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Process analysis through a Green Chemistry grid

Dissertação para obtenção do Grau de Mestre em
Engenharia Química e Bioquímica

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Setembro 2018

FACULDADE DE
CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

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2018

"Intelligence is the ability to adapt to change"

Stephen Hawking

Agradecimentos

Em primeiro lugar, quero agradecer às minhas orientadoras, a Dra. Telma Barroso e a Prof.ª Dra. Ana Isabel, por me proporem este projeto, pois sem elas este trabalho teria sido impossível de realizar.

Um grande obrigado à Dra. Telma Barroso por todo o apoio e ajuda que me deu ao longo deste projeto, estando sempre presente para me dar conselhos e discutir ideias, sendo uma fonte de motivação quando precisava. Agradeço-lhe por tudo o que ela fez, indo além dos seus deveres como orientadora e ajudando-me a melhorar não só a nível profissional, mas também como pessoa.

Quero também agradecer em especial à Prof.ª Dra. Ana Isabel por ter mostrado sempre disponibilidade para ler, analisar e sugerir correções a este projeto, mesmo quando o seu calendário preenchido o dificultava.

Quero agradecer à empresa GEO – Ground Engineering Operations Lda. por me permitir fazer a tese num ambiente empresarial, e em especial ao Eng.º Jorge Capitão-Mor pelo apoio constante que deu ao meu projeto, pelas ideias que teve e por todo o conhecimento que demonstrou nas diversas áreas.

Agradeço a todo o pessoal do laboratório da GEO – Ground Engineering Operations Lda. pelo companheirismo que demonstraram desde o primeiro dia. Ao André Praça, pelas ideias que me deu durante os primeiros meses. Ao António Cunha, por estar sempre bem-disposto e por ser um DJ de excelência. Ao Leandro Parada, por toda a ajuda que me deu na escrita da tese, pelo bom humor que sempre trouxe ao laboratório e por me ter deixado segui-lo durante uma manhã para ver os processos. À Stephanie Leal, pelas sugestões que fez para melhorar este projeto e pelas fotos de animais (em especial cães e gatos) que tornavam o dia mais animado. Ao Ricardo Silva por me ajudar a entender melhor a área de mecânica e por me ajudar nas partes finais deste projeto. Ao David Silva que, como eu, está a fazer a tese nesta empresa e sempre me ajudou quando precisava.

Por último, quero agradecer à minha família, por todo o apoio que sempre me deu. Aos meus pais, António Pinto e Teresa Machado, pela educação que me deram, por toda a paciência que demonstram comigo e por me terem dado todas as oportunidades de chegar onde cheguei. Quero agradecer também à minha irmã, Laura Pinto, por toda a força e motivação que me dá, por não me deixar desistir e por estar sempre do meu lado a lembrar-me que sou um ídolo e um exemplo para ela. Quero agradecer aos meus avós paternos, António e Carminda, à minha tia, Ilda, ao meu tio, Ricardo, e á minha prima, Inês, todo o interesse que demonstraram na minha tese e todo o apoio que me deram.

Em especial quero dedicar esta tese e agradecer à minha falecida avó Bela, que foi como uma segunda mãe para mim, que celebrou comigo todas as minhas vitórias, que sempre fez tudo para que eu fosse feliz e cuja memória é uma fonte de força e motivação por todos os bons momentos que me proporcionou. Dedico esta tese ao meu falecido avô António que, apesar de rigoroso, sempre desejou o melhor para mim e sempre me apoiou no meu percurso académico. Por fim, quero dedicar esta tese à memória do meu bisavô José, que nunca conheci mas com quem partilho o nome, e cujas histórias sempre foram uma fonte de inspiração pelo sorriso e alegria que traziam a quem as contava.

Abstract

In this work, a grid capable of evaluating the sustainability of different processes and comparing them with each other based on the Green Chemistry framework was created. The grid was made principle by principle, with it containing 15 principles (the 12 principles of Green Chemistry and an additional 3 applications of free metrics) integrated between 0 (worst scenario) and 1 (best scenario) and a green index (final value) for the process between 0 (worst scenario) and 15 (best scenario). The grid's application was studied using processes described in literature: (1) Two related to fine chemistry, the synthesis of hydrazide hydrates through the conventional route or using microwaves and (2) two related to bulk chemistry, the synthesis of anionic polyacrylamide copolymers through copolymerization or through an homopolymerization followed by a hydrolysis.

Having concluded the tests, the grid fulfilled its objectives and generated values between 0 and 1 for all principles and a green index between 0 and 15. These values allowed the processes to be compared with this assessment being carried out by industry segment: (i) For the processes related to fine chemistry, the synthesis of hydrazide hydrates using microwaves was considered superior to the conventional synthesis (respectively an 11.80 and 7.61 green index) and (ii) for the processes related to bulk chemistry, the synthesis of anionic polyacrylamide copolymers through a copolymerization was considered inferior to the synthesis through an homopolymerization followed by a hydrolysis (respectively an 8.04 and10.29 green index).

The creation of this grid has, as such, contributed for a significant advancement in the assessment of processes based on the Green Chemistry framework, due to the possibility of evaluating them in a detailed and qualitative fashion, being possible to compare and serialize different processes from a sustainability point of view, until now addressed mostly qualitatively and variably between processes.

Key words: Green Chemistry; green metrics; sustainability; Decision making tool

Resumo

Neste trabalho foi criada uma grelha capaz de avaliar a sustentabilidade de diversos processos e compará-los entre si de utilizando o enquadramento da Química Verde. A grelha foi feita principio a principio, contendo 15 principios (os 12 principios da química verde mais 3 aplicações de métricas soltas) com valores normalisados entre 0 (pior cenário) e 1 (melhor cenário) para cada e um índice verde (valor final) para o processo entre 0 (pior cenário) e 15 (melhor cenário). A sua aplicação foi estudada utilizando processos descritos na literatura: (1) Dois relativos a química fina, a sintese de hidratos de hidrazida pela via convencional ou através de microondas e (2) dois relativos a química grossa, a síntese de copolimeros de poliacrilamida aniónica através de copolimerização ou através de homopolimerização seguida de hidrólise).

Feitos os testes, a grelha cumpriu os objetivos e gerou valores entre 0 e 1 para todos os principios e um índice verde entre 0 e 15. Estes valores permitiram a comparação entre os processos, tendo esta sido feita por ramo da química: (i) Nos processos relativos a química fina, a sintese de hidratos de hidrazida utilizando microondas foi considerada superior à sintese convencional (um índice verde de 11.80 e 7.61, respetivamente) e (ii) nos processos relativos a química grossa, a sintese de copolimeros de poliacrilamida aniónica através de uma copolimerização foi considerada inferior à síntese através de uma homopolimerização seguida de hidrólise (um índice verde de 8.04 e 10.29, respetivamente).

A criação desta grelha contribui assim para um avanço significativo no que diz respeito à avaliação de processos no âmbito da química verde, visto que estes podem ser avaliados de forma qualitativa ao pormenor, sendo possível comparar processos diferentes e seriá-los do ponto de vista da sustentabilidade, até agora endereçada maioritariamente de forma qualitativa e variável entre processos.

Palavras-chave: Química Verde; métricas verdes; sustentabilidade; Ferramenta para tomada de decisões

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Abbreviations

7-ACA - 7-aminocephalosporanic acid

ACS - American Chemical Society

CMR - Carcinogenic/Mutagenic/Reprotoxic

CO_2 - Carbon Dioxide

EATOS - Environmental Assessment Tool for Organic Synthesis

ECHA - European Chemical Agency

EHS - Environment, Health and Safety

EI - Economic Importance

g - Gram

GHS - Global Harmonized System of Classification and Labelling of Chemicals

GSK - GlaxoSmithKleine

h - Hour

HAP - Hazardous Airborne Pollutant

HMDS - Hexamethyldisilazane

HREE - Heavy Rare Earth Element

kg - Kilogram

kJ - Kilojoule

kW - Kilowatt

kWh - Kilowatt hour

L - Litre

LCA - Life Cycle Assessment

LCC - Life Cycle Cost

LD50 - Median Lethal Dose

LDLo - Lethal Dose Low

LREE - Light Rare Earth Element

M - Molar concentration

MATLAB - MATrix LABoratory

mCi - Millicurie

mg - Milligram

MJ - Megajoule

mmol - Millimole

mol - Mole

MSDS - Material Safety Data Sheet

NFPA - National Fire Protection Association

°C - Degree Celsius

PGM - Platinum Group Metal

ppm - Part per million

Q1 - Lower Quartile

Q3 - Upper Quartile

REACH - Registration, Evaluation, Authorisation and Restriction of Chemicals

RME - Reaction Mass Efficiency

SR - Supply Risk

TLV - Threshold Limit Value

TRACI - Tool for the Reduction and Assessment of Chemical Impact

1. Introduction

1.1. Objectives

The purpose of this work is the creation and validation of a grid based on the Green Chemistry framework capable of comparing different processes and generating a classification list based on how sustainable they are.

1.2. Sustainability

Since the middle of the 20th century, natural resource usage has massively increased, with water consumption tripling, sea fish consumption rising to five times its value, wood demand increasing six-fold just for pulp and paper production, among other examples. Additionally, over 1000 species of animals and plants are closing in on extinction every year. The increase on the concentration of carbon dioxide concentration has also led to an increase in the greenhouse effect and, consequently, an increase in ecological disasters [1]. This created the grounds for an increased research into "Sustainability", attempting to solve those issues and understanding the relationship between nature and society in a global scale through science and technology [2].

The meaning of the term Sustainability isn't clearly defined, having first been coined to describe the act of "never harvesting more than what the forest yields in new growth" [3]. Since then, the term has evolved, being now the actions that "meet the needs of the present without compromising the ability of future generations to meet their own needs" [4]. This new definition allowed it to be applied not only from an environmental point of view, but also economic, political or social, giving rise to a new area of research on sustainable development.

The appearance of sustainable development as a major area of research caused the scientific community to take another look at their practices, defining new priorities [5], leading to new legislation, and a spike in the number of new and modified terms [6]. Presently, sustainability is an unavoidable part of industry, with a constant search for improvement in all areas to develop better alternatives, capable of facing the new need for sustainable markets [7].

