos[22] for individual reactions or entire synthesis plans; namely, the ratio of the sum of masses of all input materials (reagents, catalysts, reaction solvents, workup materials, and purification materials) needed to make a target product to the mass of the target product collected. Connecting relationships between key metrics, discussions of their merits, and their use in decision-making roles within the context of green chemistry principles have been extensively reviewed.[2,3] Radial pentagon[23] and hexagon[2,5] diagrams were also introduced as powerful visual tools to quickly assess the strengths and weaknesses of material and synthesis strategy efficiencies for any kind of reaction or synthesis plan, respectively.

Paralleling work done on material efficiency green metrics specific to stand-alone individual reactions and synthesis plans, considerable research has been done on life cycle assessment (LCA)[24−55] (sometimes called life cycle analysis in the literature[56,57]) to assess the environmental impact of chemical processes from a holistic point of view. This subject has been extensively reviewed[27−37] and historical accounts of its origin have been published.[38,39] Here we briefly describe its approaches and how the present analysis differs from it. LCA is a broad based term encompassing many levels of assessment which may be subdivided into various categories including life cycle inventory (LCI), life cycle costing (LCC), life cycle management (LCM), and social life cycle assessment (SLCA). The LCA methodology takes into account a much larger set of variables beyond the mass determination of waste production including origin of starting materials (nonrenewable and renewable feedstocks) used, risk and hazard potentials based on environmental harm and human health and safety for all materials used and products made in a process (reagents, target product, byproducts, and side products), fate and degradation of such products in the environment, energy consumption, process efficiency, economics, and social impact. Such analyses involve complex reaction networks, are necessarily broad and multilayered, and are often characterized by variables having no available data, which pose challenges in the interpretation of LCAs and can severely restrict the reliability of conclusions drawn. The problem of limited databases containing all of the required impact potentials for most chemicals is generally acknowledged.[58] Recent attempts, however, have been made to bridge the gap of missing data using algorithms that can estimate key production parameters directly from molecular structure features.[59] There are many levels of sophistication depending on time and cost resources devoted to

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such analyses: gate-to-gate[60−65] (narrowest assessment), cradle-to-gate[56,66−70] (sometimes called cradle-to-factory gate), and cradle-to-grave[71] (broadest assessment). In order to make the complex problem of assessment feasible and tractable, researchers have implemented limited or simplified LCAs[18,53,72−76] (sometimes called curtate LCAs[60]) with well-defined boundaries. These kinds of abbreviated LCAs have been applied to syntheses of fine chemicals and pharmaceutical intermediates of interest to practicing synthetic organic chemists. Examples include syntheses of dimethyl carbonate by urea and phosgene routes,[56] production of two undisclosed crop protection compounds,[77] Schmitt-Kolbe synthesis of β-resorcylic acid from resorcinol,[72] synthesis of 4-(2-methoxyethyl)-phenol,8-α-amino-2,6-dimethylergoline and enantioselective reduction of ketoesters,[73] synthesis of phenyl benzoate by microreaction processes,[74] synthesis of rose oxide by various routes,[18] synthesis of an undisclosed active pharmaceutical ingredient,[75] enantioselective reduction of α- and β-ketoesters,[53] and synthesis of heterocyclics.[76] Regardless of the model used the following core items are always included: process efficiency (materials consumption), sourcing of starting materials back to petrochemical nonrenewable resources or biofeedstock renewables, environmental impact, and energy efficiency (energy consumption). To help facilitate computations a number of software packages have been developed which are either freely available or may be purchased: Ecosolvent,[78] Ecoinvent,[79] Umberto,[80] SimaPro,[81] and EcoIndicator 95 and 99.[82]

LCAs may be applied to reaction networks that either are linear or open chain, or are closed loop or cyclic. A gate-to-gate approach is a focused assessment of a specific process that ignores upstream and downstream processes from it and the final fate of the target product once it has served its purpose. Typically, this kind of analysis deals with "readily available starting materials" and all waste materials generated along the way. Due to the arbitrary nature of what constitutes a "readily available starting material", there will always be a debate about the fair comparison of synthesis plans to a common target structure that originate from very different source materials. To circumvent potential biases in synthesis rankings using the gate-to-gate methodology, the tracing of a given product (say, phenol) via various routes is done until a common starting material is found for all routes (say, benzene). That way the starting and end points for all routes are the same. Whatever paths precede benzene will be common to all routes and are thus unnecessary to consider because they will cancel out. Such a comparison would be considered fair. This point has been made before[56] in connection with the analysis of two routes to dimethyl carbonate that originated from simple hydrocarbons and methanol as common starting materials. That analysis did not consider how methanol was made, for example, since it was a common starting material for both routes. Cradle-to-gate and cradle-to-grave approaches, which are truer to the spirit of LCAs, account for the origin and final termini of an entire process in the broadest sense. Here the origin implies the earliest generation feedstock materials in the chain of industrial commodity chemicals, either from non-renewable petrochemical sources or renewable agricultural (biofeedstock) sources. The final fate of the intended target product is also included in the assessment. A third terminology unrelated to a formal LCA, called cradle-to-cradle (C2C)[83] describes a philosophy of designing industrial systems that are entirely powered by renewable energy in which materials flow in safe, regenerative, closed-loop cycles. These correspond to idealized sustainable processes that produce the least amount of nonusable dead waste.

In an effort to broaden the current set of green metrics based on counting the mass amount of waste generated in relation to the mass amount of intended product by including a basic set of environmental impact parameters, in addition to material and energy consumption, for the assessment of overall greenness of chemical processes, a recent multivariable exercise for undergraduate students was developed.[84] The thesis of that work was that green metrics analysis based solely on material efficiency, that is, amount of raw waste produced, was inadequate in making decisions about which synthesis route was "greener". It was pointed out that decision making is heavily reliant on availability and reliability of data for all required parameters. Due to this limitation, application of this exercise would require instructors to artificially simulate data in order for students to successfully complete the exercise. This is especially true if synthesis plan examples are chosen that involve molecules more complicated than first- or second-generation industrial feedstocks from the petrochemical industry. Given this problem, from an instructional viewpoint, it was deemed better to give students an opportunity to go through the motions of conducting a basic environmental assessment and seeing how it *could* be used to make judgments while at the same time recognizing the limitations of the exercise and motivating them to pursue research in exactly those areas that would eliminate such assumptions and limitations. In the present work we extend and modify that analysis to make it applicable to real-life situations that can be used as broadly as possible in an industrial setting by practicing synthetic organic chemists and chemical engineers. Specifically, material consumption and environmental impacts of all input and output materials are considered for the example reactions examined, but energy consumption is not. Reasons for this exclusion are given *vide infra*. This exclusion and the fact that analyses were not carried back to nonrenewable starting materials make the present analysis distinguishable from a formal LCA. It is intended that the method be used as a quick tool to spot bottlenecks in both material efficiency and environmental impact before attempting more elaborate analyses based on LCA described above.

The scope and structure of the paper is as follows. The Methodology section introduces the concept of environmental potential and shows its connection to prior published *E*-factor parameters that include hazard and toxicity. The definitions and limitations of both well-known and new environmental potentials used in the analysis are described briefly and in more detail in the Supporting Information. Specifically, the acidification potential (AP) described in the literature for volatile compounds potentially causing acid rain and based only on number of ionisable hydrogen atoms[85,86] and molecular weight is replaced by a broader acidification−basification potential (ABP) definition, applied to both volatile and nonvolatile compounds and based on relative ratios of dissociation constants for Bronsted-type acids and bases with respect to water. Release of an acidic volatile compound in the atmosphere and release of an acidic nonvolatile compound directly into a body of water will both perturb the acidity of the water compartment. The current definition of AP has been applied to the former situation while ignoring the latter. The proposed ABP definition is found to be more realistic in capturing the potential to perturb the acidity of the water compartment of the environment from neutrality upon release of a given amount of compound by any means. The Supporting Information also contains fully worked out example calculations for each potential and extensive lists of source references for obtaining best available raw data needed for such calculations. Next, a new parameter called a benign index (BI) is introduced which incorporates all environmental potential parameters into one single number that ranges between 0 and 1 so that it is compatible and scalable with other well-known green metrics based on material efficiency, namely, atom economy, reaction yield, and reaction mass efficiency. Benign indices are applied to waste materials, input materials, and output materials for individual reactions and for entire synthesis plans. Keeping with the theme of depicting metric parameters in the form of easy-to-use visual diagrams, an overall radial hexagon diagram is introduced which adds the benign index for waste products as a sixth axis to the previously described radial pentagon diagram[23] with its associated material efficiency green metrics for any given chemical reaction. For tracking sequences of reactions over the course of a synthesis plan, a histogram of gains and losses in benign index differences between input and output materials is introduced as another visual tool to gauge the generation of environmental harm as a consequence of carrying out chemical transformations. In order to automate all calculations, a Microsoft Excel spreadsheet algorithm detailing the full suite of material efficiency and environmental impact calculations encompassing benign indices is included in the Supporting Information. After describing the methodology, the following fully worked out case studies are examined and discussed in detail: (a) phosgene and nonphosgene routes to diphenyl carbonate[87−90] and phenyl isocyanate,[91−94] and (b) industrial synthesis plans for aniline,[95,96] phenol,[97] and aspirin.[98,99] The former cases were recently examined thoroughly by green metrics analysis based only on material efficiency.[14] Finally, problems that need urgent addressing by the chemical community for reliable decision making are also discussed.

■ METHODOLOGY

Concept of Environmental Potential. The concept of using environmental impact potentials is an extension of the *Q*-factors that Sheldon introduced to correct raw *E*-factor data.[100] These *Q*-factors were arbitrarily chosen factors reflecting the toxicity and hazard risks caused by a given amount of waste chemical. It was a basic way of distinguishing a kilogram of sodium chloride waste from a kilogram of mercury waste, for example. When the mass of a given waste chemical is multiplied by such a *Q*-factor, it effectively amplifies its contribution to the waste profile. Waste chemicals that posed no hazards or risks were assigned *Q* values of one, meaning that the mass was not amplified. Eissen[101] developed the Environmental Assessment Tool for Organic Synthesis (EATOS) software package to calculate *E*-factors that utilized an extensive range of *Q*-factor values based on descriptor phrases associated with hazards and risks typically found in Material Safety Data Sheets (MSDS). This algorithm has been used to assess the greenness of a number of chemical processes and reactions.[8,17,18,102,103] The form of Sheldon's and Eissen's *Q*-factor analysis is illustrated in eq 1.

$$\mathrm{EQ} = \frac{w_1Q_1 + w_2Q_2 + ...}{m_\mathrm{p}} \tag{1}$$

where w_j is the mass of waste chemical *j*, Q_j is the "unfriendliness" quotient associated with waste chemical *j*, and m_p is the mass of target product collected. The concept of risk potentials introduced by the International Standards Organization (ISO) replaces the single arbitrary *Q*-factor with a set of nonarbitrary mass amplifiers that describe specific kinds of risks. A risk index is defined as shown in eq 2.[84,85]

$$I_{ij} = w_j{*}P_{ij} \tag{2}$$

where w_j is the mass of waste chemical *j*, P_{ij} is the risk potential of waste chemical *j* based on descriptor *i*, and I_{ij} is the risk index. The overall risk index that covers the entire set of kinds of potentials for a given waste chemical *j* is given by eq 3.

$$I_{1j} + I_{2j} + ... = w_j(P_{1j} + P_{2j} + ...) \tag{3}$$

Comparing eq 3 and the numerator of the EQ expression shown in eq 1, it is observed that the connecting relationship between the *Q*-factors and potentials is given by eq 4.

$$Q_j = P_{1j} + P_{2j} + ... \tag{4}$$

The overall environmental impact of all waste materials produced in a reaction or synthesis plan is found by summing all the I_j terms in eq 3 as shown in eq 5.

$$I_\mathrm{overall} = \sum_j w_j\left(P_{1j} + P_{2j} + ...\right) \tag{5}$$

In addition, the risk potential, *P*, based on any property is always defined in relative terms, that is, it is expressed as a ratio of values corresponding to compound *j* and an arbitrarily chosen reference compound as shown generally in eq 6.

$$P_{Xj} = \frac{X_j}{X_\mathrm{ref}} \tag{6}$$

where X_j is the value of property *X* for compound *j* and X_ref is the value of property X for the reference compound.

New Definition of Acidification Potential. A new definition of acidification potential (AP) is introduced that is broader in scope and justified as follows. AP as defined in the literature (see eq S6 in Supporting Information) is wholly inadequate in describing true acidification potential since acid dissociation constants, which are intrinsic measures of acidification power, are ignored. It is based on simply counting acidic hydrogen atoms per molecular weight unit regardless of their propensity to dissociate from a given molecule. The reference acid in this definition is H_2SO_3 which is formed upon hydration of SO_2. Thus, two acids with equal molecular weights and having the same number of ionisable hydrogen atoms, but with very different $\mathrm{p}K_\mathrm{a}$ values, will have identical AP values—a result which is clearly unsatisfactory. The following pairwise comparisons of well-known acids are illustrative: H_3PO_4 (MW = 98; $\mathrm{p}K_1 = 2.12$; $\mathrm{p}K_2 = 7.21$; $\mathrm{p}K_3 = 12.32$) vs H_2SO_4 (MW = 98; $\mathrm{p}K_1 = 0.4$; $\mathrm{p}K_2 = 1.92$), H_2S (MW = 34; $\mathrm{p}K_1 = 7.24$; $\mathrm{p}K_2 = 14.92$), and H_2O_2 (MW = 34; $\mathrm{p}K_1 = 11.64$), and H_3BO_3 (MW = 62; $\mathrm{p}K_1 = 9.24$) and H_2CO_3 (MW = 62; $\mathrm{p}K_1 = 6.37$; $\mathrm{p}K_2 = 10.25$). In order to circumvent this problem, one may choose to calculate the pH of an aqueous solution of a given acid at a standard concentration, such as 0.1 M, and compare that result with a similar determination for a reference acid so that a perturbation from neutrality is obtained. However, the underlying assumption of complete solubility in water for organic acids and bases at a standard concentration of 0.1 M, or any chosen concentration for that matter, may not be valid as is implicitly implied in all calculations of pH for various solutions of inorganic acids, bases, and salts customarily found in introductory general chemistry and analytical chemistry texts. Moreover, pH calculations of aqueous solutions of diprotic acids and dibasic bases having