The application of sustainable approaches can be easily seen as a chance to reduce economic costs via lower energy consumption and waste reduction as can be seen from the example of Interface, the world's largest manufacturer of modular carpet [8], that thanks to the adoption of sustainability reduced energy consumption by 33% in five years and saved US$300 million over 10 years just in waste disposal costs [9].

1.3. Green Chemistry

The need for sustainable development in chemistry started before the concept of "Green Chemistry" and it was properly introduced with independent researchers and journals using the term to refer the efforts to reduce pollution from chemical processes since 1991 [10]. This new focus appeared because of the increasing damage to the environment and human health that chemical products caused.

An important area to promote sustainability was chemistry and so, in 1994, a first draft of what is now called "Green Chemistry" was published claiming that pollution prevention should be a first choice instead of pollution control, as Paul Anastas described: "Benign by Design" [11].

This idea was further expanded in 1996, and green chemistry was presented as an evolution, in which not only pollution prevention was a priority, but also the reduction of costs to industry and society [12].

In 1998, Paul Anastas and John Warner introduced the twelve principles of green chemistry, creating the guidelines that should be considered when attempting to check the "greenness" of a chemical process [13].

Since first proposed, the usage of the term quickly grew among the scientific society, with several articles being published about it every year [14]. Furthermore, it has become accepted that due to the large scope of green chemistry, it is a responsibility for all parts of society to participate in its dissemination and application [15]. As such, several initiatives were started related to green chemistry, among them the Presidential Chemistry Awards, giving prizes to the best "green" ideas for set categories every year [16].

The importance of green chemistry is clear when we take into account how it affects all phases of a product's life cycle from a sustainable point of view in an attempt to increase profits, protect the environment and reduce the general public's fear of "chemicals" by finding green solutions [17] that will, for example, reduce waste [18], reduce carbon footprint [19] or reduce potential toxicity [20]. With these objectives in mind, several solutions have appeared across all areas of chemistry getting as close as possible to that unachievable "perfect solution" [21].

1.3.1. The Twelve Principles of Green Chemistry

Following the proposal of Paul Anastas [22], the 12 principles of green chemistry were widely accepted due to the possibility of analysing a process or product from a sustainable point of view and two different products or processes being compared in terms of relative "greenness". To facilitate their application an acronym, PRODUCTIVELY, was created (Table 1.1) [23].

Table 1.1. Condensed 12 Principles of Green Chemistry [23]

Abbreviation	Condensed Principle
P	Prevent wastes
R	Renewable materials
O	Omit derivatization steps
D	Degradable chemical products
U	Use safe synthetic methods
C	Catalytic reagents
T	Temperature, Pressure ambient
I	In-Process Monitoring
V	Very few auxiliary substance
E	E-factor, maximize feed in product
L	Low toxicity of chemical products
Y	Yes, it's safe

Nevertheless, to fully understand the principles it is important to analyse them as originally proposed in 1998 [22].

Principle 1: Prevention

"It is better to prevent waste than to treat up or clean up waste after it is formed." [22]

This principle states that it is best to reduce produced waste instead of cleaning up afterwards, due to the increased costs of the second option (both economic and environmental), and can be mathematically measured using the E-factor, proposed by Sheldon in 1992, which is the mass of waste produced by mass of product (Equation 1.1) [24].

Equation 1.1. E-factor [24]

$$E\ factor = \frac{\sum mass\ of\ waste\ (kg)}{mass\ of\ product\ (kg)}$$

Lower values of this factor mean the process is "greener", since less waste is generated.

Principle 2: Atom Economy

"Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product." [22]

Synthetic methods should strive to maximize the conversion rates and reduce losses during the synthesis, ideally having all the reagents incorporated into the product. This principle also has a mathematical measure associated, the Atom Economy, which was originally proposed in 1991 by Barry M. Trost. This value is determined as the mass of product divided by the total mass of reagents, not considering intermediary products (Equation 1.2) [25].

$$Atom\ Economy\ of\ P\ (\%) = \frac{molar\ weight\ of\ P\ (kg/mol)}{\sum molar\ weight\ of\ reagents\ (kg/mol)} * 100$$

The ideal value of the Atom Economy is 100%, being that the closer the obtained value is to that, the "greener" the process is.

An additional method was created to analyse the incorporation of materials into a product using mass instead of molar weight, the Reaction Mass Efficiency (RME) [25]. Several different ways of calculating it have been proposed: the Kernel Reaction Mass Efficiency (Equation 1.3), the Curzons Reaction Mass Efficiency (Equation 1.4 and Equation 1.5) and the Generalized Reaction Mass Efficiency (Equation 1.6).

Equation 1.3. Kernel Reaction Mass Efficiency [25]

$$Kernel\ Reaction\ Mass\ Efficiency\ (\%) = Atom\ Economy * Yield * 100$$

Equation 1.4. Curzons Reaction Mass Efficiency [25]

$$Curzons\ Reaction\ Mass\ Efficiency\ (\%) = \frac{Mass\ of\ product\ (kg)}{\sum Mass\ of\ reagents\ (kg)} * 100$$

Equation 1.5. Relation between Curzons Reaction Mass Efficiency and other metrics [25]

$$Curzons\ Reaction\ Mass\ Efficiency\ (\%)$$
$$= Yield\ * Atom\ economy\ * \frac{1}{Stoichiometric\ factor} * 100$$

Equation 1.6. Generalized Reaction Mass Efficiency [25]

$$Generalized\ Reaction\ Mass\ Efficiency\ (\%) = \frac{Mass\ of\ product\ (kg)}{Total\ mass\ into\ process\ (kg)} * 100$$

Another common metric related to this principle is the Process Mass Intensity, which is the reciprocal of the generalized reaction Mass Efficiency (Equation 1.7) [26].

Equation 1.7. Process Mass Intensity [26]

$$Process\ Mass\ Intensity\ = \frac{Total\ mass\ into\ process\ (kg)}{Mass\ of\ product\ (kg)}$$

Principle 3: Less Hazardous Chemical Syntheses

"Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment." [22]

In chemical syntheses, substances, reagents, intermediaries or products should be as non-toxic as possible to avoid health and environmental issues. This principle is applied by analysing the relative toxicity of the synthesis by-products, for example on the different synthesis methods of hydrazides [27].

For this principle there is no associated mathematical formula.

Principle 4: Designing Safer Chemicals

"Chemical products should be designed to preserve efficacy of function while reducing toxicity." [22]

The ideal chemical product is both efficient and non-toxic. To obtain that ideal product, chemists can resort to the molecular design of products for each function, using a "tailor made" approach that guarantees efficacy and reduces toxicity, albeit at a higher economical cost. It can be used, for example, to choose products to reduce aquatic toxicity, which need to be extremely efficient while also being non-toxic [28].

For this principle there is no associated mathematical formula.

Principle 5: Safer Solvents and Auxiliaries

"The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used." [22]

Although there is no standardized formula to express this principle, due to the different types of toxicity and danger that exist, this area of Green Chemistry is under extensive research, resulting in several new green solvents appearing over the years [29], and additional prospects on using water as the ideal solvent [30]. Some of these solutions so far include ionic liquids [31], supercritical carbon dioxide [32], alkyl glycerol ethers [33] and solvents derived from biomass [34]. Among these, the ionic liquids show a large potential due to their physicochemical properties [35], having been successfully used in extractions [36].

Regardless of the potential shown by these new classes of solvents, they should must always be individually tested to guarantee they abide as well as possible by the twelve principles of green chemistry [37].

For this principle there is no associated mathematical formula.

Principle 6: Design for Energy Efficiency

"Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure." [22]

This principle states that energy usage should be minimized in a chemical process while considering the environmental and economic costs. This translates into the application of energy efficient processes and renewable energies. So far, research has led to new green methods of producing energy being discovered, among them organic solar cells [38] and organic electrosynthesis [39].

For this principle there is no associated mathematical formula.

Principle 7: Use of Renewable Feedstocks

"A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable." [22]

As the Report on Critical Raw Materials and the Circular Economy [40] shows, some raw materials used in the industry are dwindling, which leads to a necessity of finding alternatives in accordance to this principle. A few of the alternatives found so far are wood, plant-oils and sugars, with extensive research being made into them [41].

For this principle there is no associated mathematical formula.

Principle 8: Reduce Derivatives

"Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible." [22]

Due to the additional energy and mass costs that derivatization steps require it is best to avoid them. As a solution to avoid those steps an enzymatic reaction can be used, thanks to their high selectivity, with the unfortunate setback that enzymes tend to be unstable outside a certain range of temperatures and pressures [42].

For this principle there is no associated mathematical formula.

Principle 9: Catalysis

"Catalytic reagents (as selective as possible) are superior to stoichiometric reagents." [22]

Due to their increased selectivity, catalytic reactions are the better options than stoichiometric reactions. Since the twelve principles of green chemistry were proposed, research on catalytic reagents has increased [43], attempting to create the perfect reagent and reaction [44]. This increased research led to an evolution on catalysts used, a few examples are: the classic catalysts using silica-gels for immobilization [45], biocatalytic processes using enzymes [46], solid acids for organic synthesis [47], hydrogen peroxide for partial oxidation reactions [45], or the use of nanomaterials [48].

For this principle there is no associated mathematical formula.

Principle 10: Design for Degradation

"Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products." [22]

Designing chemical products to be biodegradable is important as it can reduce long term impact on the environment, this can be achieved through molecular design or usage of different products, for example biomass. Using biomass also presents an additional advantage as it is a renewable material that exists in large quantities [49].

For this principle there is no associated mathematical formula.

Principle 11: Real-time analysis for Pollution Prevention

"Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances." [22]

Real-time in-process monitoring is a challenge for Green Chemistry with investigation being conducted into analytical chemistry to guarantee the application of the 12 principles of green chemistry. This means that large quantities of samples need to be prepared and analysed quickly and *in situ*, whilst also reducing the quantity of solvents required, waste generated and energy requirements [50].

Most of the Principles of Green Chemistry are based on mass, which is incompatible with analytical chemistry. As such, additional methods to assess the greenness of an analytical chemistry process are under investigation which may lead to this principle being more easily applied in the future [51]. Some of the proposed methods are the usage of electrochemical systems [52], miniaturized systems [53] or microwave-assisted extractions [54].

For this principle there is no associated mathematical formula.

Principle 12: Inherently Safer Chemistry for Accident Prevention

"Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires." [22]

Being intrinsically linked to the other principles, the 12th claims that used substances should be chosen in an effort to minimize the risks during the chemical process. Usually this is usually done during selection of solvents by choosing those with a lower amount of hazard warnings, reducing both the environmental risk (in accordance with principle 5) and the human risk. Lately, several restrictions have appeared related to the use of unsafe solvents, for example, through the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations [55].

For this principle there is no associated mathematical formula.

1.3.2. Industrial Applications

Some of the most important areas of chemistry include chemical manufacturing, chemical formulation, hydraulic fracturing and pharmaceuticals [56] [57] [58] [59]. Although not all principles can be equally applied, companies from these areas have shown interest and have applied green chemistry in their processes and products [60]. A few examples follow:

BASF Eco-Efficiency [61]

BASF designed a method to help with decision making in, among others, chemical processes. This method called Eco-Efficiency Analysis allows the "sustainability level" of different products to be compared, facilitating the application of the 12 principles of green chemistry and allowing companies to choose the best method.

This method was created in order to address strategy, marketplace, politics and research issues in an easily understandable way, carrying out an ecological and economic assessment over all steps of production.

For the calculation of the eco-efficiency the environmental impacts are determined via the consumption of raw materials (principles 2 and 7), the consumption of energy (principle 6), the resulting emissions (principle 1), the toxicity potential (principles 12 and 10) and the abuse and risk potential (principles 4 and 5). The economic assessment is carried out through the calculation of all costs along the product life cycle.

Data acquisition and calculation for the environmental impacts is done through a Life Cycle Assessment with additional arithmetic factors (Table 1.2) used for weighing and normalization.

Table 1.2. Example of arithmetic factors for raw materials [61]

Raw material	Years of reserves	Factor
Basalt	1000	1
Bauxite	200	5
Coal	160	6.3
Copper	50	20
Dolomite	500	2
Gas	63	16
Gypsum	300	3.3
Iron	72	14
Limestone	500	2
Lignite	390	2.6
Manganese	92	11
Nickel	35	29
Oil	42	24
Phosphate	85	12
Rock salt	1000	1
Rockstone	1000	1
Sand	500	2
Sulphur	30	33
Zinc	25	40

After carrying out the assessments, the results are normalized to allow for comparison. Additionally, weighting factors are used to determine the most important areas to act on and to calculate the portfolio metric. Lastly, these values are presented graphically for quick analysis.

Amgen's guide to replace dichloromethane in chromatography [62]

Chemists from Amgen proposed a guide to select replacement solvents for dichloromethane in chromatography with the objective of reducing the usage of this solvent, which is toxic to both humans and the environment. This guide shows several possible green solutions capable of substituting dichloromethane in accordance with principles 1, 5 and 12.

The solvent evaluation is carried out by determining the retention frequency of each solvent, calculating the average retention frequency of the mixture. This allows for a comparison of the relative eluting strength of each solvent system.

Having carried out these steps it becomes possible to create an easy to read chart of substitutes for dichloromethane which can be displayed in a laboratory for quick reference.

Biogen's Global Impact Report [63]

Biogen's Global Impact Report shows an emphasis on following the principles of green chemistry, giving the example of the production of antisense oligonucleotides, which was originally carried out using organic solvents and is now carried out using water. Additionally, in the production process of an active pharmaceutical ingredient material efficiency was improved, according to the Process Mass Intensity (principle 2, (Equation 1.7)), water usage was reduced by 49% (principles 1, 2 and 5) and global warming potential was reduced by 44% (principle 1 and 11).

AstraZeneca's Environmental Protection [64]

AstraZeneca created a report on Environmental Protection stating their objectives on sustainability and green chemistry, showing both their goals and progress.

This company's main focuses are to reduce the usage of chemicals and natural resources (principles 1, 2, 6 and 7), recycling and reusing solvent wastes (principles 1 and 5), and a safe active pharmaceutical ingredient discharge program (principles 4, 10 and 12). The presented results support this, produced waste in a year decreasing from 1,001 to 223 tonnes through the reduction of the Process Mass Intensity of the osimertinib (an active pharmaceutical ingredient) from 501 to 112.

Hydraulic Fracturing [65]

In order to follow the principles of green chemistry several strategies were proposed by companies related to hydraulic fracturing, for example Apache Corporation. These strategies are the reduction of used chemicals (principles 1, 2 and 5), the reduction of toxicity (principles 4, 5, 11 and 12) and increased biodegradability (principle 10). Taking these strategies into account, new additives are currently being researched and produced.

Pharmaceutical Perspective [66]

John Tucker, part of Pfizer's Global Research and Development, authored a paper on the pharmaceutical perspective on green chemistry with the objective of promoting its application in the industry. In this paper, it is explained that some principles of green chemistry are not truly applicable in the pharmaceutical area, as exemplified by the need for stability in an active pharmaceutical ingredient (as opposed to principle 10: design for degradation). As such, he proposes a list of the principles of green chemistry that can be applied and its benefits:

- Atom economy can be applied via the minimization of by-product formation, incorporating the total value of the used materials (principle 2).

- Solvent reduction (principle 5) can decrease generated waste (principle 1) and energy requirements (principles 6).

- Reagent optimization can be done through the use of catalytic reactions (principle 9) capable of being recycled.

- Convergence in chemical processes, reducing the number of required operations (principle 8).

- Reduction on required energy (principle 6).

- In situ analysis (principle 11) in order to reduce potential exposure or releases to environment.

- Safety through the use of non-hazardous materials and processes (principle 3, 4, 5 and 12).

Cement Industry [67]

Several types of cements are being researched to find a greener alternative to Portland cement, the most used in the market, which has a high environmental impact. The need for alternatives derives from the high environmental cost associated with its production and its poor durability.

To quantify this, the study conducted life cycle assessments to several building materials and alternate cements and proposed a set of rules and objectives to determine how green a cement is. These objectives are minimal energy requirements (principle 6), reduced emissions (principle 1), renewable raw materials (principle 7), ability to incorporate value-added wastes (principle 2).

Opportunities for greener alternatives in chemical formulations [68]

A group of industrial chemical formulators (American Chemical Society (ACS) Formulator's Roundtable) created a list of products that need to be substituted by greener alternatives. This list encompasses 10 classes of components where further investigation is needed, with the evaluation of proposed solutions being carried out based on sets of rules. The classes of components that need further investigation are:

- Antimicrobials, which are used during product manufacture to avoid contamination. The main objective for this class is to be biodegradable (principle 10), stable, not prone to causing antimicrobial resistance and low human toxicity (principle 4).

- Solvents, which are crucial for several chemical formulators. The main objective for this class is to be biobased, renewable (principle 7) and non-toxic (principles 5 and 12).

- Small amines, used in chemical formulation to lower viscosity and increase solubility of surfactants. The main objective for this class is to be renewable (principle 7), non-toxic for humans (principles 5 and 12).

- Chelants and sequestering agents, used to bind metals. The main characteristic required is a low price, while maintaining functionality.

- Boron, used mainly in cleaning products. The main characteristic required is the capability of acting in every way like boron, while being renewable (principle 7) and non-toxic (principles 5 and 12).

- Fragrance raw materials. The main characteristics are biodegradability (principle 10) and non-toxicity (principle 4).

- Corrosion inhibitors, used mainly as coating in the machinery to prevent corrosion. The main characteristics required are for it to be biodegradable (principle 10), non-toxic in the environment (principle 4) and renewable (principle 7).

- Alkanolamides, used in cleaning products to increase viscosity or stabilize foam. The main characteristics should be non-toxicity (principle 5 and 12), renewability (principle 7).

- Surfactants, used in a wide variety of ways. The required characteristics should be biodegradability (principle 10) and non-toxicity (principle 4).

- UV screens, used in sunscreens. The required characteristics are biodegradability (principle 10), low toxicity (principle 4), made from renewable materials (principle 7).

1.3.3. Limitations of Green Chemistry

The lack of a standard method of evaluating the greenness of a process or even of a holistic approach to green chemistry causes severe limitations to the application of green chemistry, as it does not allow two processes to be properly compared in their whole [69].

The developments of new types of products with unique characteristics, like nanoparticles, can also be an issue when a green approach is not taken from a start due to lack of information or opportunity, these new products may also have characteristics which the principles do not assess [70], since they were proposed in 1998 and have not evolved since then [71] [72].

The application of the principles of green chemistry is also limited by the fact that they are intrinsically linked and the analyses of one may not give a proper image of the process or product in a whole, with an important challenge to address is to address these principles on a molecular level [69].

The inexistence of proper economic assessments capable of taking into account the evolution from a linear economy to a circular economy that green chemistry proposes can further limit its application since it does not add the value of a production loop, which translates outside of the principles into a higher resource efficiency when possible [73].

1.4. Green Engineering

The need for sustainability and greener processes could not be tackled only from a chemist's point of view due to the nature of new technologies and a chemical production facility including a large component in engineering science and technology [74]. To solve this, a new area of investigation was proposed called "Green Engineering", which focused on sustainable development through the change of engineering practices [75].

This area was proposed by Paul Anastas, Lauren Heine and Tracy Williamson in 2000 and was presented as an approach to sustainability through more technological methodologies than green chemistry, being capable of implementation side by side with it [76].

At the same time as its proposal, and similarly to green chemistry, the twelve principles of green engineering were created as guidelines to help standardize the application of this new approach in existing or new products and processes [77].

The importance of applying green engineering to process development is clear due to its emphasis on optimization, leading not only to the protection of the environment but also increased profits from the process [78]. Green engineering can also be used to assist in low-impact development, due to its ideals being fundamentally similar [79].

1.4.1. The Twelve Principles of Green Engineering

Serving as additional principles to use beside the 12 principles of green chemistry or as standalone principles to use on engineering processes, it is important to be able to convey them as simply as possible. To allow that a condensed version and a mnemonic for it were proposed (Table 1.3) [23].

Table 1.3. Condensed 12 Principles of Green Engineering [23]

Abbreviation	Condensed Principle
I	Inherently non-hazardous and safe
M	Minimize material diversity
P	Prevention instead of treatment
R	Renewable material and energy inputs
O	Output-led design
V	Very simple
E	Efficient use of mass, energy, space & time

M	Meet the need
E	Easy to separate by design
N	Networks for exchange of local mass & energy
T	Test the life cycle of design
S	Sustainability throughout product life cycle

However useful the condensed version is, a full analysis of the principles as originally proposed [74] is necessary to understand and apply them correctly.