Table 1. Summary of dissociation data for substituted benzoic acids

benzoic acid	pK_a	σ = pK_a(X) − pK_a(H)	AP	relative AP[a]	pH of 0.1 M soln	change in pH from neutrality	pH perturbation potential[a]	difference[b]
X = H	4.2	0	10.402	1	2.605	−4.395	1	0.000
X = *m*-Br	3.86	0.34	10.742	1.033	1.438	−4.562	1.038	−0.005
X = *m*-Cl	3.82	0.38	10.782	1.037	1.125	−4.582	1.043	−0.006
X = *m*-CN	3.6	0.6	11.002	1.058	2.709	−4.689	1.067	−0.009
X = *m*-F	3.86	0.34	10.742	1.033	2.438	−4.562	1.038	−0.005
X = *m*-CHO	3.84	0.36	10.762	1.035	2.418	−4.572	1.040	−0.006
X = *m*-I	3.85	0.35	10.752	1.034	2.311	−4.567	1.039	−0.006
X = *m*-MeO	4.09	0.11	10.512	1.011	2.438	−4.449	1.012	−0.002
X = *m*-NO_2	3.49	0.71	11.112	1.068	2.428	−4.743	1.079	−0.011
X = *m*-PhO	3.95	0.25	10.652	1.024	2.433	−4.518	1.028	−0.004
X = *m*-^{t}Bu	4.2	0	10.402	1.000	2.551	−4.395	1.000	0.000
X = *p*-NH_2	4.87	−0.67	9.732	0.936	2.257	−4.062	0.924	0.011
X = *p*-Br	3.96	0.24	10.642	1.023	2.482	−4.513	1.027	−0.004
X = *p*-Cl	3.98	0.22	10.622	1.021	2.605	−4.503	1.025	−0.004
X = *p*-CN	3.55	0.65	11.052	1.062	1.946	−4.713	1.073	−0.010
X = *p*-Et	4.35	−0.15	10.252	0.986	1.984	−4.320	0.983	0.002
X = *p*-F	4.15	0.05	10.452	1.005	2.151	−4.419	1.006	−0.001
X = *p*-CHO	3.77	0.43	10.832	1.041	1.955	−4.606	1.048	−0.007
X = *p*-HO	4.48	−0.28	10.122	0.973	2.551	−4.256	0.968	0.005
X = *p*-MeO	4.47	−0.27	10.132	0.974	1.641	−4.261	0.970	0.004
X = *p*-NO_2	3.42	0.78	11.182	1.075	2.277	−4.777	1.087	−0.012
X = *p*-PhO	4.52	−0.32	10.082	0.969	2.243	−4.236	0.964	0.005
X = *p*-^{t}Bu	4.38	−0.18	10.222	0.983	2.282	−4.306	0.980	0.003

[a] Reference acid is benzoic acid. [b] Relative AP−pH perturbation potential.

similarly valued pK_a and pK_b values respectively for first and second ionizations are necessarily tedious because of the need to solve complex cubic and quartic equations. Therefore, the best option chosen was to define an acidification−basification potential (ABP) covering both directions of perturbation from neutrality as the ratio of dissociation equilibrium constants relative to that of water, K_w, corrected for the number of acidic and basic sites found in the given chemical structure as required. Water is chosen as the natural reference acid and base since it is the ubiquitous solvent found in the environment. For monoprotic acids and monobasic bases, ABP is given by eqs 7 and 8, respectively.

$$\mathrm{ABP} = \mathrm{AP} = \log\left(\frac{2q}{p}\right) - \mathrm{p}K_\mathrm{a} + \mathrm{p}K_\mathrm{w} \tag{7}$$

$$\mathrm{ABP} = \mathrm{BP} = \log\left(\frac{2p}{q}\right) - \mathrm{p}K_\mathrm{b} + \mathrm{p}K_\mathrm{w} \tag{8}$$

where, p is the number of equivalent acidic sites on acid HA and q is the number of equivalent basic sites on conjugate acid A^-. Note that ABP reduces to AP when dealing with acidic species and to BP when dealing with basic species. Expressions are given in the Supporting Information along with worked out examples for ABP for diprotic acids, dibasic bases, and general mixtures of acids and bases including ionic species from salts. Weighted average equilibrium constants are determined for acids and bases with multiple acidic and basic sites.

The justification for implementing this new definition of ABP is illustrated in Table 1 and Figure 1 for various substituted benzoic acids. Table 1 compares the calculated AP values using eq 7 with the calculated pHs of a standard 0.1 M aqueous solution of the benzoic acids assuming complete solubility. Relative AP values are determined with respect to the parent unsubstituted benzoic acid. The pH perturbation potential (PPP) from neutrality (pH = 7) is defined according to eq 9.

$$\mathrm{PPP} = \frac{\mathrm{pH(substituted - benzoic - acid)} - 7}{\mathrm{pH(benzoic - acid)} - 7} \tag{9}$$

It is observed that the PPP and relative AP values are consistent as evidenced by the small differences shown in the last column of Table 1. As an example, for *m*-bromobenzoic acid, $p = 1$, $q = 2$, pK_a = 3.86, and AP = 10.742 which is 1.033 times larger than the AP value for benzoic acid. Similarly, a 0.1 M solution of *m*-bromobenzoic acid has a pH 4.562 log units lower than pH 7, whereas, the parent acid is 4.395 log units lower. Hence, PPP = 4.562/4.395 = 1.038. Figure 1 shows three linear correlation plots, including a Hammett-like plot, that nicely illustrates the trends exemplified by the newly defined AP parameter.

Potentials Used. The Supporting Information lists all of the environmental potentials mentioned in this work including definitions, equations, units, and reference compounds. Worked out example calculations are given for each potential. For the purpose of illustrating their usage in the reactions and synthesis plans discussed in this work, the following environmental potentials were specifically used since data are available in the literature: ABP (acidification−basification), ODP (ozone depletion), SFP (smog formation), GWP (global warming), INHTP (inhalation toxicity), INGTP (ingestion toxicity), BCP (bioconcentration), and ARDP (abiotic resource depletion). Due to lack of availability and unreliability of data (see Discussion), the following potentials were not used: CPP (cancer potency), PER (persistence), EDP (endocrine disruption), INHCP (inhalation carcinogenicity), and INGCP (ingestion carcinogenicity). TD_{50} (tumour dose) values required for INHCP and INGCP calculations are not available for chemicals used in the syntheses described in this work. Similarly, oral and inhalation slope factors are not available in the U.S. EPA IRIS database. Literature

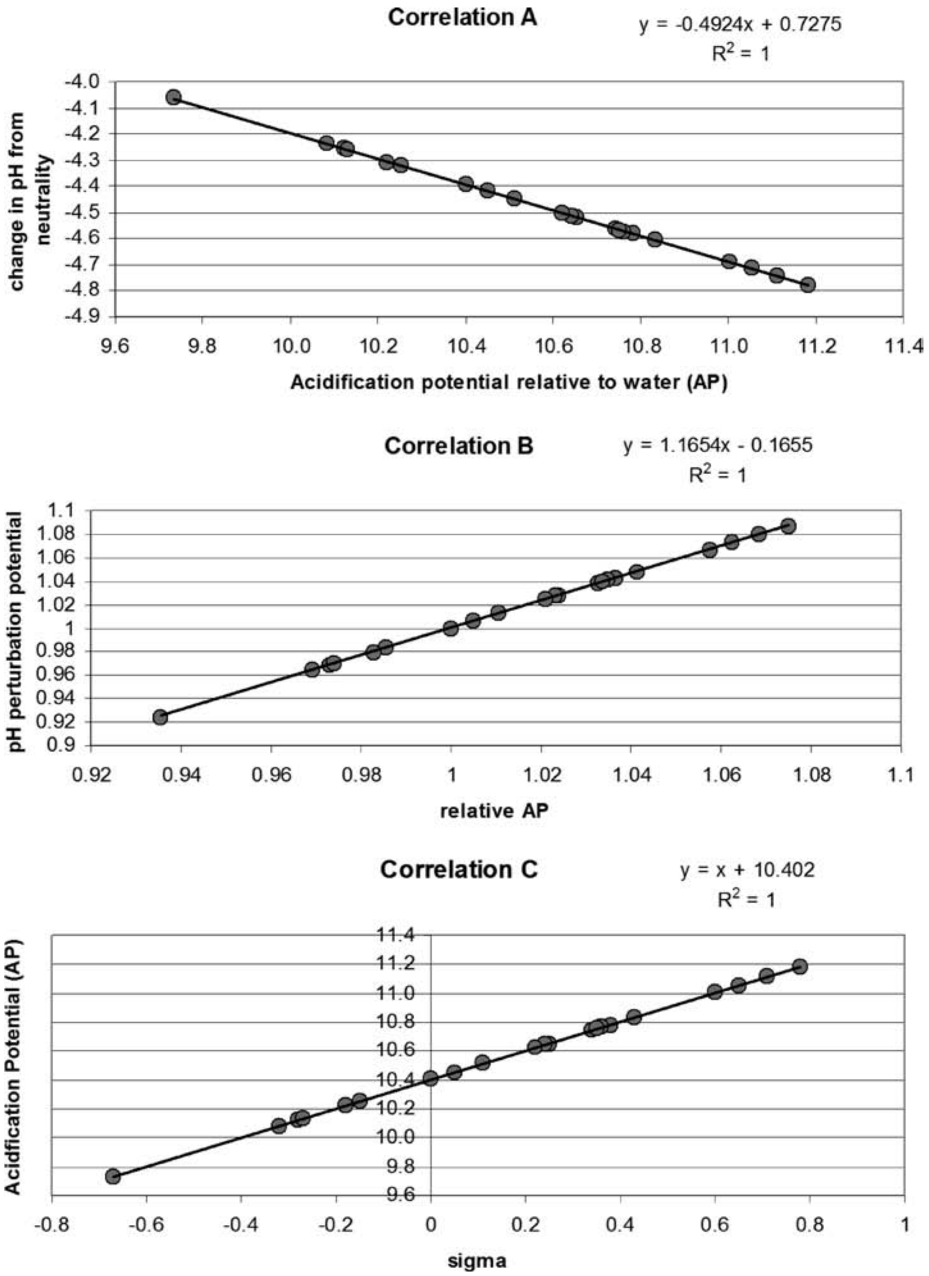


Figure 1. (A) Correlation between change in pH from neutrality for 0.1 M aqueous solutions of substituted benzoic acids vs acidification potential relative to water. (B) Correlation between pH perturbation potential with respect to parent benzoic acid vs relative acidification potential. (C) Correlation between acidification potential and σ constants for substituted benzoic acids.

compilations of half-lives of chemicals in soil are restricted to pesticides only. No endocrine disruptor data are available for any of the chemicals discussed in this work.

Multicompartment Model (MCM). For determining INHTP and INGTP the Mackay multicompartment model (Level I) was used.[104−109] This model determines the fate concentrations of a given mass of a chemical released into four environmental compartments: air, water, soil, and sediment. For all calculations a mass of 1000 kg was used as a common basis. The Supporting Information gives a complete list of eqs (S1−S5) used along with a template Microsoft Excel spreadsheet to facilitate calculations.

Assumptions. When dealing with missing LD_{50} or LC_{50} data for chemicals, these were left blank so that their associated toxicity potentials were not counted. If multiple values of these parameters were found in the literature for a given chemical, then the lowest value was used to reflect maximum toxicity. For missing Henry's law constants (HLC) for solids, such as inorganic salts, a value of 1×10^{-100} was used in the computation to avoid division by zero errors in the spreadsheet algorithm. For missing log K_{ow} (octanol−water partition coefficients) for solids (inorganic salts fully soluble in water but insoluble in *n*-octanol), a value of -1×10^{100} was used meaning that K_{ow} is close to zero. Experimental procedures for reactions were sufficiently described so that all masses or volumes of reagents and other materials were specified. In the case when there were missing amounts of catalysts, a 0.1 mol % loading was assumed. The full list of parameters necessary for environmental impact calculations for all reactions discussed in this work is given in Table S1 in the Supporting Information.

Limitations. Equivalent CO_2 emissions as a consequence of energy consumption were not evaluated since these are formally relevant to an energy consumption audit of a chemical process and not to a material consumption assessment. Though this is admittedly a handicap in the present evaluation, which makes it fundamentally different than an LCA evaluation and has consequences for the determination of GWP, there are legitimate reasons for excluding energy consumption which are explained here. An energy evaluation demands disclosure on details of energy consumption in experimental procedures, which was not done for the examples selected for this study and, unfortunately, not done as a matter of standard protocol for any description of syntheses of compounds reported in the literature. Often significant assumptions are made based on reaction temperature and pressure which may be wholly in error with actual energy consumption. The problems associated with disclosure of energy consumption for chemical processes have been mentioned before.[56] For example, heat capacities for pure solvents are used in thermodynamic calculations when, in fact, those solvents have reagents dissolved in them. More importantly, intrinsic efficiencies of apparatuses used such as heating and cooling devices are not taken into account. The problem of energy efficiency of reactions carried out under microwave irradiation has been mentioned.[110] This is a technique widely used by green chemists for which it was assumed, without verification, that the energy consumption was always more efficient than standard methods of heating. In view of these problems, an attempt was made to *experimentally* determine energy consumption for organic reactions relevant to the fine chemicals industry that were run under various conditions: heating in oil baths, heating using conventional heating mantles, and heating via microwave irradiation.[111] However, despite this effort, the disclosure of the mass inventory of those reactions fell short in that work which meant that a proper full analysis of both material and energy efficiencies could not be done. The assumption stated in prior work[84] that "0.1% of the mass of every compound used is emitted to the environment if the compound can be incinerated afterward (e.g., organic solvents, organic byproducts), and 100% is emitted if the compound cannot be incinerated (e.g., inorganic compounds, gases, drying agents)" is revised so that separate benign indices (see following heading) are determined for all input materials used, all output materials produced, and only waste materials produced (i.e., all output materials minus target product). Inclusion of all impact potentials for all three general classes of materials accommodates the unfortunate possibility of occurrence of accidents or emission releases at any stage of a process due to faulty equipment or human error where any material from a reaction or process may be potentially released to the environment and cause harm. In other words, a worst-case scenario approach is taken for the analysis where the possibility of emission into the environment of any chemical used in a given reaction is taken into account. Unlike the prior analysis,[84] this stringent criterion also includes emissions from unreacted reagents destined for waste, which is particularly significant for reactions having low conversions to products and low reaction yields.