Principle 1: Inherent rather than circumstantial

"Designers need to strive to ensure that all material and energy inputs and outputs are as inherently non-hazardous as possible." [74]

The use of inherently non-hazardous material and energetic inputs/outputs can minimize the environmental and economic fallout of both prevention and treatment, as such, research unto inherently safe materials and energy is being conducted, for example, on high-energy materials [80].

For this principle there is no associated mathematical formula.

Principle 2: Prevention instead of treatment

"It is better to prevent waste than to treat or clean up waste after it is formed." [74]

This principle, stated the same as the 1st principle of green chemistry, can be applied in an engineering sense with the concept of material economy, which is the acknowledgement that waste is human and whatever is considered "waste" should instead be used for another purpose [74]. This kind of approach is being used in order to produce phosphorous from several sources of what is considered waste [81].

For this principle there is no associated mathematical formula.

Principle 3: Design for separation

"Separation and purification operations should be designed to minimize energy consumption and materials use." [74]

Separation and purification operations tend to be material and energetic intensive, as such, focus on their optimization can massively reduce costs. Some of the main examples of the application of this principle reside in the pharmaceutical industry, where extraction techniques play a large role [82].

For this principle there is no associated mathematical formula.

Principle 4: Maximize mass, energy, space, and time efficiency

"Products, processes, and systems should be designed to maximize mass, energy, space, and time efficiency." [74]

Maximizing the efficiency of all parts of engineering can increase its greenness by reduction of waste, not only of mass and energy but also of space and time, due to its limited nature. This can be achieved using miniaturized systems and nanotechnology [75].

For this principle there is no associated mathematical formula.

Principle 5: Output-pulled versus input-pushed

"Products, processes, and systems should be "output pulled" rather than "input pushed" through the use of energy and materials." [74]

All reactions require a driving force to occur, this can be pressure, temperature, concentration gradients. This driving force can be applied by acting on the inputs or the outputs of the system, but not all of those actions consume the same mass/energy. What this principle states, is that action should be taken by producing only what is required, reducing the amount of resources necessary [74].

For this principle there is no associated mathematical formula.

Principle 6: Conserve complexity

"Embedded entropy and complexity must be viewed as an investment when making design choices on recycle, reuse, or beneficial disposition." [74]

The relative complexity of a product must be taken into account when deciding the best course of action for it. Higher complexity products should be treated as an investment and reused, whilst lower complexity products may be recycled or dismantled without an economic loss [74].

For this principle there is no associated mathematical formula.

Principle 7: Durability rather than immortality

"Targeted durability, not immortality, should be a design goal." [74]

An important part of a product is its biodegradability since, if designed for immortality, it may become harmful on a long-term analysis. As such, one of the principles of green engineering is that a product should be durable (capable of performing its function) but not immortal in order to reduce the potential for after-life hazard [83].

For this principle there is no associated mathematical formula.

Principle 8: Meet need, minimize excess

"Design for unnecessary capacity or capability (e.g., "one size fits all") solutions should be considered a design flaw." [74]

Solutions should be design with the objective of solving a particular problem, this way resources can be optimized and can be waste reduced. This can be achieved using molecular design, assessing their properties before they are produced and allowing them to act on a single function with minimal waste generation [84].

For this principle there is no associated mathematical formula.

Principle 9: Minimize material diversity

"Material diversity in multicomponent products should be minimized to promote disassembly and value retention." [74]

By reducing material diversity, ideally to a single material, all parts of a product can be treated at once. Research into this area has led to a rise in the usage of materials with highly malleable properties such as carbon nanotubes [85]. From a chemical standpoint, this same principle can be followed using pot economy: making a set of synthetic transformations occur sequentially in a single reactor [86].

For this principle there is no associated mathematical formula.

Principle 10: Integrate local material and energy flows

"Design of products, processes, and systems must include integration and interconnectivity with available energy and materials flows." [74]

The integration of local energy and material flows allows generated "waste" to have a use. This can be used in chemical engineering by using excess energy in some sections (for example, from a chemical reaction) to heat another, which can be easily achieved through the use of flow chemistry instead of batch [87].

For this principle there is no associated mathematical formula.

Principle 11: Design for commercial afterlife

"Products, processes, and systems should be designed for performance in a commercial "afterlife"." [74]

By designing with commercial "afterlife" in mind additional value is created since even after its commercial life has ended it can still be used elsewhere for another function. This can be used, for example, in biofuel production by designing the process to gather the produced glycerol, which is capable of being used as a green solvent [88].

For this principle there is no associated mathematical formula.

Principle 12: Renewable rather than depleting

"Material and energy inputs should be renewable rather than depleting." [74]

The use of renewable energy and materials has a major impact on the sustainability since renewables can be used in cycles, sometimes serving as feedstocks after their function has been completed. The most common examples are the biobased chemicals industry, where biomass is used to produce chemicals [89].

For this principle there is no associated mathematical formula.

1.4.2. The Sandestin Principles

Although capable of being applied outside of chemical engineering, the 12 principles of green engineering were created with the 12 principles of green chemistry in mind [74]. As such, a conference was held by engineers from several areas during the week of May 19, 2003 where the principles of green engineering were redefined and condensed in order to be properly applicable in all areas with greater ease (Table 1.4) [90]. Unlike the principles of green chemistry, no in-depth studies exist related to the Sandestin principles at the time of writing.

Table 1.4. The Sandestin Principles [90]

Principle	Description
Principle 1	Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools
Principle 2	Conserve and improve natural ecosystems while protecting human health and well-being
Principle 3	Use life-cycle thinking in all engineering activities
Principle 4	Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible
Principle 5	Minimize depletion of natural resources
Principle 6	Strive to prevent waste
Principle 7	Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures
Principle 8	Create engineering solutions beyond current or dominant technologies; improve, innovate, and invent (technologies) to achieve sustainability
Principle 9	Actively engage communities and stakeholders in development of engineering solutions

1.4.3. Industrial Application

Several areas of engineering have focused on development via the principles of green engineering in order to make processes more economic, environmental and socially sustainable [91]. Among them, a few important examples are:

BASF Eco-Efficiency [92]

BASF updated its process comparison tool called Eco-Efficiency Analysis to abide by the 12 principles of green engineering. This method, mostly applied as previously described in chapter Industrial Applications under BASF Eco-Efficiency , was slightly altered to clearly apply the principles of green engineering. Being done from cradle to grave, BASF Eco-Efficiency takes into account commercial afterlife (principle 11).

During the Life Cycle Analysis, primary energy consumption is calculated including conversion losses which encourages the use efficient processes (principle 4), and minimization of energy costs (principle 3).

Raw material consumption is calculated with the application of a "resource factor", which is based on how long the exploration of that resource is viable (Table 1.2). As such, the use of efficient processes (principle 4), low consumptions (principle 3) or use of renewable resources (principle 12) is highly advisable.

Emissions are calculated separately for air, water and soil (waste). For air emissions, the values correspond to the global warming potential, the photochemical ozone creation potential, the ozone depletion potential and the acidification potential. Water emissions, due to no comparable standards, are calculated through a critical volume based on wastewater regulations. Solid wastes are separated on special wastes, domestic refuse wastes, building rubble materials and overburden. The calculation is made through the average disposal costs, with a "hazard factor" used for dangerous wastes. These impact factors encourage the use of less wasteful (principle 2) and hazardous (principle 1) materials and processes.

Toxicity potential is done considering the European classification used in life cycle assessments for the determination of ecotoxicity burdens and exposure potential. This is done in order to minimize the inherent hazards of chemical processes (principle 1).

Risk potential is established differently in each study, with the objective always being the reduction of hazards (principle 1).

Use of area is considered through the effects on the ecosystem from occupying the production site, the need for transportation and the treatment/disposal facilities. This area is done for all materials in the life cycle with different factors being used based on area categories. This encourages a reduction on required area and increased efficiency (principle 4).

Production of biodiesel and biofuels [91]

Petrochemical sources, coal and natural gas are being substituted by biofuels as an environmentally friendly option thanks to their renewability (principle 1), reduced emissions (principle 2), higher cetane number (principles 4 and 6), biodegradability (principles 2 and 11) and non-toxicity (principle 1).

Research is also being conducted unto greener production methods for biodiesel and biofuels through, for example, a change on raw materials for renewable sources (principle 12) that don't put pressure on other sectors of the economy (principle 10). Some alternatives that have appears so far include the usage of specific enzymes (principle 8) or microalgae, which are independent from food sources.

Synthesis of organic carbonates from carbon dioxide [91]

Synthesis of organic carbonates is generally done through the use of toxic raw materials, including solvents. Research is being made into substituting the standard production method into one that utilizes carbon dioxide as a raw material due to it being renewable (principle 12), the need to reduce its atmospheric concentration, ease of access (principle 10) and the elimination of solvents (principles 1, 2 and 9).

Key green engineering research areas for sustainable manufacturing [93]

A group of pharmaceutical and fine chemistry manufacturers created a list of important research areas to implement green engineering into their processes. Special focus was put into the areas of "continuous processing", "bioprocesses", "separation and reaction technologies", "solvent selection, recycle and optimization" and "process intensification".

In the area of "continuous processing" the need for green engineering solutions arises due to excessive usage of batch reactors in the pharmaceutical industry. By employing continuous processing, production costs can be reduced by reducing energy and material requirements for production and separation through flow engineering (principles 2, 3, 4, 5, 6 and 10). The use of continuous processing can also reduce the explosion hazard potential of a closed batch reactor (principle 1).

In the area of "bioprocesses" the need for green engineering solutions is because of the highly selective nature of these reactions, as opposed to those currently applied in the pharmaceutical industry. These solutions can lead to a reduction on required raw materials (principles 3, 4, 5 and 8), the usage of renewable materials (principle 12), lower energy needs (principles 3 and 4) and lower hazardous waste (principles 1 and 2).