Concept of Benign Index. In order to tie all environmental potentials into a single parameter that satisfies the constraint that it ranges between 0 and 1 like other material efficiency metrics such as atom economy, reaction yield, and reaction mass efficiency, a benign index (BI) is defined according to eq 10. The concept of unifying several parameters into one index has been proposed before with the goal of coming up with an overall sustainability metric.[112]

$$\mathrm{BI} = 1 - \mathrm{EI} = 1 - \frac{\sum_j f_j \Omega_j}{\sum_j \Omega_j} \tag{10}$$

where, EI is the environmental impact, j refers to the jth compound, Ω_j is the sum of all potentials given by

$$\Omega_j = (\mathrm{ABP})_j + (\mathrm{ODP})_j + (\mathrm{SFP})_j + (\mathrm{GWP})_j + (\mathrm{INHTP})_j + (\mathrm{INGTP})_j + (\mathrm{BCP})_j + (\mathrm{ARDP})_j$$

and f_j = (mass of compound j)/(total mass of compounds of type j involved in reaction). Each of the potentials comprising Ωj is defined according to eq 6 (see Supporting Information). The sum of potentials can in principle be expanded to include any number of environmental potentials so long as they are defined according to eq 6. The environmental impact potential for each compound is multiplied by a fractional weighting factor corresponding to the fractional contribution by mass of that compound with respect to the overall mass of waste produced in the reaction. Such a formalism appears to be reasonable since a highly toxic waste product produced in small quantity in proportion to other waste products will be counted differently than if it were produced proportionately in high quantity. The same logic applies to the handling of a less toxic waste product produced proportionately in small vs large quantity. The resulting mass weighted ratio appearing in eq 10 may be interpreted as an environmental impact (EI) parameter. If BI = 0 (EI = 1), then this implies that the overall chemical process results in maximum harm; whereas, if BI = 1 (EI = 0), then this implies that it results in no harm, that is, it is determined to be ideally "green" by the set of potentials used. There is, however, one mathematical condition that exists for which the BI expression cannot be used. This is the unique case of having only one material to consider in eq 10. When this happens, $f_1 = 1$ ($j = 1$) and automatically EI = 1 and BI = 0 regardless of how environmentally damaging that material really is. To get around this problem one needs to examine, not the relative environmental impacts, but the absolute values of those impacts, that is, the value of Ω_1 ($j = 1$) and its individual contributors, when ranking such a reaction against others leading to the same target product. Admittedly, such a scenario would be practically not feasible since we would be effectively dealing with a unimolecular reaction that selectively and completely converts a starting material into only one product under solventless conditions and without use of auxiliary workup or purification materials. This case can be safely discounted since the likelihood of its occurring in reality will be extremely low.

For any given chemical reaction, BI may be applied to three cases: all input materials used, all output materials produced, and all waste output materials produced. Input materials include reagents, catalysts and other additives, reaction solvent, workup materials, and purification materials. Output materials include the target product, all side and byproducts, unreacted reagents, reaction solvent, catalysts and other additives, workup materials, and purification materials. Waste materials include all side and byproducts, unreacted reagents, reaction solvent, catalysts and other additives, workup materials, and purification materials. For the purposes of this work everything except the intended target product is considered waste and nothing is reclaimed for recycling. The corresponding expressions for the associated BI parameters are given by eqs 11a−11c.

$$\mathrm{BI(input)} = 1 - \frac{\sum_j f(\mathrm{input})_j \Omega_j}{\sum_j \Omega_j} \tag{11a}$$

$$\mathrm{BI(output)} = 1 - \frac{\sum_j f(\mathrm{output})_j \Omega_j}{\sum_j \Omega_j} \tag{11b}$$

$$\mathrm{BI(waste)} = 1 - \frac{\sum_j f(\mathrm{waste})_j \Omega_j}{\sum_j \Omega_j} \tag{11c}$$

where $f(\mathrm{input})_j$ = (mass of input compound j)/(total mass of input compounds used in reaction), $f(\mathrm{output})_j$ = (mass of output compound j)/(total mass of output compounds produced in reaction), and $f(\mathrm{waste})_j$ = (mass of waste compound j)/(total mass of waste compounds produced in reaction), respectively.

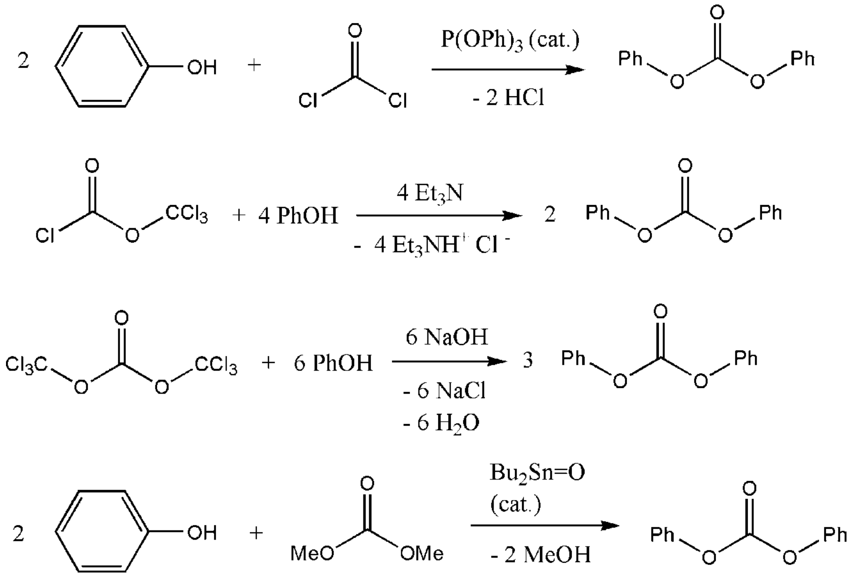
The difference BI(out) − BI(in) has particular significance. A positive difference implies that carrying out a given chemical transformation results in a material mixture (target product + unreacted reagents + byproducts + side products + reaction solvent + catalysts + workup materials + purification materials), which is overall more benign than the starting input materials (reagents + reaction solvents + catalysts + workup materials + purification materials). Therefore, there is a net benefit with respect to environmental impact. This case is suitable for decontamination reactions such as dechlorination of PCBs (polychlorinated biphenyls), for example. On the other hand, a negative difference implies the opposite effect; namely, that a given chemical transformation results in a net gain in environmental harm. Such chemical reactions are to be avoided in a green chemistry context. Creating a histogram of these changes with respect to reaction step count in a synthesis plan helps to track the net gains and losses in environmental impact. This will be illustrated later in the case of comparing five synthesis routes to aspirin via phenol. BI(waste) covers those materials formally comprising waste materials in a chemical reaction; namely, unreacted reagents, byproducts as a mechanistic consequence of producing target product, side products as a consequence of competing side reactions occurring in parallel to the intended reaction, reaction solvent, workup materials, and purification materials. In keeping with the worst-case scenario cradle-to-grave analysis it is assumed that the masses of the aforementioned materials are destined for waste are not reclaimed or recycled. Note that masses of reaction solvents, catalysts, workup materials, and purification materials appear in both BI(in) and BI(out). The constraint condition that BI values fall between 0 and 1 allows BI(waste) to be readily plotted as another axis in the radial pentagon diagram. The resulting radial hexagon gives a convenient global visual indicator of reaction “greenness” that covers both material efficiency and potential environmental impact that is easy to determine and interpret. Just as before this diagram may be used to spot bottlenecks or “hot spots” which may be addressed by further optimization until an acceptable degree of greenness is attained. This is reminiscent of similar radial polygon or “spider” diagrams described before in connection with such algorithms as Eco-efficiency,[113] fast life cycle assessment of synthetic chemistry (FLASC) tool applied to pharmaceutical syntheses,[114] and a simplified LCA used to evaluate the synthesis of phenyl benzoate by microreaction processes.[74] Those diagrams were multiaxial where each non-normalized axis corresponds to the absolute magnitude of a particular environmental impact potential. In the present case all environmental impacts are amalgamated into one variable (the benign index) and all axes in the radial hexagon are normalized so that the ideal green condition is shown as a bounded domain and the performance of a given reaction is shown graphically in relation that that boundary. For convenience, a radial hexagon spreadsheet algorithm is given in the Supporting Information as a downloadable Microsoft Excel spreadsheet. This spreadsheet augments the previously published one based on material efficiency alone[23] and contains all embedded formulas for all material efficiency metrics, environmental impact parameters, and the three BI parameters. For the purpose of ranking overall “green” performances of several reactions leading to the same target product, a vector magnitude ratio (VMR) is calculated for each reaction based on the six radial axis parameters used to construct the associated radial hexagon diagram. Equation 12 gives the overall magnitude of the vector comprising the six green metrics for a given reaction relative to that for an ideal situation (green condition) when all six variables are equal to 1.

$$\mathrm{VMR} = (1/\sqrt{6})\left[\sum_{j=1}^{6} (r_j)^2\right]^{1/2} \tag{12}$$

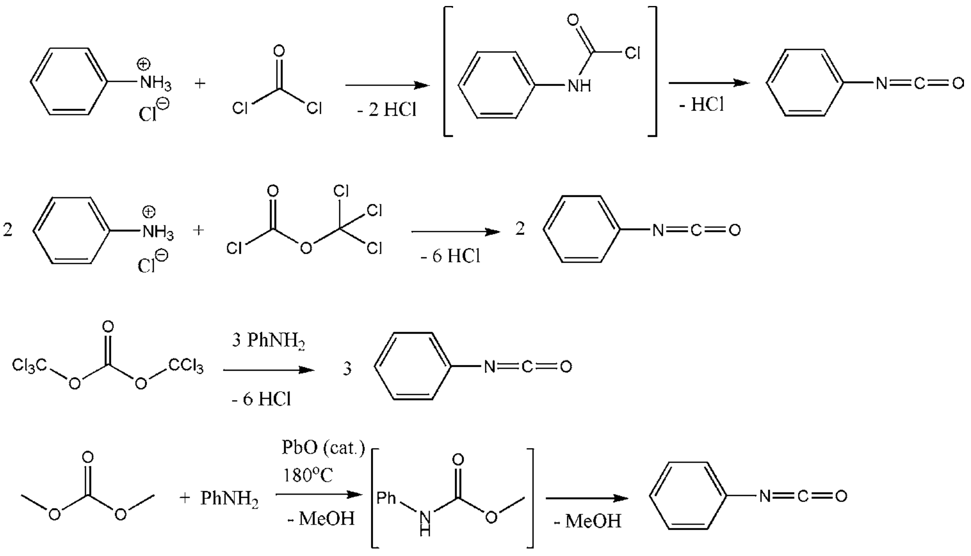
where r_j refer to atom economy, reaction yield, inverse of the stoichiometric factor (SF) that accounts for excess reagent consumption, auxiliary material recovery factor accounting for consumption of workup and purification materials, overall reaction mass efficiency (RME), and BI(waste).

Application to Synthesis Plans. BI(waste) parameters for synthesis plans were determined in the following way. All synthesis plans to a given target product were scaled to a common basis of 1 ton (907.2 kg) production. A scaling factor of 1 was assigned to the final reaction step in the sequence. Scaling factors for all preceding intermediates along the synthesis route were determined by working backwards from the final target product toward cradle starting materials. All three aniline plans and four out of five phenol plans originated from benzene, the fifth phenol route originated from toluene. The five aspirin plans followed the five routes to phenol. Using the radial hexagon spreadsheet algorithm applied to the final step in the linear sequence set for a basis mass of 1 ton of product, the masses of all waste materials were first determined along with the mass of limiting reagent corresponding to the product of the previous step. The same spreadsheet calculation was repeated for the previous step using experimental masses reported for all materials used and product collected. The scaling factor for this penultimate step was determined by taking the ratio of masses of limiting reagent from the final step and product collected from the penultimate step. This scaling factor was then multiplied by all masses of waste materials produced in that step to obtain adjusted masses. As an example, if 907.2 kg of aspirin is produced from 771.1 kg salicylic acid (limiting reagent) and 589.7 kg acetic anhydride, it is found that the waste materials consist of 75.6 kg each of unreacted salicylic acid and acetic anhydride plus 302.4 kg acetic acid byproduct. The experimental procedure for the prior step states that 907.2 kg salicylic acid is produced from 725.8 kg phenol. The scaling factor for the prior step is then 771.1/907.2 = 0.85. Then all masses of waste materials produced in this step will be multiplied by this factor. This process is repeated for each

Scheme 1. Synthesis routes to diphenyl carbonate



Scheme 2. Synthesis routes to phenyl isocyanate



reaction in the linear sequence until the starting material is reached. Once all of the masses of waste contributors for the entire sequence are determined and their environmental impact potentials assigned, eq 11c is then used to determine BI(waste). The Supporting Information contains a sample spreadsheet for the three-step Faith G1 synthesis of aspirin.

■ CHEMICAL REACTIONS: PHOSGENE VS NONPHOSGENE CHEMISTRY

In this section the syntheses of two important industrial commodity chemicals, diphenyl carbonate and phenyl isocyanate, are described and analyzed using the new methodology. Each compound is made using one of the following reagents: phosgene, diphosgene (trichloromethyl chloroformate), triphosgene (bis(trichloromethyl) carbonate), and dimethyl carbonate as shown in Schemes 1 and 2. The radial hexagons and parameter summaries for the reaction performances are shown in Figures 2 and 3 and Tables 2 and 3, respectively.

For the syntheses of diphenyl carbonate, the following observations can be deduced:

- The phosgene reaction has the least E_{kernel} and E_{total}.
- The DMC reaction has the highest E_{excess} since it is both a solvent and a reactant.
- The diphosgene reaction has the highest E_{aux} since it uses a significant volume of water in the workup giving it the highest E_{total}.
- Both the phosgene and DMC transformations show the greatest gains in BI.
- The DMC reaction has the least BI(waste) since there is a significant amount remaining after the reaction is over even when the theoretical limit in converting starting material to product is taken into account; the DMC reaction also has the lowest reaction yield and hence the lowest conversion of starting material to product.
- The phosgene reaction appears to have the highest material efficiency and also the highest overall VMR performance which includes environmental impact potentials.

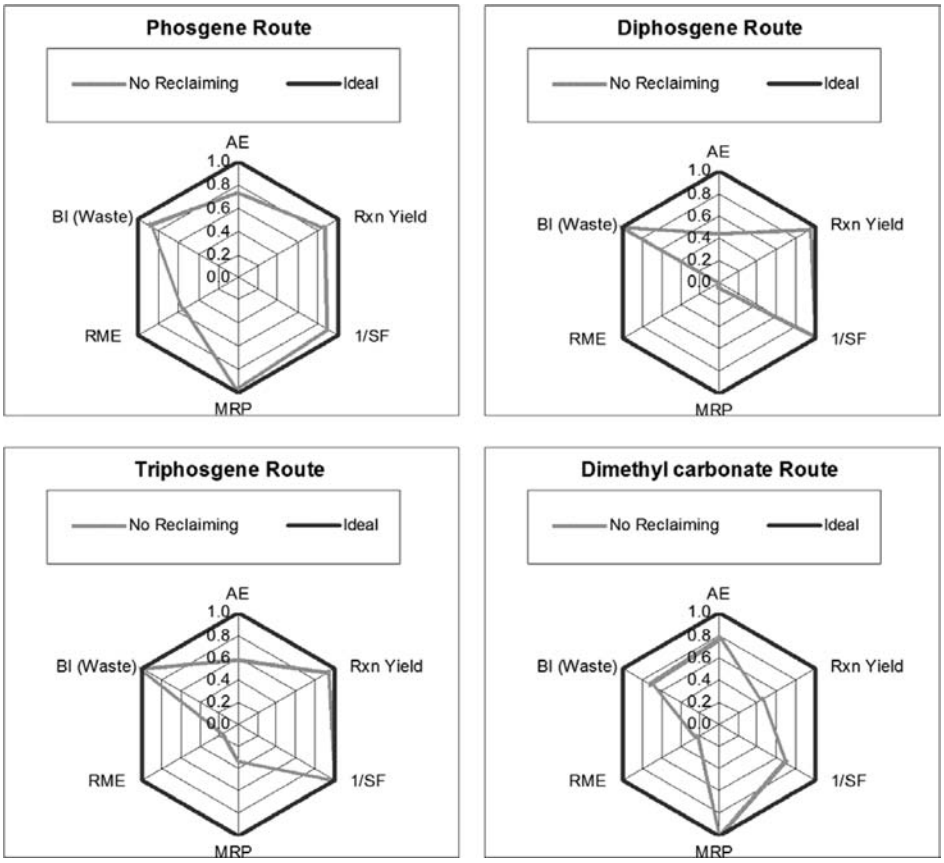


Figure 2. Radial hexagons for syntheses of diphenyl carbonate.