In the area of "separation and reaction technologies" the need for green engineering solutions comes from the high number of steps used in the production of an active pharmaceutical ingredient, contributing to 40-90% of the Process Mass Intensity (Equation 1.7) , with distillation and drying steps consuming over 50% of the energy needed for the process, overall this contributes to a large increase on the required mass, energy, space and time when compared to the chemical reaction. Proposed solution for this area includes real-time monitoring to reduce time consumption (principle 4), continuous processing for its previously explained characteristics, automation of the processes and mathematical modelling to optimize the steps (principles 6, 8 and 10).

In the area of "solvent selection, recycle and optimization" the need for green engineering is due to the immense amounts of solvents required during production of an active pharmaceutical ingredient, contributing largely to its Process Mass Intensity (Equation 1.7). By attempting a substitution and optimization for greener solvent, these processes can generate less waste (principle 2, 3 and 4), can be less hazardous (principle 1) and can be based on renewable feedstocks (principle 12).

In the area of "process intensification" green engineering techniques are required to develop tools and methods capable of monitoring separation techniques in order to optimize the space-time yield (principle 4), reduce the hazard potential (principle 1) and maximize the driving force (principle 5).

1.4.4. Limitations of Green Engineering

As is the case with green chemistry, green engineering also suffers from the fact that it is mostly based on qualitative methods failing to give an absolute value for comparison, even though its higher focus on engineering allows for a more holistic approach. The need to implement green engineering systematically and across all scales also causes additional difficulties, since the principles require that, in the end, the problem be redefined to search for a better answer [74].

The large focus on improving sustainability at the process level that green engineering proposes also fails to consider the large role that market conditions, economical regulations and social acceptance can have on the acceptance of the new green processes, systems and products that green engineering proposes [91].

The need to handle green engineering differently depending on the scientific area involved also causes severe limitations on its application, as each part of the industry has to further research what principles can truly be applied and how, even in the midst of quickly developing or changing areas [93]. This effort is further complicated and delayed by the appearance of new technologies which have to be assessed from a green point of view before they can be used [85].

1.5. Comparison between Green Chemistry and Green Engineering

Green chemistry and green engineering are intrinsically connected through their principles and objectives, with green chemistry focusing mainly in chemical processes and green engineering focusing on engineering design. Both work on the concept of "waste", attempting to reduce it from a sustainable point of view. As a consequence of their objective being the same, although with different approaches, their principles tend to be similar and they tend to be applied simultaneously (Table 1.5) [94].

Table 1.5. 24 Principles of green chemistry and green engineering [94]

Principle	Green Engineering	Green Chemistry
1	Inherent rather than circumstantial	Prevention
2	Prevention instead of treatment	Atom economy
3	Design for separation	Less hazardous chemical use
4	Maximize efficiency	Design for safer chemicals
5	Output-pulled vs input-pushed	Safer solvents and auxiliaries
6	Conserve complexity	Design for energy efficiency
7	Durability rather than immortality	Use renewable feedstocks
8	Meet need, minimize excess	Reduce use of derivatives
9	Minimize material diversity	Catalytic reagents rather than stoichiometric reagents

10	Integrate material and energy flows	Design for degradation
11	Design for commercial afterlife	Use real-time analysis for pollution prevention
12	Renewable rather than depleting	Use safer chemistry to prevent accidents

Although application of the green chemistry and green engineering design philosophies is increasing, there is still scope for improvement due to the lack of a satisfactory set of metrics, capable of giving complete and measurable results. To balance this, an important tool used in unison with green chemistry and green engineering is the Life Cycle Assessment [95].

1.6. Life Cycle Assessments

Life Cycle Assessment (LCA), also called environmental product life cycle assessment, is a technique that considers analyses of the environmental impact of a product's life cycle, from production to disposal, through four or five steps (Figure 1.1): goal definition, inventory analysis, classification, evaluation and, optionally, improvement analysis [96]. However, this technique isn't perfect and so, ever since it became a standard technique attempts have been made to improve it, for example, though better classification and evaluation methods [97]. Furthermore, mathematical models and computer software can simplify an LCA, reducing the required time and investment to carry it, being applied, for example, in the automobile industry by Ford or the electronics industry by Hewlett-Packard [98].
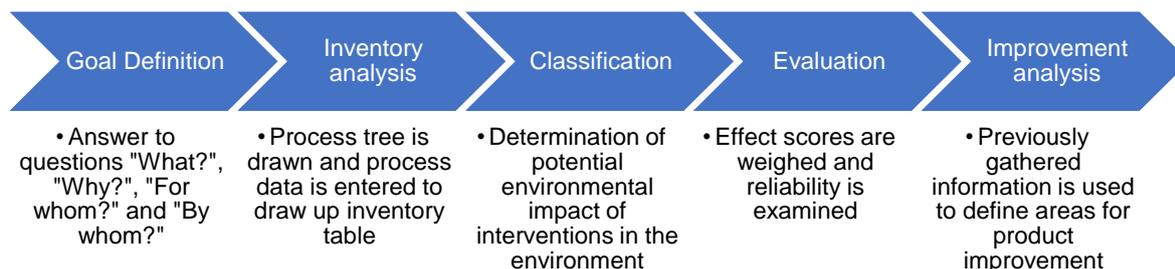
Figure 1.1. Life Cycle Analysis flowchart [96]

An example of an LCA model is the economic input-output model (Figure 1.2) which carries out an LCA through the use of flow diagrams or matrices with the system boundaries being defined as the entire economy. This model allows for a large scale LCA analysis without requiring data on all steps of a process, unfortunately, this may lead to lack of data about the intermediary steps. As such, the economic input-output model is particularly useful when a general LCA is sufficient, as it allows quick calculations [99].
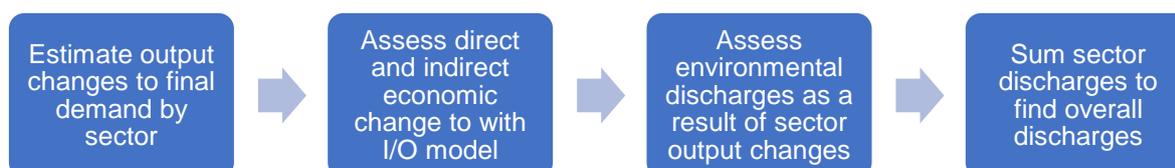
Figure 1.2. Steps for Economic Input-Output model [100]

For this type of assessment, an economic input-output matrix (Table 1.6) with the following characteristics is used:

- X_{ij} is the economic input from sector i to sector j.

- The total output of a sector i (TO) can be calculated as the sum of all outputs from that sector ($X_{i1} + X_{i2} + \ldots + X_{in}$) or the sum of the intermediate output (O) with its final demand (Y).

- The total input of a sector j (TI) can be calculated as the sum of all inputs from that sector ($X_{1j} + X_{2j} + \ldots + X_{nj}$) or the sum of the intermediate input (I) with the value added (V).

A simplified matrix A can be created by dividing each value of X_{ij} by the total output of the row (TO_i) (Table 1.7). This matrix has only values ranging from 0 to 1 and can be used to determine the environmental impacts per currency unit of output (*b*) (Equation 1.8) obtained through the use of the impact per currency unit (*R,*), the desired output vector (γ, which describes the desired number outputs) and the identity matrix (I)).

Table 1.6. Example of an Economic Input-Output Matrix [100]

	Sector Input (j)			Intermediate Output (O)	Final Demand (Y)	Total Output (TO)
Sector Output (i)	1	2	n			
1	X_{11}	X_{12}	X_{1n}	O_1	Y_1	T_1
2	X_{21}	X_{22}	X_{2n}	O_2	Y_2	T_2
n	X_{n1}	X_{n2}	X_{nn}	O_n	Y_n	TO_n
Intermediate Input (I)	I_1	I_2	I_n			
Value added (V)	V_1	V_2	V_n			
Total Input (TI)	TI_1	TI_2	TI_n			

Table 1.7. Example of a simplified Economic Input-Output Matrix [100]

	Sector Input (j)		
Sector Output (i)	1	2	n
1	X_{11} / T_1	X_{12} / T_1	X_{1n} / T_1
2	X_{21} / T_2	X_{22} / T_2	X_{2n} / T_2
n	X_{n1} / T_n	X_{n2} / T_n	X_{nn} / T_n

Equation 1.8. Environmental burdens through the Economic Input-Output Model [100]

$$b = R * (I - A)^{-1} * \gamma$$

Because of LCA's focus on the environment and to allow an economic analysis, Life Cycle Cost (LCC) analysis was proposed as an additional framework that gave information on the economic impact of all parts of a product's life cycle [101]. Another possible approach for a sustainability analysis using LCA was suggested to be a multi-objective optimization, this approach allowed optimisations to be carried out on an environmental, economic, technical, or even other criteria [102].

1.6.1. Life Cycle Assessment and Green Chemistry and Engineering

With the emergence of green chemistry and engineering it became critical to find methodologies capable of assessing the greenness of a product or process, and so, LCAs were the obvious solution, thanks to their thorough results. Unfortunately to obtain the desired results, large amounts of information are required (for example, resource consumptions and waste produced in every phase of the life cycle [99], or the relative environmental and human health impacts of all releases [103]), which is not always feasible [103].

Regardless of its limitations, LCA usage for environmental assessment of products or technologies has increased over time, especially when coupled with the previously mentioned methods of LCC or multi-objective optimization [104].

1.6.2. Industrial Application

Industrial application of an LCA is not always easy, mostly due to the need of large quantities of information which may not always be readily available [105]. Even so, the existence of multiple models and simplifications allows it to be applied around the industry, with special emphasis on green products and processes [106]. A few examples follow from several areas of science and engineering:

Chemical reactions

New chemical reactions can be assessed to determine their greenness relative to others, a critical part of green chemistry. An LCA had been carried out to determine which of two synthesis routes for maleic anhydride is greener. The first process was through the oxidation of benzene using a vanadium pentoxide (V_2O_5) catalyst carried out at 3 to 5 bar of pressure and at a temperature of 350 to 450ºC. The second process was carried under the same conditions but using a butene feedstock. Since both reactions presented the same conditions, the LCA was carried out without considering solvent, catalyst and energy consumption. Having carried out the LCA, the results show that the second process (butene route) is the greener alternative, in accordance with the Atom Economy (Equation 1.2) for carbon (100% in process 2 vs 67% in process 1). The results also show that to

further improve this synthesis the main point of interest should be the optimization of the production process of the used reagent (preferably butene) [107].