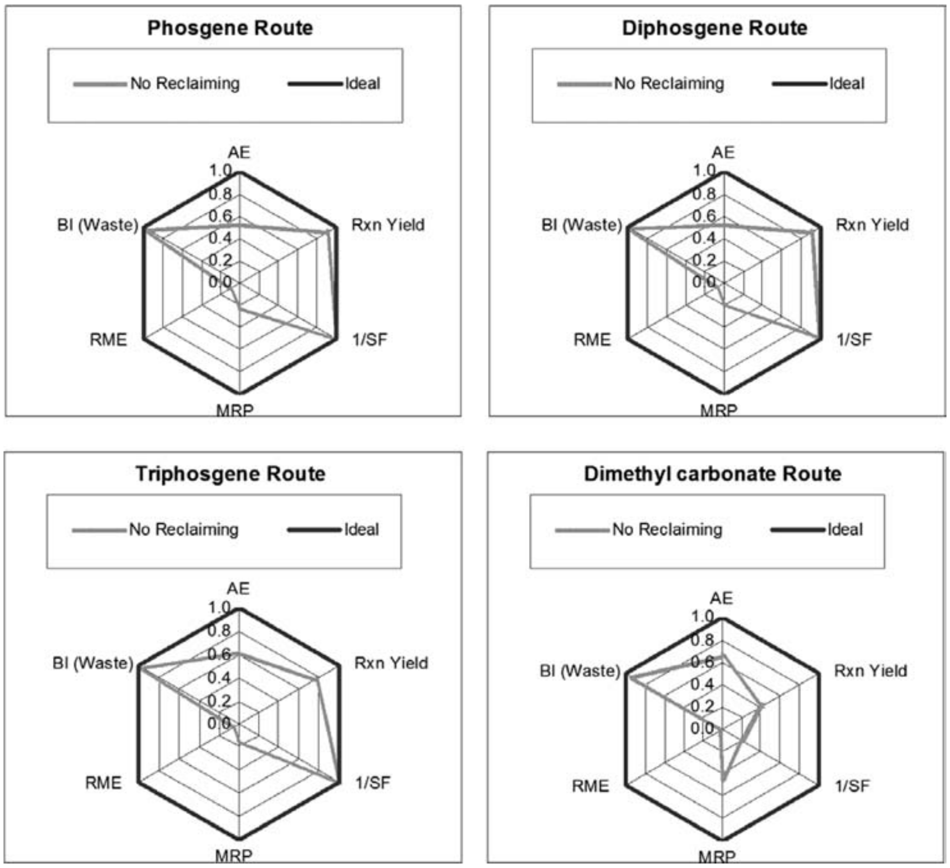


Figure 3. Radial hexagons for syntheses of phenyl isocyanate.

Table 2. Summary of E-factor and benign indices for industrial plans to diphenyl carbonate

route	E_{kernel}	E_{excess}	E_{aux}	E_{total}	BI input	BI output	% change	BI waste	VMR[f] (6-gon)
phosgene[a]	0.56	0.19	0.04	0.79	0.693	0.948	36.9	0.884	0.8306
diphosgene[b]	1.44	0.0076	61.1	62.55	0.989	0.997	0.8	0.997	0.7134
triphosgene[c]	0.85	0.0026	3.75	4.6	0.923	0.994	7.6	0.993	0.7443
DMC[d]	1.95	1.31	0.053	3.31	0.541	0.766	42.0	0.695	0.6806
DMC[e]	1.12	0.94	0.038	2.10	0.541	0.825	52.6	0.750	0.7176

[a] Used Henry's law constant and log K_{ow} values from *ChemDraw Ultra 7.0* for triphenoxyphosphine. [b] Missing LD_{50} and LC_{50} for triethylammonium chloride. [c] Missing K_{ow} for NaOH (assume 1×10^{-100}), assumed Henry's law constant of 1×10^{-100} for NaCl and NaOH; used log K_{ow} with respect to n-butanol instead of n-octanol for NaCl. [d] DMC = dimethyl carbonate; missing Henry's law constant for di-n-butyltin oxide; data based on a single reaction pass with a reaction yield of 44%. [e] Data based on maximum possible yield of product of 61% practically achieved after four reaction passes using same mass of di-n-butyltin oxide catalyst as for a single reaction pass. [f] VMR = vector magnitude ratio.

Table 3. Summary of E-factor and benign indices for industrial plans to phenyl isocyanate

route	E_{kernel}	E_{excess}	E_{aux}	E_{total}	BI input	BI output	% change	BI waste	VMR[c] (6-gon)
phosgene	1.13	0.0051	7.69	8.83	0.878	0.948	7.9	0.953	0.7120
diphosgene	1.18	0.025	9.75	10.96	0.908	0.949	4.5	0.970	0.7074
triphosgene	1.12	0.00042	11.96	13.08	0.916	0.940	2.6	0.964	0.6977
DMC[a]	2.64	14.87	22.30	39.81	0.915	0.962	5.3	0.929	0.5336
DMC[b]	1.51	10.25	15.36	27.11	0.915	0.956	4.5	0.932	0.5647

[a] DMC = dimethyl carbonate; assumed Henry's law constant of 1×10^{-100} for PbO, and K_{ow} of 1×10^{-100} for PbO; data based on a single reaction pass with reaction yield of 42%. [b] Data based on maximum possible yield of product of 61% practically achieved after four reaction passes using same mass of PbO catalyst as for a single reaction pass and recycling THF reaction solvent in each pass. [c] VMR = vector magnitude ratio

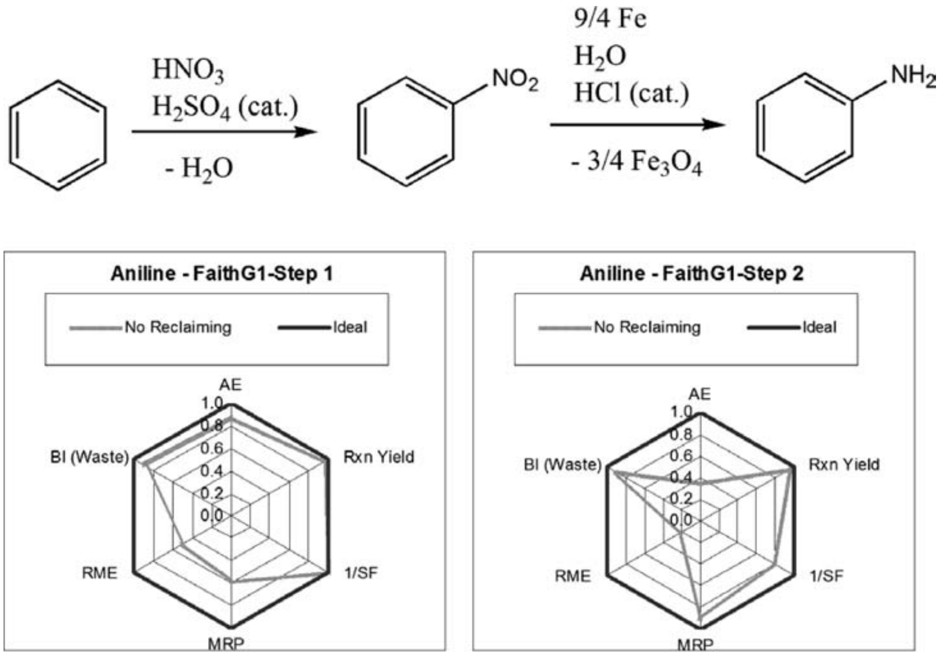


Figure 4. Synthesis of aniline via Faith G1 plan (Faith, W. L.; Keyes, D. B.; Clark, R. L. *Industrial Chemicals*, 3rd ed.; Wiley: New York, 1966; pp 101, 541; Shreve, R. N. *Chemical Process Industries*, 3rd ed.; McGraw-Hill Book Co.: New York, 1967; p 812).

For the syntheses of phenyl isocyanate, the following observations can be deduced:

- The phosgene reaction has the lowest E_{total}.
- The DMC reaction has the highest E_{total} with the highest contribution coming from E_{excess} (as in the case of the diphenyl carbonate synthesis, it is used as both a reagent and a solvent); it also has the highest E_{aux} contribution due to a significant volume of THF used as a reaction solvent.
- The DMC reaction has the lower reaction yield and conversion of starting material to product.
- Compared to diphenyl carbonate reactions the phenyl isocyanate syntheses show lower magnitude gains in BI, yet the phosgene reaction shows the highest difference between BI(out) and BI(in).
- The phosgene reaction again has the highest all round VMR performance.

■ SYNTHESIS PLANS: ANILINE, PHENOL, ASPIRIN

In this section, the results of industrial synthesis plans for aniline, phenol, and aspirin are summarized. Figures 4 to 6 show the radial hexagons for the synthesis of aniline from benzene by the following sequences: nitration−reduction with iron (Faith G1); nitration−reduction via hydrogenation (Faith G2); and chlorination−amination (Faith G3). Figure 7 shows both the

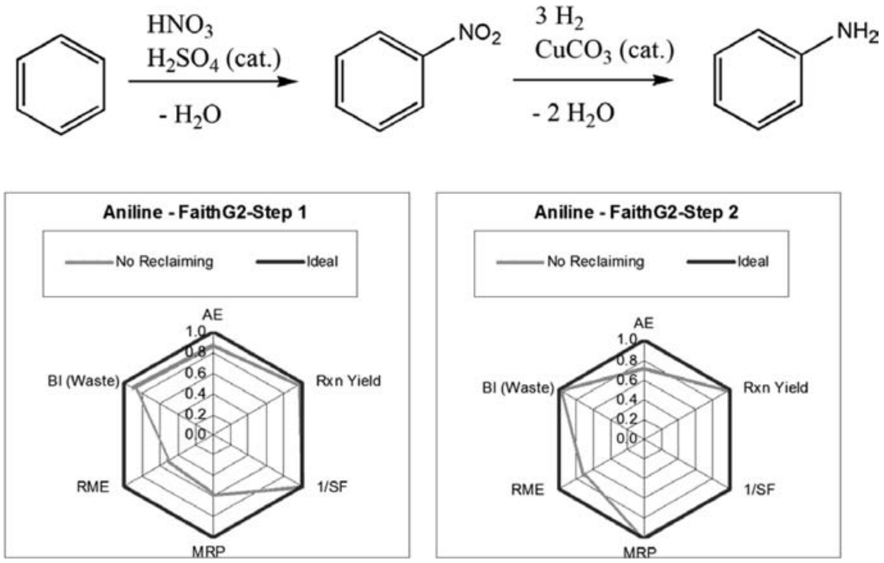


Figure 5. Synthesis of aniline via Faith G2 plan (Faith, W. L.; Keyes, D. B.; Clark, R. L. *Industrial Chemicals*, 3rd ed.; Wiley: New York, 1966; pp 101, 541; Shreve, R. N. *Chemical Process Industries*, 3rd ed.; McGraw-Hill Book Co.: New York, 1967; p 812).

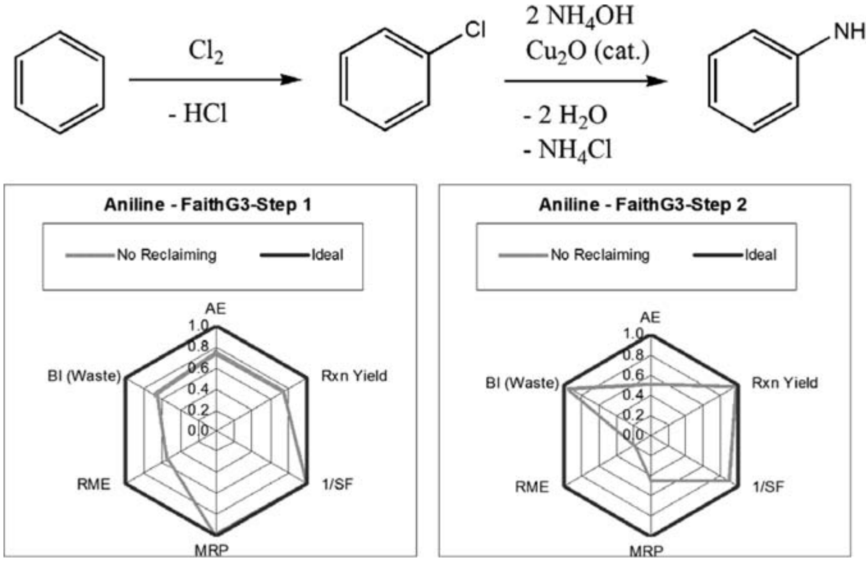


Figure 6. Synthesis of aniline via Faith G3 plan (Faith, W. L.; Keyes, D. B.; Clark, R. L. *Industrial Chemicals*, 3rd ed.; Wiley: New York, 1966; pp 101, 261; Shreve, R. N. *Chemical Process Industries*, 3rd ed.; McGraw-Hill Book Co.: New York, 1967; p 812).

environmental and *E*-factor profiles for these three routes. Table 4 summarizes the *E*-factor, BI, and VMR performances.

From these data the following observations can be made:

- Reaction solvents were significant for Faith G3.
- Catalyst consumption was significant for Faith G1.
- Reaction byproducts were significant for Faith G1.
- Faith G2 has the least unreacted reagents and has the lowest overall *E*-factor.
- The greatest contributing environmental impact potential for all three plans is INGTP.
- for Faith G1 (nitration–iron reduction of nitro group): INHTP for HCl catalyst in step 2, INGTP for unreacted iron in step 2, HCl catalyst in step 2, H_2SO_4 catalyst in step 1
- for Faith G2 (nitration–hydrogenation): INGTP for H_2SO_4 catalyst in step 1
- for Faith G3 (chlorination–substitution): INHTP for unreacted Cl_2 in step 1, INGTP for unreacted NH_4OH in step 2
- Faith G2 has the least overall environmental impact.