Raw materials

Various different cropping systems can be used for the production of bioethanol and biodiesel. In order to determine what alternative is greener an LCA was carried out to compare the options of 4 different cropping systems: corn-soybean rotation, continuous corn, continuous corn with 50% removal rate and continuous corn with 70% residue removal rate and wheat production in winter. In order to carry out this LCA, the soil dynamics were assumed to be based on the DAYCENT model, corn grain and soybeans were converted to ethanol and biodiesel via wet milling, with required energy inputs coming from a coal-fired power plant. The calculated values for the LCA were the non-renewable energy, global warming impact, acidification and eutrophication. The final results showed that there is no clear "greener" alternative, with the corn-soybean system having the best performance in acidification and eutrophication *vs* continuous corn with 70% residue removal rate and wheat production in winter showing the best performance in non-renewable energy and global warming impact. Considering this, the paper suggests that the best alternative is the utilization of corn stover and planting winter crops thanks to its higher production rate [108].

New technologies

New technologies can be assessed using an LCA in order to assure their potential efficacy before entering the market, for example on renewable energy systems. For this assessment, the impact caused by the energy resources, global warming, acidification and eutrophication were calculated for several different renewable electricity and heat systems. The results show no clear trend in both acidification and eutrophication potentials favour or against renewable energies, with a high dependence on the exact technology used, the energy carrier and the operational context. On the other hand, renewable energy systems show a clear advantage in finite energy resources consumed and global warming potential. Unfortunately, M. Pehnt concludes, in his work, that these results did not permit an objective decision [109].

Food products

LCAs are used to analyse food products in an attempt to find more environmentally friendly alternatives and reduce human health risk. For these assessments several variables are required to reach a conclusion due to the complexity of these systems. Among the used variables, the most important ones include:

- Land usage, with an in-depth analysis of soil erosion, organic matter, structure, pH, phosphorous, potassium and biodiversity;

- Water usage, due to the high water demands on the food industry;

- Global warming potential, including the packaging system;

- Generated waste.

Additionally, the functional unit of the LCA should be chosen based on the specific food product under study, for example, 1 g protein and 1kJ energy for different types of meat [110].

Active pharmaceutical ingredients

LCAs have been carried out to assess the greenness of active pharmaceutical ingredients, one of the main limitations of green chemistry due to the need for high degrees of purity and large amounts of used solvents. In this example, an LCA was done to determine the impacts of the different steps of the synthesis process of an unidentified active pharmaceutical ingredient produced by La Roche (substance A) to determine where it could be optimized, furthermore it was compared to another unidentified active pharmaceutical ingredient from GlaxoSmithKline (substance B) and the chemical industry in a whole as benchmarks. Several different parameters were analysed, among them stand out the cumulative energy demand, the global warming potential and the Eco-Indicator 99 (a Life Cycle impact assessment method used to assess the damage that a process causes based on the impacts on resources, human health and ecosystem quality) [111]. Additional parameters that were not used in the discussion of the results are Ecological Scarcity 2006, the Tool for the Reduction and Assessment of Chemical Impacts (TRACI) values, ReCiPe and IMPACT2002+. The Ecological Scarcity 2006 is an impact assessment parameter calculated through the relation between the critical flow (set by legislative or political guidelines) and the current flow of a substance (Equation 1.9). Although it can only be applied when the substance is a political target, it gives information on the performance relating to the region's political agenda [112].

Equation 1.9. Ecological Scarcity 2006 [113]

$$Ecological\ Scarcity\ \left(\frac{points}{flow\ unit}\right)$$

$$= \frac{1e12\ points}{year} * \frac{1}{Normalization\ Flow\left(\frac{flow\ units}{time\ frame}\right)} * \left(\frac{Current\ Flow\ (flow\ units)}{Critical\ flow\ (flow\ units)}\right)^2$$

TRACI is a software tool that evaluates the environmental and human health impacts of several raw materials and chemicals through the use of a North American database. Among these impacts are smog, respiratory effects, global warming, ozone depletion, non-carcinogenics, eutrophication, carcinogenics and acidification [114].

ReCiPe, IMPACT2002+ and Eco-Indicator 99 are point based systems that based on certain commonly calculated parameters (for example ozone depletion potential, radiation potential or marine ecotoxicity potential) determine the human health, ecosystem quality, resource impacts and, in the case of IMPACT2002+, climate change. Afterwards these values are normalized, and points are given with higher scores corresponding to bigger impacts [115].

Although the difference in the processes and substances did not allow for a direct comparison of results, the Eco-Indicator shows that substance A has a higher impact on the eco-system and

human health, while substance B is a lot more resource intensive, with solutions being possible in the optimization of energy and material usage. A comparison with other areas of chemistry also shows that active pharmaceutical ingredients have much lower annual productions resulting in less generated waste and environmental impact in total when compared with other chemical products.

Biodiesel production

An LCA was made in order to determine if the upscaling of biodiesel production from microalgae is viable from an environmental point of view [116]. To proceed with this LCA it was considered the production would be carried out by *Chlorella vulgaris*, the chosen parameters for the assessment were abiotic depletion, potential acidification, eutrophication, global warming potential, ozone layer depletion, human and marine toxicity, land competition, ionizing radiation and photochemical oxidation. Afterwards the results were compared with production from rapeseed methyl ester, soybean methyl ester, palm methyl ester, and oil diesel (Figure 1.3).
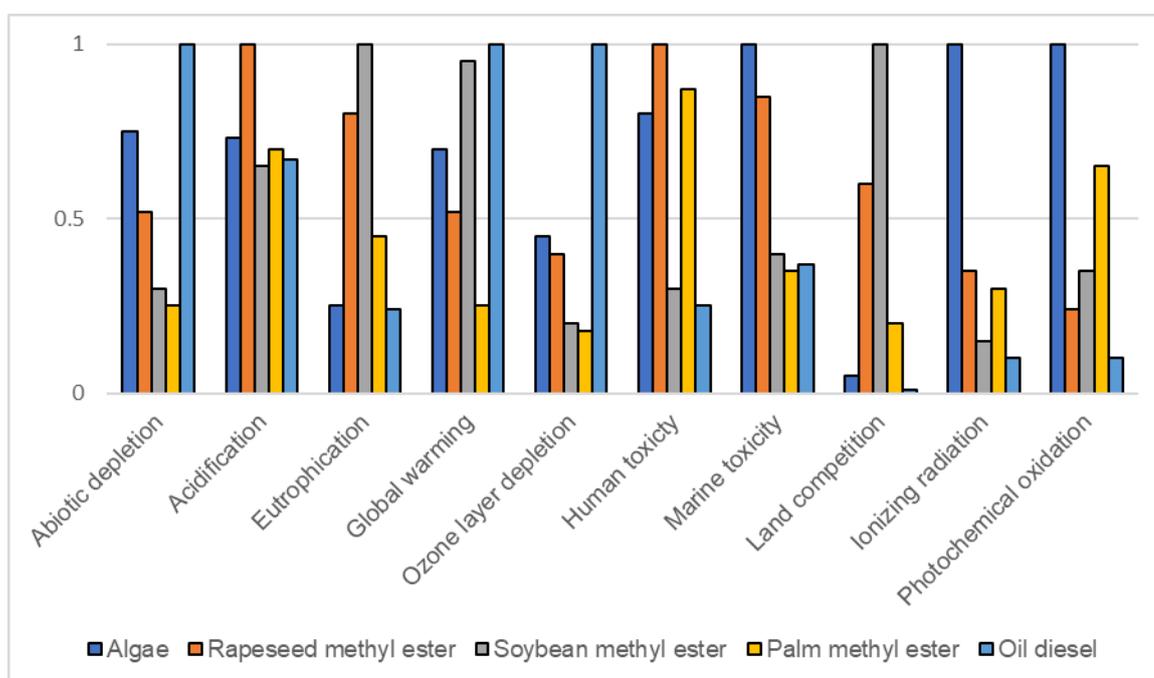
Figure 1.3. Normalized impact results for the combustion of 1 MJ of biodiesel from different sources [116]

The end results show that biodiesel production from microalgae has the highest ionizing radiation, photochemical oxidation and marine toxicity impacts, abiotic depletion is also high. On the other hand, it shows low impacts for eutrophication and land use and average results for acidification, human toxicity and ozone depletion. This means that, while not being outperformed by any other option it does not outperform them either, with further improvements to this technology being recommended.

Building materials

Several LCAs were carried out to determine the best building material to use, from a green point of view [117]. To carry out these assessments, the impact categories under scrutiny were the

primary energy demand, the global warming potential and the water demand. The results were grouped by type with no clear "greener" materials, being necessary to choose the best material for each job, for example, ceramic roof tiles are superior to fibre cement roof slates while, on the other hand, ceramic tiles are overall inferior to other tiling options.

Solvent selection

An LCA assessment was carried out to compare two different solvents (1-butyl-3-methylimidazolium chloride and N-methyl-morpholine-N-oxide) used in cellulose dissolution to determine which was greener [118]. The impact assessment was done using the abiotic resource depletion potential, the global warming potential, the ozone depletion potential, the human toxicity potential, the acidification potential, the eutrophication potential, the photochemical ozone creation potential, the freshwater aquatic ecotoxicity potential, the terrestrial ecotoxicity potential and the emission of volatile organic compounds.

The results showed that usage of N-methyl-morpholine-N-oxide is a better option to 1-butyl-3-methylimidazolium chloride in most categories. The LCA also showed that the synthesis of the solvent plays a large part on the impact assessment, which means that recycling of the solvent or optimization of the synthesis can play a crucial role in minimizing environmental impacts.

Supermarket carrier bags

Research has been carried out for supermarket carrier bags by the Environment Agency via an LCA, the presented types were conventional high-density polyethylene bags, high-density polyethylene bags with a prodegradant additive, starch-polyester blend bags, paper bags, low-density polyethylene bags, non-woven polypropylene bags and cotton bags [119]. To carry out the impact assessment, the parameters under study were the global warming potential, the abiotic depletion, the acidification, eutrophication, human toxicity, fresh water aquatic ecotoxicity, marine aquatic ecotoxicity, terrestrial ecotoxicity and photochemical oxidation. The final results show that the conventional high-density polyethylene bags had the lowest environmental impact of all lightweight bags in eight categories, the high-density polyethylene bags with a prodegradant additive was always worse than the conventional one, the starch-polyester bag had the highest impact in seven categories. In terms of reusable bags, low-density polyethylene bags were shown to have the lowest environmental impacts of all bags in eight categories if reused five times, and the cotton bags presented the largest impacts in seven categories, even when reused one hundred and seventy-three times.