Scheme 3 summarizes the five routes to phenol from benzene or toluene: sulfonation–fusion with caustic soda, benzene sulfonate process (Faith G1), chlorination–substitution, caustic process (Faith G2), oxidative chlorination–hydration, Raschig process (Faith G3), cumene peroxidation, Hock process (Faith G4), and oxidation–decarboxylation (Faith G5). Figure 8 shows both the environmental and *E*-factor profiles for these five routes. Table 5 summarizes the *E*-factor, BI, and VMR performances.

From these data the following observations can be made:

- Faith G3 has the highest catalyst waste contribution.
- Reaction solvents are not used in any of the five plans hence there are no E-solvent contributions.
- Faith G1 has the highest byproduct contribution.
- Faith G3 has the highest unreacted reagents contribution and the least byproduct contribution.
- Faith G5 has the least *E*-factor overall.
- For all routes, INGTP again dominates the environmental impact potentials contribution.

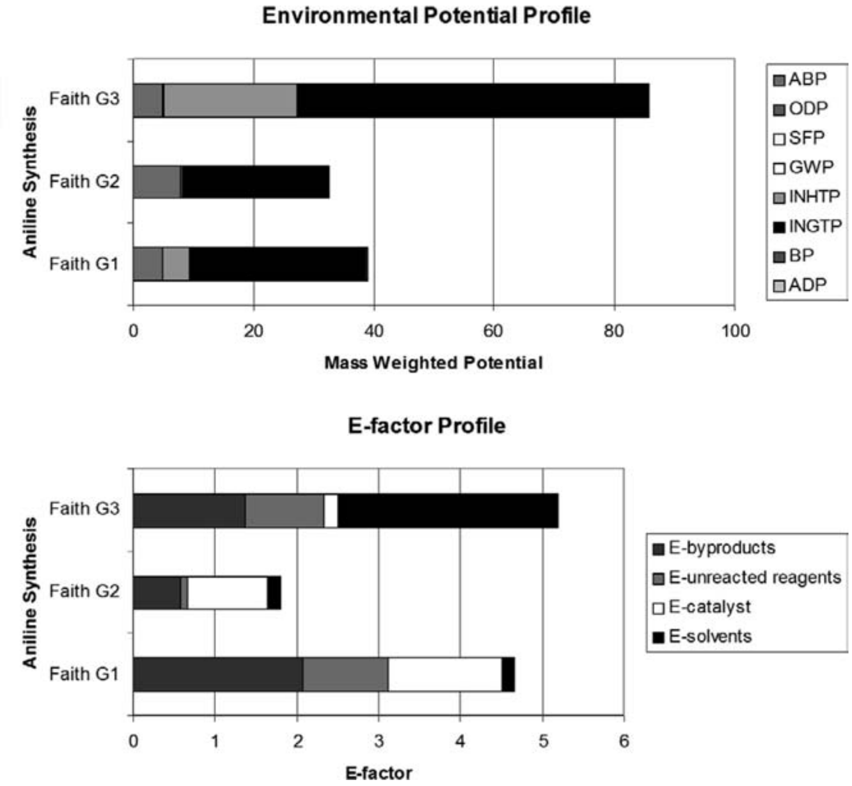


Figure 7. Environmental and *E*-factor profiles for three industrial synthesis plans to aniline.

Table 4. Summary of *E*-factor and benign indices for three industrial plans to aniline

route	E_{kernel}	E_{excess}	E_{aux}	E_{total}	BI input	BI output	% change	BI waste	VMR[b] (6-gon)
Faith G1									
nitration	0.18	0.00096	0.84	1.03	0.744	0.870	16.9	0.882	0.8228
reduction with Fe	2.01	0.85	0.38	3.24	0.754	0.853	13.1	0.890	0.7432
OVERALL	2.27	0.86	1.54	4.67				0.953	
Faith G2									
nitration	0.18	0.00096	0.84	1.03	0.744	0.870	16.9	0.882	0.8228
hydrogenation	0.42	0.00053	0.00075	0.42	0.766	0.612	−20.1	0.983	0.9075
OVERALL	0.66	0.0022	1.13	1.80				0.956	
Faith G3									
chlorination	0.81	0.011	0	0.83	0.520	0.845	62.5	0.668	0.7997
substitution	1.03	0.26	2.86	4.15	0.827	0.904	9.3	0.928	0.7158
OVERALL	2.04	0.28	2.85	5.17				0.938[a]	

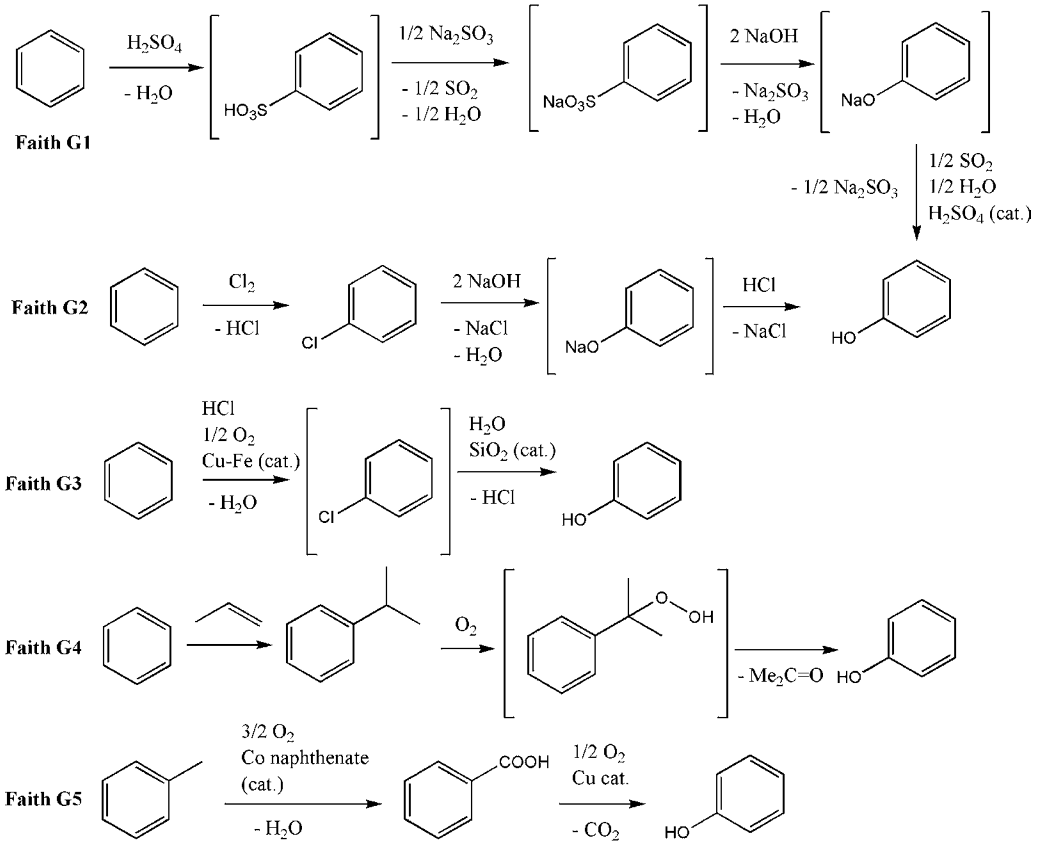
[a] Upper limit. [b] VMR = vector magnitude ratio.

- Faith G1 and G2 have by far the worst environmental impacts:
- for Faith G1 (sulfonation–fusion with caustic soda, benzene sulfonate process): INGTP for unreacted NaOH in step 1
- for Faith G2 (chlorination–substitution, caustic process): INGTP for unreacted NaOH in step 2, INHTP for unreacted Cl2 in step 1
- for Faith G3 (Raschig process, oxidative chlorination–hydration): INGTP for HCl catalyst in step 1
- for Faith G4 (cumene peroxidation, Hock process): INGTP for byproduct acetone in step 2, GWP for cumene and acetone in step 2
- for Faith G5 (oxidation–decarboxylation): INGTP for unreacted benzoic acid in step 2

Aspirin is synthesized from phenol as shown in Scheme 4. When this two-step sequence is linked to the five routes previously described for phenol, there are then five routes to aspirin to consider in the calculations. Figure 9 summarizes the environmental and *E*-factor profiles for the five industrial synthesis plans to aspirin where the route numbers correspond to the same order as those for phenol, i.e., Route 1 corresponds to Faith G1 for phenol plus the two steps shown in Scheme 4, etc. Figure 10 shows the difference profile of BI(out) − BI(in) with respect to reaction step number for each route and Table 6 summarizes the *E*-factor, BI, and VMR performances.

The performances of the five routes to aspirin parallel the five routes to phenol. As expected, INGTP is the highest contributing environmental impact potential. Route 3 has the least environmental

Scheme 3. Five industrial routes to phenol



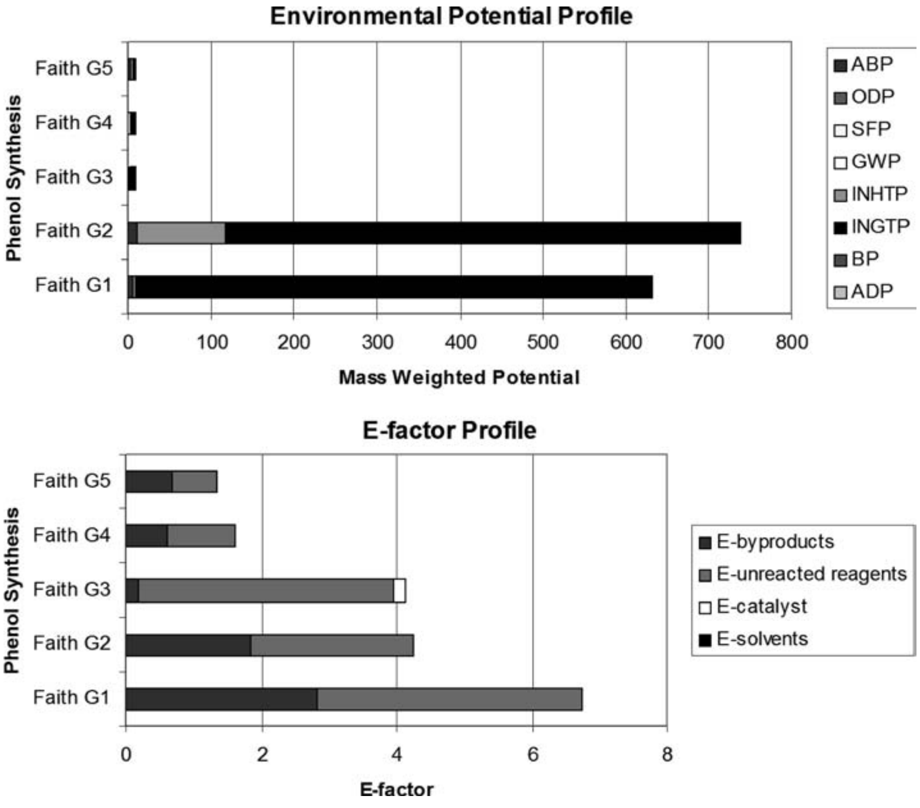


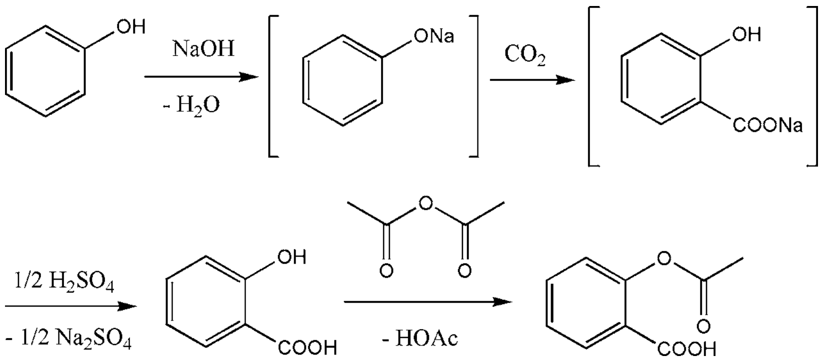
Figure 8. Environmental and *E*-factor profiles for five industrial synthesis plans to phenol.

Table 5. Summary of *E*-factor and benign indices for five industrial plans to phenol

route	E_{kernel}	E_{excess}	E_{aux}	E_{total}	BI input	BI output	% change	BI waste	VMR[b] (6-gon)
Faith G1									
sulfonation−alkoxidation	3.62	3.13	0	6.75	0.783	0.891	13.8	0.876	0.6947
Faith G2									
chlorination	0.81	0.89	0	1.7	0.357	0.697	95.2	0.519	0.7026
alkoxylation−acidification	1.54	0.59	0	2.13	0.573	0.830	44.9	0.761	0.7557
OVERALL	2.55	1.69	0	4.24				0.870[a]	
Faith G3									
chlorination−hydroxylation	0.58	3.37	0.19	4.14	0.979	0.931	−4.9	0.984	0.7236
Faith G4									
aromatic alkylation	0.23	0.0014	0	0.23	0.519	0.608	17.1	0.519	0.8747
peroxidation−Hock rearrangement	1.15	0.072	0	1.23	0.236	0.569	141.1	0.557	0.7522
OVERALL	1.56	0.073	0	1.63				0.740	
Faith G5									
oxidation	0.41	0.0046	0.0041	0.42	0.674	0.441	−34.6	0.791	0.8695
oxidation−decarboxylation	0.63	0.11	0.00075	0.74	0.882	0.745	−15.5	0.955	0.8553
OVERALL	1.21	0.12	0.0067	1.34				0.981[a]	

[a] Upper limit. [b] VMR = vector magnitude ratio.

Scheme 4. Synthesis of aspirin from phenol



impact, and Routes 1 and 2 have the highest environmental impact. The following observations can be made:

- Route 1: INGTP for unreacted NaOH in step 1.
- Route 2: INHTP for Cl_2 gas in step 1, INGTP for unreacted NaOH in step 2.
- Route 3: INGTP for unreacted NaOH in step 2.
- Route 4: INGTP for unreacted NaOH in step 3.
- Route 5: INGTP for unreacted NaOH in step 3.
- Reaction solvents do not figure in the *E*-factor profile for any of the routes.
- Route 3 has the least byproduct waste.
- Route 1 has the highest byproduct waste.
- Route 5 has the least unreacted reagent waste.
- Routes 1 and 3 have the highest unreacted reagent waste.
- Route 5 has the lowest *E*-factor overall closely followed by Route 4.
- Route 5 shows the greatest progressive positive changes in BI performance throughout the synthesis plan.
- Route 4 exhibits the greatest oscillation in BI differences.
- Route 2 shows a steady decline in BI performance for the first three reaction steps before bouncing back up in the positive direction.