Cement industry

An environmental study using LCA was conducted to determine the impact of applying a carbon dioxide (CO_2) post-combustion capture to the cement industry [120]. This assessment was carried out with the objective of comparing two scenarios: a 2030 scenario with the best available technologies and a 2030 scenario with the added CO_2 post-combustion capture. An additional 2010 base scenario was also used for comparison.

The impact categories chosen for this assessment were global warming, ozone depletion, human toxicity with cancer effects, human toxicity with non-cancer effects, particulate matter, ionising radiation, photochemical ozone formation, acidification, terrestrial eutrophication, freshwater eutrophication, marine eutrophication, freshwater ecotoxicity, land use and abiotic depletion potentials.

After carrying out the LCA it was possible to conclude that by applying the best available technologies in the market it is possible to reduce the environmental impact in all categories, with the reduction varying between 22% for global warming potential and 94% for ionizing radiation. On the other hand, while application of CO_2 post-combustion capture does reduce the global warming potential by an additional 15%, the ozone depletion by 27% and the abiotic depletion by 11% it worsens the other categories. This allowed the study to conclude that further research and impact assessments are required before CO_2 post-combustion capture can be applied.

Nanotechnology

An LCA has been carried out to the synthesis on nanoparticles to assess its greenness, one of the critical areas of research in both green chemistry and green engineering [70]. For this assessment, three conventional methods and thirteen green methods for the synthesis of gold nanoparticles were compared. For the impact assessment, the chosen categories were the cumulative energy demand, the climate change potential, the metal depletion potential, the agricultural land occupation and the freshwater ecotoxicity. The results obtained by this assessment showed that all methods considered "green" for the synthesis of gold nanoparticles from a green chemistry and engineering point of view obtained worse results than the best conventional method (synthesis using sodium borohydride). The study concludes that this happened due to the usage of limited raw materials (gold), where yield becomes a critical parameter and a "simple" approach of substituting toxic chemicals without clear metrics can be ineffective or even negative.

1.6.3. Limitations on Life Cycle Assessments

Despite all the possible applications of LCAs, it is not without flaws. Its holistic and complete approach comes at the cost of large amounts of data that needs to be measured or simulated. This means that to apply LCAs it becomes necessary to resort to simplifications and assumptions which can lead to increased uncertainty on the results [99]. As a result, it becomes necessary to consider how much uncertainty is acceptable in each part of the assessment, leading to increased costs and time consumption [121].

LCAs also suffer from being static, meaning that they can only be applied in specific timeframes and locations in each study, as such, they don't take into account long term effects of what is being assessed nor changes in the location (for example, due to transportation). The aggregation of chemical types can also lead to bias in the final results, for example, one of the used impact categories is "total organic compounds", although not all organic compounds have the same effect on the environment [122].

1.7. Green Metrics

Most of the principles of green chemistry are purely qualitative [22] and Life Cycle Assessment, even being as powerful a tool as it is, can only go so far [121]. As a result, it becomes necessary to create a set of green metrics capable of following the 12 principles of green chemistry [123]. These metrics need to be capable of giving a clear answer to the question "Is this product/process greener?", while still being easy enough to apply on a laboratory scale [124].

1.7.1. Existing Metrics, Methods and Tools

To give a way to quickly measure how green a product or process is, several different metrics, methods and tools have been created, with some being more easily applicable in some areas of chemistry than others, for example the E-factor may be hard to apply in the pharmaceutical industry due to the definition of waste [125]. Several examples of green metrics exist with more appearing constantly [126], a few examples and practical applications follow:

E-factor

The E-factor (Equation 1.1), based on the 1st principle of green chemistry, is the amount of waste produced by kg of product with the original definition of waste being "everything but the desired product" and not considering water [24]. Depending on the area of the chemical industry being assessed, however, what is or isn't considered waste can sometimes vary leading to differing results for the same process.

Three different calculations of the E-factor were done for the Pfizer process for the manufacture of sildenafil citrate. One of them, considering 10% of solvents as waste, obtained a value of 6.4 kg/kg, another one, excluding all solvents and water, obtained a value of 3.9 kg/kg and the final one including all water and solvents obtained a value of 50.3 kg/kg. When comparing the average E-factor in the pharmaceutical industry (25 to 100 kg/kg) to the E-factor of the Pfizer process for the production of sildenafil citrate considering only 10% of solvents as waste (6.4 kg/kg) it can be concluded that the Pfizer process is greener. Additionally, when the E-factors are compared with each other and analysed in further detail, it can be seen that water and organic solvents play a large part in generated waste [127].

Atom Economy, Reaction Mass Efficiency and Mass Intensity

Atom Economy (Equation 1.2), based on the 2nd principle of green chemistry, is a simple metric that calculates the amount of reagent that actually went to the desired product. Reaction Mass Efficiency can be defined as the product of the Atom Economy and the yield (Equation 1.3), the mass of desired product per mass of reagents used (Equation 1.4) or the mass of desired product per mass of other materials (Equation 1.6). This means that reaction Mass Efficiency takes into account both the yield and the Atom Economy (Equation 1.5) [25].

By calculating the reciprocal of the general Mass Efficiency, Mass Intensity (Equation 1.7) can be obtained. This metric is used to determine how many times larger is the material input when

compared to the product output, with the ideal value being 1 (the mass input in the system is equal to the product output, meaning 100% conversion) [26].

These metrics have been used to compare catalytic and non-catalytic processes, for example on the hydrogenation of nitrobenzene, where the traditional Béchamp process has an Atom Economy of 35% and the nickel catalysed process has an Atom Economy of 72%. This is a large increase (more than doubles the Atom Economy) especially when considering the valuable reactants used in the Béchamp process. Further comparisons using other metrics have also been made to determine what route (chemical or biocatalytic) is greener for the synthesis of 7-aminocephalosporanic acid (7-ACA). The results showed that, with a better Atom Economy, reaction Mass Efficiency and E factor (when not considering water) the biocatalytic route was the greener alternative [25].

Carbon Efficiency

Carbon Efficiency (Equation 1.10) is a metric used to determine what percentage of the carbon present in the reagents is incorporated into the product. This metric presents similar trends to the Curzons reaction Mass Efficiency (Equation 1.4) and should be applied instead or in parallel of it when carbon is a main concern (for example, when attempting to reduce carbon-based gas emissions) [125].

Equation 1.10. Carbon Efficiency [125]

$$Carbon\ efficiency\ (\%) = \frac{Amount\ of\ carbon\ in\ the\ product\ (mol)}{Amount\ of\ carbon\ in\ the\ reagents\ (mol)} * 100$$

GlaxoSmithKline metrics

GlaxoSmithKline, prepared a set of metrics with higher relevance within the pharmaceutical and chemical industries [128]. This set of metrics (Table 1.8) measures the number of steps required to produce the product, the overall yield, the solvents required, the need for extreme conditions and the generated waste of water, solvents and other inputs (these three calculated separately, with their sum representing the E-factor (Equation 1.1) and each of them representing a Mass Intensity (Equation 1.7)). Albeit capable of being applied less than 1-2 hours, the information given by these metrics is limited, with a separate full environmental assessment required.

Table 1.8. Template for GlaxoSmithKline metrics [128]

Compound number
Route designation
Date of assessment and reference
Number of chemistry steps
Number of purification steps
Number of stages
% Overall Yield
List of solvents used
List of extreme conditions
List of reagents with known environmental, safety or health problems

Overall kg solvent/kg final product
Overall kg water/kg final product
Overall kg input material (excluding solvent and water)/kg final product
Total waste/kg of final product (sum of 3 boxes above)
Overall kg input material (excluding solvent and water)/kg final product if all stage yields are 100%
Projected peak year tonnage
Catalytic chemistry used
Asymmetric chemistry used
Additional comments

An example on the reductions in volumes of solvent, aqueous and input materials caused by introducing and optimising new production routes is also presented. The example shows the mass intensities for the production of an unidentified compound "A" by three different routes (route A and route B and optimised route B) . The presented results show that route B's 1st run has lower mass intensities than route A's 1st run (about 50% reduction), with optimization reducing them even further (an additional 50% reduction when comparing route B's 1st run with route B's optimised route.).

EATOS

In organic synthesis, an important tool is EATOS (Environmental Assessment Tool for Organic Synthesis) allowing a quick comparison of different synthesis pathways for a same product based on inserted metrics [129]. A proposed set of metrics to use in EATOS is the mass index (mass of raw materials per mass of product) and the E-factor. This method allows for a graphical analysis of what is having a highest impact in the synthesis process, unfortunately it allows only for a first approach with little detail and requires large amounts of data. To illustrate the process four different methods of the synthesis of 4-methoxyacetophenone were compared, three classic ones (reactions a, b and c) and a new method (reaction d).

The results showed that the even though the new process has better yield its E factor and mass index is substantially higher than two of the classic methods (reactions b and c). This difference is in a large part due to the higher amounts of solvents needed, sewage water released and generated by-products of the catalyst. This also shows that solvents play a critical role in the environmental impacts of reactions for organic synthesis, contributing to over 50% of it in reactions a, b and d.

Eco-scale

A semi-quantitative method called Eco-scale was produced to allow the application of the principles of green chemistry on a small scale [130]. This method is point based, with the evaluation starting with 100 points that are reduced based on penalties (Equation 1.11). These penalties are

based on economic costs, safety, required setup, temperature and time required, and if workup and purification is necessary (Table 1.9). The lack of waste analysis is due to its relative lack of importance on a laboratory scale.

Equation 1.11. EcoScale calculation [130]

$$EcoScale = 100 - sum\ of\ individual\ penalties$$

Table 1.9. EcoScale individual penalties [130]

Parameter	Penalty points
1. Yield	(100 – %yield)/2
2. Price of reaction components to obtain 10 mmol of end product	
Inexpensive (<10$)	0
Expensive (>10$ and <50$)	3
Very expensive (>50$)	5
3. Safety	
N (dangerous for environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals	1
Unconventional activation technique	2
Pressure equipment, >1 atm	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3
5.Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0

Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction	3
Classical chromatography	10

An example is also shown for the comparison of four synthetic transformations of high purity products (reduction of nitrobenzene to aniline, oxidation of benzyl chloride to benzoic acid, a standard synthesis of benzamide and synthesis of benzamide using hexamethyldisilazane (HMDS)), with the final results being ranked as: >75, excellent; >50, acceptable; and <50, inadequate.