DISCUSSION

The trends described in the previous section for the syntheses of diphenyl carbonate phenyl isocyanate are exactly the same as those described in an earlier analysis based on material efficiency alone.[14] However, when the analysis is extended to include environmental impact parameters, the BI results do not support the conclusion that the phosgene routes cause the greatest environmental harm. The routes using dimethyl carbonate which was selected as a phosgene replacement reagent, show two significant drawbacks: (a) they are energy intensive on two fronts—the first is in the preparation of the catalysts by calcination reactions at high temperatures (500 °C), and the second is in the distillation required in carrying out the reaction and separating the products; and (b) the respective radial hexagons shown in Figures 2 and 3 represent results based on a single reaction cycle to product. Since energy consumption was formally not included in this analysis from the outset, the first drawback has no effect on the results; however, the second drawback, which depends on material consumption, does. These reactions appear not to be material efficient since the conversion of starting material to product is low as a direct consequence of the reaction being reversible. Indeed, there is an expected increase in performance if the maximum yield is taken into account on the basis of repeating the reaction three more times

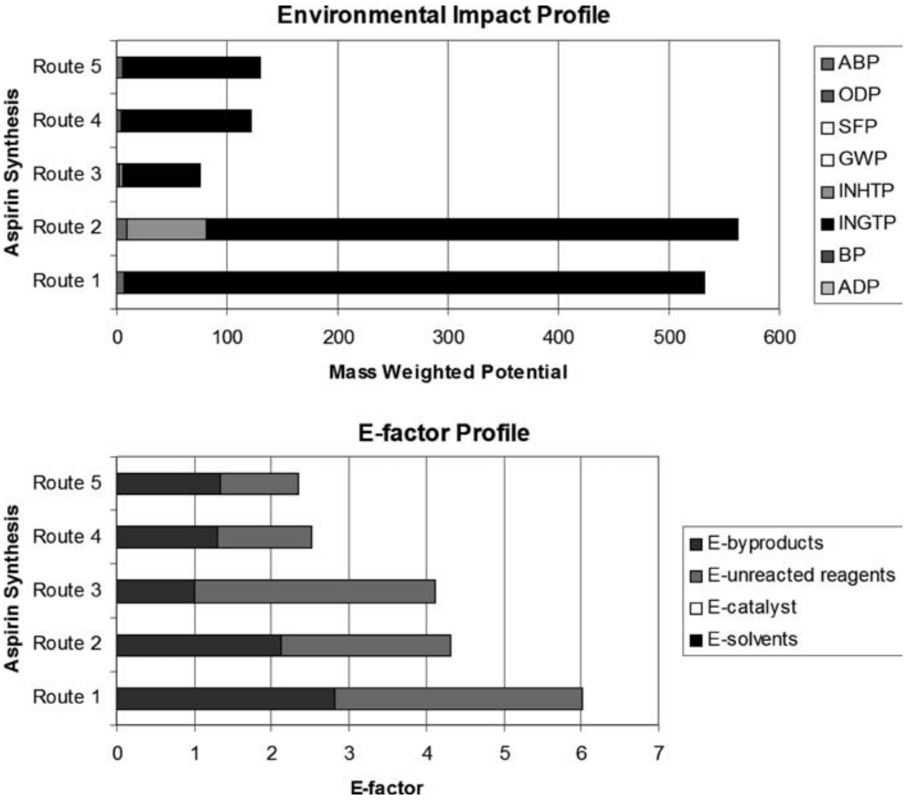


Figure 9. Environmental and *E*-factor profiles for five industrial synthesis plans to aspirin following five routes to phenol.

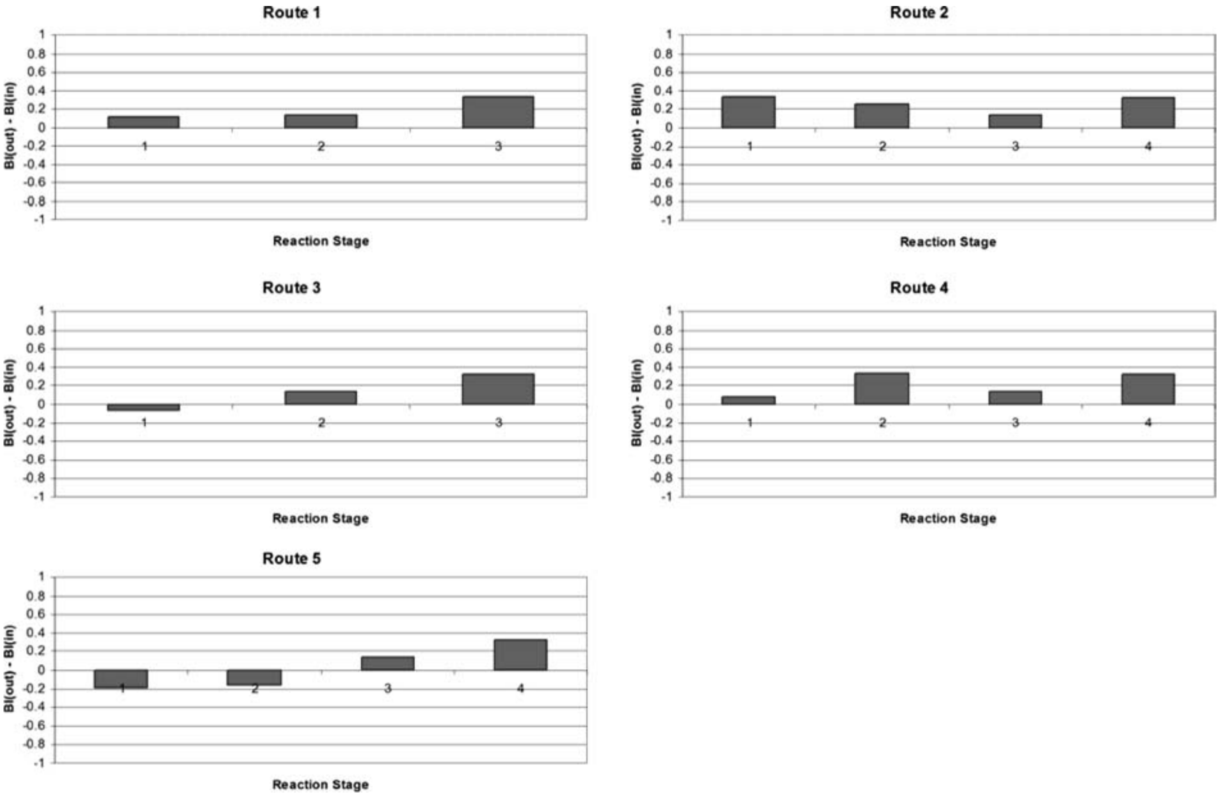


Figure 10. Difference profiles for BI(out) − BI(in) for five industrial plans to aspirin.

until practically all of the starting material is converted to the desired product (see last rows in Tables 2 and 3). On this point of conversion of starting materials to products, the phosgene reactions have very little unreacted phosgene left compared to those involving dimethyl carbonate and so the much greater mass of unreacted dimethyl carbonate amplifies its environmental impact. It is clear that the phosgene routes are more material efficient and more energy efficient and have less overall

Table 6. Summary of overall *E*-factor and benign indices for five industrial plans to aspirin

route	$E_{\text{byproduct}}$	$E_{\text{unreacted}}$	E_{aux}	E_{total}	BI waste
Route 1, Faith G1	2.81	3.21	0	6.02	0.950
Route 2, Faith G2	2.13	2.19	0	4.33	0.950
Route 3, Faith G3	1.01	3.11	0.19	4.25	0.987
Route 4, Faith G4	1.3	1.23	0	2.53	0.978
Route 5, Faith G5	1.34	1	0.00075	2.34	0.978

environmental impact based on the set of impact potentials examined, though it must be conceded that ozone depletion, global warming, and smog formation potentials used in this study for this compound are severely underestimated due to lack of available data (see Table S1 in Supporting Information). The presence of chlorine in this molecule will surely have nonzero values for these parameters. If these potentials are properly taken into account, it may reverse the conclusion that the phosgene routes are more benign than the dimethyl carbonate routes according to the BI calculation. Nevertheless, the real problem with avoiding phosgene is its notoriety as a chemical weapon and not so much that it is environmentally damaging. Its greatest impact is shown by its very low LC_{50} value for inhalation with respect to acute toxicity (0.0072 g/m^3, 4 h).[115] With respect to its persistence, its half-life in water is about 0.13 s.[116] Since it is a gas, it is quickly dispersed in the atmosphere, and its lifetime in air is expected to be short. The locations in Europe where it was used in great quantity in World War I have no trace of it in any of the four environmental compartments there, unlike pesticides or PCB residues which can linger for decades after the environment is exposed to them. Phosgene has, however, a great potential to be hazardous only if operators are not properly trained or slack off on safety procedures in using this substance in carrying out chemical reactions as illustrated by the recent phosgene leak accident at duPont's Belle, West Virginia, plant in 2010[117] which resulted in three workers being injured with one fatality. Here it is worth mentioning the circumstances surrounding this unfortunate occurrence. Phosgene was stored in one-ton tanks in a shed open to the atmosphere. This incident resulted as a consequence of not following proper maintenance procedures for the upkeep of storage tanks for this gas and of having large capacity storage tanks of this substance in the first place. This highly corrosive gas is known for attacking the material of gas lines. The braided metal hose made of Teflon-lined stainless steel is susceptible to corrosion by phosgene. According to the company's best practices such hoses are supposed to be replaced monthly. The one involved in the industrial accident had not been replaced for 7 months. A better material for gas hoses is Monel, a nickel alloy that is specific for corrosive substances. Moreover, phosgene is best made and used right away so that it is quickly transformed into other substances that are much safer to handle. This point is nicely illustrated by the positive differences found for BI(out) − BI(in) for the preparation of diphenyl carbonate and phenyl isocyanate from phosgene (see first rows in Tables 2 and 3). In fact, a positive difference is also found for the manufacture of phosgene itself from sulphuric acid and carbon tetrachloride according to the Grignard[118] and Erdmann[119] methods as shown by the results of Table 7. A negative difference, however, was found for the ferric chloride-catalyzed hydration of carbon tetrachloride using the Hill[120] method. The lesson of reducing or eliminating storage of hazardous chemicals was learned the hard way at Flixborough, UK, in 1974 when a chemical plant producing cyclohexanone from cyclohexane and cyclohexanol for nylon production was leveled killing 28 people.[121] Explosions were propagated due to ignition of stockpiles of flammable cyclohexane solvent in storage facilities on site. The key issue exemplified by the present analysis is that potential to cause environmental harm is a different matter from occupational safety/hazard concerns. When used responsibly and safely with proper training of personnel and proper upkeep of equipment, the risk profile of hazardous compounds such as phosgene can be dramatically reduced. From a green chemistry perspective, it is true that avoidance of toxic or hazardous reagents is the best option. However, this almost always comes at a price since chemistry is a science of compromise. A reviewer has pointed out that "relying on administrative controls as opposed to engineering or designing out process safety risks through elimination, substitution, or minimization principles is a recipe for accidents to occur." In the case of phosgene vs dimethyl carbonate the trade-offs are in the different safety profiles, consumption of energy, and maximum conversion of starting material to product in a single reaction cycle.

The results and conclusions reported here for phosgene- vs nonphosgene-based reactions may be directly compared with prior work reported by Aresta and Galatola[56] on two reaction pathways leading to dimethyl carbonate. Their analysis of a urea vs phosgene route to this target molecule showed that the phosgene route was both less material- and less energy-efficient in direct contrast with the conclusions of the present investigation albeit for different target molecules. This may be explained by noting that their analysis included both material and energy consumption consistent with a more complete LCA. The authors noted, however, that they had to make significant assumptions about energy consumption because of lack of available data. More significantly, with respect to material consumption, the reaction networks used for both routes were extrapolated all the way back to nonrenewable petrochemical feedstocks, again consistent with an LCA. Both routes traced back to C_xH_y hydrocarbons and methanol as common starting materials.

With respect to the overall trends in the syntheses of aniline, phenol, and aspirin the following conclusions may be drawn. In the aniline syntheses, the nitration−hydrogenation sequence is clearly the most material efficient; however, there is little overall difference in environmental impact between this sequence and the competing nitration−iron reduction. The chlorination−fusion with caustic soda sequence is easily ruled out as the least

Table 7. Summary of *E*-factor and benign indices for three routes to phosgene

route	E_{kernel}	E_{excess}	E_{aux}	E_{total}	BI input	BI output	% change	BI waste	VMR[c] (6-gon)
Grignard[a]	1.72	0.04	0.73	2.49	0.655	0.716	29.8	0.722	0.7339
Erdmann[a]	1.83	0.70	0	2.52	0.494	0.719	41.8	0.708	0.7339
Hill[b]	0.93	3.10	0.41	4.44	0.909	0.820	−9.7	0.863	0.6980

[a] $H_2SO_4 + CCl_4 \rightarrow COCl_2 + 2\ HCl + SO_3$; assume HLC = 1×10^{-100} for SO_3 and H_2SO_4; assume log $K_{ow} = -1 \times 10^{100}$ for SO_3. [b] $H_2O + CCl_4 \rightarrow COCl_2 + 2\ HCl$, catalyzed by $FeCl_3$; assume log $K_{ow} = -1 \times 10^{100}$ for $FeCl_3$. [c] VMR = vector magnitude ratio.

material efficient and causing the greatest environmental impact. In the phenol syntheses, the most material efficient routes are the toluene oxidation−benzoic acid decarboxylation−oxidation sequence followed closely by the Hock process. The former route is also the most benign followed closely by the benzene chlorination−hydroxylation route (route G3). Routes G1 and G2 are clearly ruled out as being worst performers on both material efficiency and environmental impact counts. Since the synthesis of aspirin depends on the synthesis of phenol, it is obvious that the best performing route will be governed largely by the best performing phenol route. However, there is a bit of a compromise in choosing between the overall most material efficient route (route G5) and the overall most benign route (route G3). Reaction solvents play a role in contributing to the waste profile in the aniline routes but not at all in the phenol and aspirin routes. Surprisingly, in all synthesis routes examined the ingestion toxicity potential (INGTP) made the greatest contribution to overall environmental harm compared to the other impact potentials. The inhalation toxicity potential (INHTP) which would be expected to be important for occupational health and safety for chemical workers in the plant was found to be insignificant for the synthesis plans examined. More startlingly, potentials related to climate damage (ODP, SFP, GWP) had the least contribution. This is because these potentials are grossly underestimated due to lack of available data for the compounds considered in the synthesis plans examined here. Also, since energy consumption was not included in the analysis (see "Limitations" subheading under Methodology section) in the form of CO_2 equivalents, the GWP contribution was necessarily lowered. Life cycle assessments can evaluate trade-offs between energy and materials, comparing for example a low-temperature process releasing toxic emissions vs a high-temperature process releasing nontoxic emissions. The production of energy will itself produce toxic emissions that need to be counted. Such trade-offs, however, must be taken with caution since intrinsic efficiencies of apparatuses used in chemical processes are explicitly not taken into account in energy calculations, which typically only consider thermodynamic parameters such as free energy (ΔG) and heat of reaction (ΔH). The trade-offs may be more believable for chemical processes producing first- and second-generation feedstocks from nonrenewable petrochemical resources, but much less so for syntheses of fine chemicals and intermediates, as described here, that would be made further along the manufacturing/supply chain of commodity chemicals (see Limitations subsection under Methodology). Literature data on ODP, SFP, and GWP are restricted mainly to CFCs (chlorofluorocarbons) and other simple halogen containing hydrocarbons and simple aliphatic and aromatic hydrocarbons. Clearly, the compilation of these potentials needs to be significantly expanded to include the full set of chemicals commonly used in the chemical industry. For all synthesis plans examined, the percent contribution of the newly defined acidification−basification potential (ABP) to overall environmental impact is found to be on average an order of magnitude higher than that of AP according to the previous definition.

There are several problems, discrepancies, and inconsistencies with respect to environmental potentials that impact on the present BI calculations and ultimately in decision making based on reaction or plan greenness. The BI results and conclusions made in this work are based on the best currently available data and are open to revision upon future findings that address the limitations and assumptions pointed out in the Methodology section. Kollig[122−124] and others[125−128] describe the kinds of questions one needs to ask about assessing the reliability of published data on environmental process constants. Figure 11 shows the interdependence of two key physical parameters; namely, K_{ow} (octanol−water partition coefficient) and HLC (Henry's law constant), on the calculation of various impact potentials that are necessary to carry out a basic environmental impact assessment. The strong links make it imperative that these particular parameters are reliably determined otherwise incorrect decision making will result. A call for making a universally accessible database containing reliable experimentally determined K_{ow} values has already been made,[129−137] particularly by scientists at the U.S. Geological Survey. Similar concerns were raised with respect to K_{oc} (organic carbon−water partition coefficient).[138] For the sake of clarity, the following discussion will be divided into subsections that will highlight issues related to specific physical constants and environmental potentials.

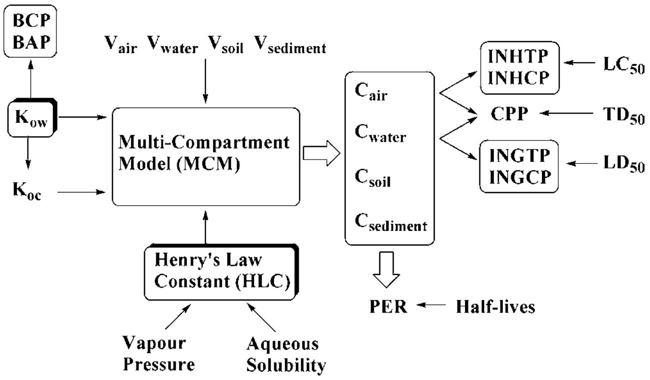


Figure 11. Diagram showing interdependence of various environmental impact potentials on core physical parameters K_{ow} and Henry's law constant (HLC).

General Comments about Environmental Impact Parameters. Most source data needed for environmental impact assessments are restricted to hydrocarbons (aliphatic and aromatic), halogenated hydrocarbons (CFCs, HFCs, and PCBs), pesticides, simple alcohols and amines, simple inorganics (acids and bases), and gases. Fine chemicals used by the pharmaceutical industry would be considered too exotic to apply a thorough analysis based on real experimental data as is done in the present work. Generally, more difficulties will be encountered the longer a synthesis plan is and the more complex the target product structure is. For example, based on the method described in this work a similar analysis of ibuprofen syntheses would have more gaps than those found for aspirin. When such problems arise, QSAR modeling programs[139,140] or other graph theoretical methods[86,141] based on functional group contributions obtained from correlations of training data sets are used to estimate missing variables, such as K_{ow} using Hansch's procedure.[142−144] Analyses done this way require significant assumptions and guesses to be made for key parameters, especially for intermediates along a synthesis path, which ultimately results in a high uncertainty in decision making.

The following points are made regarding key impact potentials:

- ABP relies on reliable K_a and K_b values for acids and bases respectively.
- ODP data only exist for chlorofluorocarbons by and large and need huge expansion to include effects from all main industrial feedstock compounds.

Table 8. Comparison of GWP values using simple eq S24 and integrated eq S25 (see Supporting Information)

substance	formula	# C atoms	MW (g/mol)	GWP[a]	GWP[b]
carbon dioxide	CO_2	1	44	1	1
carbon tetrachloride	CCl_4	1	153.8	0.29	1300
CFC-11	CCl_3F	1	137.35	0.32	3400
CFC-113	CCl_2FCClF_2	2	187.35	0.47	4500
CFC-114	$CClF_2CClF_2$	2	170.9	0.51	7000
CFC-115	CF_3CClF_2	2	154.45	0.57	7000
CFC-12	CCl_2F_2	1	120.9	0.36	7100
CFC-13	$CClF_3$	1	104.45	0.42	13000
chloroform	$CHCl_3$	1	119.35	0.37	25
dichloromethane	CH_2Cl_2	1	84.9	0.52	9
HALON-1211	$CBrClF_2$	1	165.35	0.27	4900
HALON-1301	$CBrF_3$	1	148.9	0.30	4900
HCFC-123	$C_2F_3HCl_2$	2	152.9	0.58	90
HCFC-124	C_2F_4HCl	2	136.45	0.64	440
HCFC-141b	$C_2FH_3Cl_2$	2	116.9	0.75	580
HCFC-142b	$C_2F_2H_3Cl$	2	100.45	0.88	1800
HCFC-22	CF_2HCl	1	86.45	0.51	1600
HFC-125	C_2HF_5	2	120	0.73	3400
HFC-134a	CH_2FCF_3	2	102	0.86	1200
HFC-143a	CF_3CH_3	2	84	1.05	3800
HFC-152a	$C_2H_4F_2$	2	66	1.33	150
methane	CH_4	1	16	2.75	21
nitrogen oxides	NO_x	0		0	40
nitrous oxide	N_2O	0	44	0	310
perfluorobutane	C_4F_{10}	4	238	0.74	7000
perfluorocyclobutane	$c\text{-}C_4F_8$	4	200	0.88	8700
perfluoroethane	C_2F_6	2	138	0.64	9200
perfluorohexane	C_6F_{14}	6	338	0.78	7400
perfluoromethane	CF_4	1	88	0.50	6500
perfluoropentane	C_5F_{12}	5	288	0.76	7500
perfluoropropane	C_3F_8	3	188	0.70	7000
sulfur hexafluoride	SF_6	0	146	0	23900
1,1,1-trichloroethane	CH_3CCl_3	2	133.35	0.66	100

[a] Based on carbon count and MW relative to CO_2. [b] Data taken from Allen and Shonnard's book Appendix D.[86]

- SFP data also need to be expanded to include industrial feedstocks; composition of ROG (reactive organic gases) used as a reference is not explicitly specified in the vast volume of accessible literature pertaining to this parameter (see Supporting Information for an approximate percent composition).
- GWP: eq for indirect GWP (see eq S24 in Supporting Information) grossly underestimates the impact of this parameter; Table 8 compares results for halogenated hydrocarbons by the integration relation (eq S25 in Supporting Information) and the simple formula based on number of carbon atoms and molecular weight (eq S24); since use of eq S24 is a serious handicap in determining GWP, the range of chemicals needs to be significantly expanded to include industrial feedstocks beyond the usual list of well-known chemicals that have been designated as greenhouse gases.
- INGTP, INGCP, INHTP, INHCP, CCP: LC_{50}, LD_{50}, and TD_{50} data need to be significantly expanded to cover all industrial feedstocks; validity of linear extrapolation formula (see eq S29 in Supporting Information) for inhalation data; limited oral and inhalation slope factors available to estimate reliable cancer potentials calculations; not all compounds are referenced to rats inhalation or rats ingestion.
- MCM model: main limitations are arbitrarily chosen volumes of compartments (Mackay[104−109] uses one set of data, whereas Allen and Shonnard[86] use another which differs by a factor of 10); final concentrations of chemicals in all four compartments are highly sensitive to input HLC and K_{ow} values; based on arbitrary release of 1000 kg of material.
- ARDP: it is unclear why antimony is selected as the reference element (see Supporting Information).
- EDP: data are limited to estrogen-like molecules and famous compounds such as bisphenol A; a massive amount of work is needed to include industrial feedstocks.
- BCP: formula based only on K_{ow} (see eq S32 in Supporting Information) may be too simplistic since it ignores specific biological species; other formulas for bioconcentration factor are based on various fish species, mainly the fathead minnow.[104]
- PER: literature half-life data are available for pesticides only; these compilations of data on soil persistence do not specify soil type or a soil reference; results will obviously depend on various soil parameters;[146] a massive amount of work is needed to include industrial chemical feedstocks.

Octanol−Water Partition Coefficients. As discussed earlier K_{ow} is a central parameter in environmental impact calculations. Compared to Henry's law constants it would appear

Table 9. Comparison of Henry's law constants for various gases at 20 °C

chemical	vapour pressure (atm)[a]	aqueous solubility (mol/L)[b]	calculated HLC (atm m^3/mol)[c]	HLC from tables (atm m^3/mol)[d]	% maximum discrepancy[e]
acetylene	4.27×10^1	4.04×10^{-2}	1.06	2.33×10^{-2}	4.43×10^3
ammonia	8.40	2.59×10^1	3.24×10^{-4}	1.51×10^{-5}	2.05×10^3
n-butane	2.07	1.25×10^{-3}	1.66	9.15×10^{-1}	8.11×10^1
carbon dioxide	5.64×10^1	3.42×10^{-2}	1.65	2.32×10^{-2}	7.01×10^3
chlorine	6.68	1.05×10^{-1}	6.36×10^{-2}	1.13×10^{-2}	4.63×10^2
ethane	3.71×10^1	1.89×10^{-3}	1.96×10^1	2.61×10^{-1}	7.42×10^3
hydrogen sulfide	1.81×10^1	1.03×10^{-1}	1.76×10^{-1}	1.03×10^{-2}	1.60×10^3
isobutane	3.00	9.22×10^{-4}	3.26	1.18	1.76×10^2
nitrous oxide	5.04×10^1	2.43×10^{-2}	2.08	5.26×10^{-1}	2.95×10^2
n-propane	8.25	1.52×10^{-3}	5.43	6.95×10^{-1}	6.81×10^2
sulfur dioxide	3.30	1.40	2.36×10^{-3}	7.29×10^{-4}	2.23×10^2

[a] Data taken from Daubert and Danner's compilation. [b] Data taken from *Lange's Handbook of Chemistry* (1961)[148] and *CRC Handbook of Chemistry and Physics* (2011–2012).[149] [c] Calculated as ratio of vapour pressure and aqueous solubility. [d] Average values taken from data found in Excel file in Supporting Information. [e] Calculated as 100*(|calc HLC − exp. HLC|)/min(calc HLC, exp. HLC).

to be operationally easier to measure the partitioning of a compound between two liquid phases (water and octanol), rather than between a liquid (water) and a gas (air) phase. Several errors in log K_{ow} data for inorganic substances compiled in the U.S. EPA list are found in EPA-600-R-94–177. For inorganic substances log K_{ow} are entered as 0 which implies $K_{ow} = 1$, that is, the substances are equally soluble in water and *n*-octanol. Clearly this conclusion is not true. What was meant was that $K_{ow} = 0$ since the solubility of inorganic substances is very large compared to that of *n*-octanol. Hence, log K_{ow} would be negative infinity. Also, a code of "−99" was entered for a few cases, but this was left undefined.

Henry's Law Constants. The Henry's law constant (HLC) is defined by eqs S40–S43 given in Table S2 of the Supporting Information. When expressed in dimensionless form, it represents the equilibrium ratio of concentrations of a substance in air vs water. In units of atm m^3 per mole it corresponds to the ratio of vapour pressure of a compound in air vs its solubility in water. The ratio definition poses four problematic scenarios in the experimental determination of HLCs pertaining to limiting cases of volatility and solubility properties of substances: (a) compounds with very high vapour pressures and very high water solubilities (e.g., fuming acids such as sulfuric acid or volatile organic solvents that are hydrophilic such as small alcohols, where limiting HLC (infinity/infinity) → 1); (b) compounds with very high vapour pressures and very low water solubilities (e.g., gases, where limiting HLC (infinity/0) → very large); (c) compounds with very low vapour pressures and very high water solubilities (e.g., inorganic salts, where limiting HLC (0/infinity) → very small); and (d) compounds with very low vapour pressures and very low water solubilities (e.g., nonvolatile hydrophobic molecules such as PCBs, where limiting HLC (0/0) → 1). The best scenario for a contaminant, from an environmental perspective, is that it should preferably be very volatile and/or highly water-soluble since this implies low persistence in the environment. An increase in water solubility facilitates dilution to low-level concentrations in the water compartment which in turn facilitates breakdown by various chemical or biological means, whereas an increase in volatility facilitates dispersal in the atmosphere again by dilution. Available data for gases illustrate the problem of determining reliable HLCs. Table 9 summarizes vapour pressure and solubility data and compares HLC values obtained by simply taking their ratio with those obtained by direct measurement. It is clear that data for vapour pressure taken from the Daubert compilation[147] and solubility data taken from *Lange's Handbook*[148] and the *CRC Handbook of Chemistry and Physics*[149] yield ratios that do not agree well with values obtained from HLC compilations found elsewhere. This suggests that estimations of HLC made by simply taking the ratio of separately determined vapour pressure and aqueous solubility data are crude at best. Whenever possible, reliable HLC data obtained from direct experimental methods such as static headspace methods[150,151] or EPICS (equilibrium partitioning in closed systems)[152] should be used. The former option should be made only when experimental data are not available in the literature.

Mackay[153] gives a brief discussion of errors in HLC measurements suggesting that the best achievable error is 10%. Dunnivant and co-workers[154] have noted that "HLCs obtained from indirect methods require validation with direct measurement techniques prior to acceptance". Experimental methods of HLC determination that involve extraction methods are subject to material losses. Gossett[155] lists the following drawbacks with various experimental methodologies: (a) use of vapor pressure and solubility data: drawback is the lack of reliable solubility data; (b) direct measurement of air and aqueous concentrations in a system at equilibrium: drawback is the difficulty in obtaining accuracy at the low concentrations typical of environmental levels; and (c) measurement of relative changes in concentration within one phase, while effecting a near-equilibrium exchange with the other phase: drawback is that there are experimental deficiencies in achieving adequate approach to equilibrium. Kieckbusch and co-workers[156] point out that dimensionless HLCs obtained by flame ionization GC (gas chromatography) are "greatly affected by sorption phenomena during sampling and during injection of vapour and liquid phases into the GC apparatus particularly for dilute solutions of organic solutes". The error is particularly high for determination of concentrations from the vapour phase. Moreover, the choice of syringe needle can also significantly affect measurements. Ten Hulsher and co-workers[157] remark that, when HLCs are estimated from data on vapour pressure and aqueous solubility, "erroneous values may be obtained if vapor pressure and solubility data do not refer to the same state". They also suggest that more reliable values may be obtained by measuring HLC directly though they concede that obtaining equilibrium concentrations for hydrophobic compounds, such as PCBs and pesticides, having low water solubilities and low partial pressures is difficult. This would correspond to the fourth limiting case discussed earlier.

In the present study two problematic cases were encountered for the HLCs of aniline and nitric acid. For aniline, the value 14 kPa m^3/mol or 0.14 atm m^3/mol reported in the *CRC Handbook of Chemistry and Physics*[158] is incorrect. *Mackay's Handbook*[104] lists this value along with 2.28×10^{-6} atm m^3/mol (see Vol. 4, p 3243). Verschueren[159] and Howard and Meylan[160] give 1.08×10^{-6} atm m^3/mol and 1.90×10^{-6} atm m^3/mol, respectively. A value of 2.30×10^{-6} atm m^3/mol is calculated from a vapour pressure of 0.0875 kPa given in *Mackay's Handbook*[104] and an aqueous solubility of 1 g/28.6 mL given in the *Merck Index*.[161] The value used in this study was 1.90×10^{-6} atm m^3/mol taken from Howard and Meylan's extensive compilation since this was judged to be most reliable for key constants necessary for environmental fate analysis. Unlike aniline, the case of nitric acid could not be resolved because there was only one literature source that could not be verified elsewhere. Sander's compilation[162] gives $1/H = 7.77 \times 10^5$ mol/L atm which can be converted to $H = 1.29 \times 10^{-6}$ atm L/mol $= 1.29 \times 10^{-9}$ atm m^3/mol. By using this value the half-life of nitric acid in water based on the methodology described by Lyman[163] works out to be 91.8 years, whereas the half-life in soil based on Briggs' equation[164] is 1.96×10^{-4} h. Though Sander's compilation is extensive, the data should be taken with caution since they are expressed in reciprocal form which may contain errors in computation.

Toxicity Data. EPA data with respect to LD_{50} and LC_{50} parameters are generally higher in magnitude than those reported in RTECS. Tables S3 and S4 in the Supporting Information list LD_{50} and LC_{50} values, respectively, that are common to both compilations. The results show that 71/126, or 56%, of the compounds listed in Table S3 are ranked by U.S. EPA as being less toxic than RTECS according to LD_{50}, and that 37/93, or 40%, of compounds listed in Table S4 are ranked by U.S. EPA as being less toxic than RTECS according to LC_{50}. It appears that RTECS is stricter with respect to LD_{50} data, whereas U.S. EPA is stricter with respect to LC_{50} data. In this work whenever multiple values were encountered for a given compound for either acute toxicity parameter, minimum values were selected from both databases to reflect maximum toxicity. Data taken from the *Merck Index*[161] are less reliable than either U.S. EPA or RTECS databases. For example, for aniline: LD_{50} = 250 (RTECS), LD_{50} = 440 (Merck Index), and LD_{50} = 250 (U.S. EPA EPA-600-R-94−177) mg/kg, respectively. The linear relationship (see eq S29 in Supporting Information) used to convert LC_{50} data given at one time frame to another does not always work. For example, RTECS reports the following LC_{50} data for 1,1,1-trichloroethane: 14250 ppm (7 h); 17000 ppm (4 h); 20000 ppm (2 h). Equation S29 yields $14250 \times (7/4) = 24938$ ppm and $20000 \times (2/4) = 10000$ ppm, respectively when the first and third data entries are converted to the 4-h exposure time, which are different from the second entry. If this compound is encountered, it is advisible to use the 17000 ppm figure for LC_{50} since it is an experimentally determined value at the standard exposure time of 4 h. (Equation S29) would be used only when no LC_{50} data are available for a 4-h exposure.

Persistence Data. The U.S. Department of Agriculture acknowledges that half-life data for pesticides are difficult to pin down since there are too many variables in soil that can affect the half-life of a compound, there is no standard soil sample that is used as a reference, and there is a great variation in soil types.[165] The persistence parameter is unique because it is the only potential that describes the length of time that all environmental impacts of a given chemical will last. The Boelthing index[166] based on atom groupings cannot be considered reliable since it completely ignores the expectation that persistence of a compound will be different in each of the four compartments: air, water, soil, and sediment. Thorough and reliable half-life data are not available for standard industrial chemicals in each of these compartments. Moreover, when data are available, discrepancies abound. For example, half-life data available for toluene are as follows: Allen and Shonnard[86] (air - 17 h; water - 550 h; soil - 1700 h; sediment - 5500 h) vs Mackay[104] (air - 1.9 d; water - 96−528 h; soil - 96−528 h; sediment - no data given). The environmental parameter database given in Microsoft Excel format in the Supporting Information lists persistence estimates for a few chemicals, mainly pesticides.

Effect of Missing Data. Encountering missing data probably has a more devastating impact on analyses of synthesis plans than having unreliable data. In the present work, it is expected that missing data for impact potentials related to climate damage (ODP, SFP, and GWP) severely underestimates overall BI results and gives a skewed distribution for the overall environmental impact profile as shown in Figures 7, 8, and 9. The fairness of comparisons will clearly be compromised. The exclusion of energy consumption in the present analysis will have a significant effect on the GWP contribution. Those plans with unknown quantities will be artificially ranked as more benign than those that have actual data inputs. One is faced with an all or nothing proposition—it is better to choose complete sets of input data to ensure fair comparisons of reaction or synthesis performances.

QSAR Modelling vs Experimental Data. Most papers on computer modelling justify their approach by stating that 58,000 industrial chemicals are routinely used with only about 5000 having some kind of experimental data sets for environmental fate constants. It is generally acknowledged that there is an urgent need to speed up the process of assigning values in order for any kind of environmental assessment to be implemented at low cost. Hence, current research in environmental science is heavily favored toward QSAR modelling to try to meet this challenge. Though QSAR modelling has been successful, it has also been criticized.[167−170] Typically, small-sized training sets based on limited experimental data are used to generate correlation equations between parameters having the form of Collander log−log plots.[171] These are then used to obtain environmental parameters, by extrapolation, for new or unknown compounds having no experimental data. Extrapolations are bound to fail, the more exotic the structures of compounds are from the training set. This is reminiscent of the problem encountered with linear free energy relationships (Hammett etc.) when they were used for explaining mechanistic trends in reactions that were very different structurally from the reference reactions on which the substituent constants were first derived. This resulted in the development of several sets of substituent constants describing different electronic effects, and then when these were still insufficient, multivariable regression data fitting according to linear combinations of these parameters was used. The central problem is that the quality of the experimental data does not always support the use of sophisticated modelling. Collander log−log equations, like their Hammett analogues, can be fit to most data with moderate correlation coefficients. Such plots tend to compress errors, thus making them less sensitive to scatter in the data. The real drawback in obtaining experimental data is that it is tedious, mundane, and repetitive and is not compatible with funding agencies that seek to support innovative cutting-edge research. This is short-sighted thinking. By this argument research done in obtaining experimentally determined pK_a data, for example, would be considered nonfundable, yet it is a critically important parameter for understanding the fundamental chemical behaviour of a substance. In the long run, there is no substitute for obtaining good experimental data, particularly since many environmental impact parameters and concepts are interdependent (see Figure 11). This means an error in one parameter will propagate throughout and therefore ultimately lead to wrong decision making. The problem is that significant erroneous conclusions can be drawn from a QSAR-only approach, and therefore, incorrect decision making about the choice of the synthesis plan to pursue is based on such flawed analyses.

Clearly, more research is needed to obtain reliable experimental values for both physical and toxicological parameters. Environmental scientists should move away from relying only on QSAR modelling calculations. Performing calculations should not be done as an excuse not to do experimental work. There is no substitute for doing careful experiments and getting reliable data. Moreover, such an endeavour would need to be done once in order to create a lasting database of good-quality data. Agreement between experiment and model calculations results in mutual reinforcement of both approaches, whereas an observed discrepancy means that either the calculation method needs refinement or the experiment is flawed or both. A recent new initiative by the EPA introducing how it anticipates using computational toxicology data for regulatory decisions will need to be scrutinized closely by all chemists and environmental scientists working in academia and industry.[172]

■ CONCLUSIONS

The present work has achieved the following:

- A new definition of acidification−basification potential is presented, justified, and found to be more realistic than the currently used definition.
- A new benign index (BI) parameter is introduced which describes the global environmental impact of any given chemical reaction based, in principle, on an unlimited number of potentials.
- A spreadsheet algorithm incorporating BI calculations is presented along with a visual radial hexagon depiction.
- A spreadsheet algorithm for handling sequences of reactions in the form of a synthesis plan is presented.
- An extensive user-friendly environmental impact parameter database with best available data for each environmental fate constant is given in Microsoft Excel format.

A first attempt at applying this methodology to specific industrially important reactions and synthesis plans has revealed the following:

- Phosgene reactions are found to be both more material efficient and environmentally benign than dimethyl carbonate reactions within the constraint of data available for environmental impact potentials used in the present analysis. These results will likely change when missing data are addressed, a safety metric is incorporated in the analysis, energy consumption is accounted for, and the reaction networks are expanded back to nonrenewable feedstocks for all reagents used, as was found by Aresta and Galatola.[56]
- The ingestion toxicity potential has the greatest contribution to overall environmental impact for chemical reactions.
- The inhalation toxicity potential has a low contribution to overall environmental impact although it is of particular concern for occupational health and safety in the workplace; this finding may be an artefact due to a combination of unavailable and unreliable data.
- Environmental impact potentials related to climate change (GWP, ODP, and SFP) appear to have a negligible contribution to overall EI for chemical reactions unless they involve CFCs or HFCs; this is interpreted as an artefact due to a combination of a lack of available data and an underestimation of their true values using the existing definitions of those impacts; also, GWP is underestimated because energy consumption was not considered in the analysis.
- BI values were found to be generally high for the reactions examined; however, this may change if persistence is included in the calculation and the other issues related to the rest of the impact potentials are addressed adequately.

The following challenges in applying environmental impact assessments broadly and routinely to the analysis of the greenness of synthesis plans of important target molecules relevant to the pharmaceutical, agricultural, dyestuffs, and other chemical industries have been identified:

- A massive amount of experimental work is needed to obtain reliable environmental fate constants for the 58,000 industrial chemicals currently manufactured; less emphasis should be placed on QSAR modelling.
- Databases of reliable K_{ow} and HLC parameters are urgently needed.
- Impact potentials dealing with acute and chronic toxicity and cancer risk need to be significantly augmented.
- Impact potentials dealing with endocrine disruption need to be extended to all industrial chemicals since presently there is no clear understanding of the mechanism of this phenomenon that is linked to chemical structure.

In summary, if a compound has hazard data that are absent, fragmented, unreliable, simulated by computer methods, or assumed arbitrarily, then any reaction or synthesis in which such a compound is used will necessarily result in environmental assessments that carry some degree of uncertainty and therefore should be taken with a great deal of caution. There is no escape—if one has to deal with such a compound, then an environmental analysis involving it must have the appropriate cautionary notes declared with all assumptions stated. The more such compounds exist, the weaker will be the overall conclusions drawn from such environmental impact analyses. The merits of any algorithm regardless of sophistication will be governed by available and reliable data inputs. There is no sense or justification in using sophisticated algorithms when significant assumptions need to be made to circumvent faulty data. The next challenges are to expand BI to include a safety metric and, in light of the length of time needed to address the daunting task to fill in missing experimental data, to find a way of assigning a quantifiable degree of uncertainty to the BI parameter.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Radial hexagon spreadsheet (Microsoft Excel 2000) for material efficiency and environmental impact calculations applied to chemical reactions; sample spreadsheet for reaction of triphosgene with phenol to produce diphenyl carbonate; sample spreadsheet for three-step Faith G1 synthesis of aspirin; Microsoft Excel 2000 database spreadsheet for the following parameters used including source references: TD_{50} (tumour dose), LD_{50} (lethal dose), LC_{50} (lethal concentration), ODP (ozone depletion potential), GWP (global warming potential), SFP (smog formation potential), ARDP (abiotic resource depletion potential), log K_{ow} (octanol–water partition coefficients), log K_{oc} (organic carbon–water partition coefficients), HLC (Henry's law constants), RBA (estrogen receptor binding affinities), MCM (multicompartment model) including sample calculation for toluene, K_a (organic substances), K_a (inorganic substances), ABP (inorganics), ABP (organics), K_{sp} (solubility product constants), gas solubilities in water, and half-lives of pesticides in soil; table of parameters for all chemicals used in syntheses described in this work; and sample calculations of acidification–basification potential. Tables S1–S4 and other documentation including sample calculations and references concerning all environmental impact potentials discussed in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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ABBREVIATIONS USED

AP = acidification potential
ABP = acidification–basification potential
AE = atom economy
ARDP = abiotic resource depletion potential
BAP = bioaccumulation potential
BCP = bioconcentration potential
BI = benign index
BP = basification potential
CFC = chlorofluorocarbons
CPP = cancer potency potential
CRC = Chemical Rubber Company
DMC = dimethyl carbonate
DPC = diphenyl carbonate
EATOS = Environmental Assessment Tool for Organic Synthesis
EDP = endocrine disruption potential
EI = environmental impact
GWP = global warming potential
HEAST = Health Effects Assessment Summary Tables
HFC = hydrofluorocarbons
HLC = Henry's law constant
INGCP = ingestion carcinogenicity potential
INGTP = ingestion toxicity potential
INHCP = inhalation carcinogenicity potential
INHTP = inhalation toxicity potential
IRIS = Integrated Risk Information System
ISO = International Standards Organization
LCA = life cycle assessment; life cycle analysis
LCC = life cycle costing
LCI = life cycle inventory
LCM = life cycle management
LC_{50} = lethal concentration to kill 50% of population
LD_{50} = lethal dose to kill 50% of population
MCM = multicompartment model
MRP = material recovery parameter
MW = molecular weight
ODP = ozone depletion potential
PCB = polychlorinated biphenyl
PER = persistence
PI = phenyl isocyanate
PMI = process mass intensity
ppm = parts per million
QSAR = quantitative structure–activity relationship
RME = reaction mass efficiency
ROG = reactive organic gases
RTECS = Registry of Toxic Effects of Chemical Substances
SF = stoichiometric factor
SFP = smog formation potential
SLCA = social life cycle assessment
TD_{50} = tumour dose that causes cancer in 50% of population
U.S. EPA = United States Environmental Protection Agency
VMR = vector magnitude ratio

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