The final classification of these processes was of 64 points for the reduction of nitrobenzene to aniline (acceptable), 78 for the oxidation of benzyl chloride to benzoic acid (excellent), 53 for the synthesis of benzamide (acceptable) and 32 points for the synthesis of benzamide using HMDS. This allowed the paper to conclude that usage of HMDS during the synthesis of benzamide is a worse option to the standard synthesis, with further research being advisable.

Tree Analysis

A tree graphic analysis (Table 1.10) was proposed as a way to quantify the parameters required to calculate the reaction Mass Efficiency, total energy required for product and raw material cost [131]. Branching index, Wiener index, Hendrickson parameter and Randic connectivity index depend on the connectivity of the tree nodes; the number of reaction stages is the number of times reactions need to occur (simultaneous reactions count as one); the number of parallel reactions is the number of reactions that occur simultaneously; the co-ordinates of the final product and angle depend on the relative position of the nodes; the degrees of convergence and the rates of convergence define how well and how fast this method works, the Kernel RME is the formula that should be used to determine it via this method.

Table 1.10. Example of the parameters of a tree analysis for a single stage chemical reaction with four reagents [131]

Characteristic	Value for a single stage chemical reaction with 4 reagents
Branching Index	6
Wiener Index	16
Hendrickson parameter	4
Randic connecctivity Index	2
Number of reaction	1
Number of reaction stages	1
Number of parallel reactions	0
Co-ordinates of final product	$(1,\frac{3}{2})$
Angle fo final product (degrees)	112.620
Degrees of convergence	1
Rate of convergence	1.5
Relative rate of convergence	1
Asymmetry parameter	0
Kernel RME	$\dfrac{Product\ molar\ weight\ \left(\frac{kg}{mol}\right) * yield}{\sum Inputs\ molar\ weight\ (\frac{kg}{mol})}$

The need to understand all parts of the analysis is one of the major issues with this method, as suppliers may not give production information on their materials. Several examples (like the synthesis of triclosan) appear in the paper, with the results being shown by reaction stage. This allowed the determination of which stages need to be optimized in order to improve the greenness of the processes.

Solvent selection guides

Based on a set of qualitative rules (Table 1.12), Pfizer developed a solvent selection guide (Table 1.11), a list of solvent alternatives (Table 1.13) and a reagent guide (Table 1.14). The rules for solvent selection were worker safety (carcinogenicity, mutagenicity, reprotoxicity, skin absorption/sensitisation, and toxicity), process safety (flammability, potential for high emissions through high vapour pressure, static charge, potential for peroxide formation and odour issues) and environmental and regulatory consideration (ecotoxicity and ground water contamination, potential environmental, health and safety (EHS) regulatory restrictions, ozone depletion potential, photoreactive potential). On the other hand, the reagent guide was created based on yield, possibility of scaling-up and a greenness assessment including worker safety, ecotoxicity and Atom Economy [132].

Table 1.11. Solvent selection guide [132]

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane

Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl t-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-Methylterahydrofuran	Dimethyl formamide
Methyl ethyl ketone	Tetrahydrofuran	N-Methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethyl acetamide
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Table 1.12. Application of solvent selection rules [132]

Undesirable solvent	Reason
Pentane	Very low flashpoint, good alternative available.
Hexane(s)	More toxic than the alternative heptane, classified as a hazardous airborne pollutant (HAP) in the US.
Di-isopropyl ether	Very powerful peroxide former, good alternative ethers available.
Diethyl ether	Very low flash point, good alternative ethers available.
Dichloromethane	High volume use, regulated by EU Solvent Directive, classified as HAP in the US.
Dichloroethane	Carcinogen, classified as a HAP in the US.

Chloroform	Carcinogen, classified as a HAP in the US.
Dimethyl formamide	Toxicity, strongly regulated by EU Solvent Directive, classified as a HAP in the US.
N-Methylpyrrolidinone	Toxicity, strongly regulated by the EU Solvent Directive.
Pyridine	Carcinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, very low threshold limit value (TLV) for worker exposures.
Dimethyl acetamide	Toxicity, strongly regulated by the EU Solvent Directive.
Dioxane	CMR category 3 carcinogen, classified as HAP in the US.
Dimethoxyethane	CMR category 2 carcinogenic, toxicity
Benzene	Avoid use: CMR category 1 carcinogen, toxic to humans and environment, very low TLV (0.5 ppm), strongly regulated in the EU and the US (HAP).
Carbon tetrachloride	Avoid use: CMR category 3 carcinogen, toxic, ozone depleter, banned under the Montreal protocol, not available for large-scale use, strongly regulated in the EU and US (HAP).

Table 1.13. Solvent alternatives [132]

Undesirable solvent	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-methyltetrahydrofuran or tert-butyl methyl ether
Dioxane or dimethoxyethane	2-methyltetrahydrofuran or tert-butyl methyl ether
Chloroform, dichloroethane or carbon tetrachloride	Dichloromethane
Dimethyl formamide, dimethyl acetamide or N-Methylpyrrolidinone	Acetonitrile

Pyridine	Triethylamine
Dichloromethane (extractions)	Ethyl acetate, tert-butyl methyl ether, toluene or 2-methyltetrahydrofuran
Dichloromethane (chromatography)	Ethyl acetate or heptane
Benzene	Toluene

Another guide has also been suggested by GSK (GlaxoSmithKleine) (Table 1.14) based on generated waste, environmental impact, health, flammability, reactivity and life cycle score, with these parameters being calculated qualitatively (Table 1.15). Recommendations about the solvents are further given based on their lowest score on these parameters [133].

Table 1.14. GSK's solvent selection guide [133]

Solvent type	Few issues	Some issues	Major issues
Chlorinated			Dichloromethane Carbon tetrachloride Chloroform 1,2-Dichloroethane
Greenest option	Water		
Alcohols	1-Butanol 2-Butanol	Ethanol t-Butanol	2-Methoxyethanol
Esters	t-Butyl acetate Isopropyl acetate Propyl acetate Dimethyl Carbonate		
Ketones		Methyl isobutyl ketone Acetone	Methyl ethyl ketone
Aromatics		p-Xylene Toluene	Benzene
Hydrocarbons		Isooctane Cyclohexane Heptane	Petroleum spint 2-Methylpentane Hexane
Ethers		t-Butyl methyl ether Cyclopentyl methyl ether 2-Methyltetrahydrofuran	Diethyl ether Bis (2-methoxyethyl) ether

Dipolar aprotics		Dimethyl sulfoxide	1,4-Dioxane Tetrahydrofuran 1,2-Dimethoxyethane Diisopropyl ether Dimethyl formamide N-Methyl formamide N-Methyl pyrrolidone Dimethyl acetamide Acetonitrile

Table 1.15. Example of parameters application to water and alcohols [133]

Classification	Solvent	CAS number	Melting Point ºC	Boiling Point ºC	Waste	Environmental Impact	Health	Flammability & Explosion	Reactivity / stability	Life Cycle Score	Legislation Flag
Greenest	Water	7732-18-5	0	100	4	10	10	10	10	10	
Alcohols	1-Butanol	71-36-3	-89	118	5	7	5	8	9	5	
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6	
	Ethanol	64-17-5	-114	78	3	8	8	6	9	9	
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8	
	Methanol	67-56-1	-96	65	4	9	5	5	10	9	
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4	
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7	
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7	Regulatory restrictions apply

Metrics for polymer production

For polymer production the efficacy of green metrics was tested using the Atom Economy for waste analysis, density for material efficiency, TRACI health and ecotoxicity impacts for hazard avoidance, total energy demand for energy efficiency, percent of renewable resources, feedstock distance to optimize local sources, percent of recycled, biodegradability and price. This methodology was tested along with an LCA in order to determine which of twelve polymers was greener [134]. The results showed a considerable difference between the application of green metrics or the LCA, with the polymers ranked 1, 2, 3 and 4 in the green metrics corresponding respectively to positions 6, 4, 8 and 9 in the LCA. Likewise, the polymers ranked 1, 2 ,3 and 4 by the LCA corresponded to positions 9, 5, 7 and 2 of the green metrics assessment. This demonstrated that further work is needed in the field of sustainable metrics to allow for a unified approach to greenness.

UBIOCHEM CM0903 COST

According to UBIOCHEM CM0903 COST Action some recommended metrics for isoprene production using microalgae or bacterium are material efficiency, total energy input, economics and land use. For this comparison, theoretical and real values were used for both possible routes. Due to large discrepancies between the theoretical and real production of isoprene from the microalgae the results were limited, allowing only for a comparison of theoretical values. The chosen metrics showed that the microalgae produce more waste and require more energy but require less land and produce

more revenue. This led to the conclusion that from an economic standpoint the theoretical microalgae production is more attractive, but from an environmental standpoint bacterium (more specifically, *Escherichia coli*) are the superior option [135].

Nanoparticles

A nanoparticle synthesis classification method was created based on the reduction agent, the capping agent, the solvent, the use of local resources, the reaction time, the reaction temperature, the equipment types and the size range using "if… then…" rules. For this method the choice of reducing agent, capping agent and solvent is based the principles of green chemistry 1, 3, 4, 5, 7, 8, 10 and 12; the choice of local resources is due to principal 7; the reaction time and temperature are analysed due to principles 6 and 12; the equipment type is chosen with principles 1, 6, 11 and 12 in mind. The synthesis methods are then ranked from A to E (A > B > C > D > E), based on how well they follow the criteria. An example is present in the study using 48 protocols for the synthesis of silver nanoparticles [136]. The results from the paper show that through the application of this strategy, it is possible to quickly sort different synthesis methods from a qualitative point of view. The use of transparent and easily understandable conditions with a semi-quantitative approach also makes this method repeatable by others with the same results.

GREEN MOTION

A tool called GREEN MOTION was created to make greenness evaluations based on raw material origin, solvent selection, usage of raw materials and solvents with little or no toxicity to human health and environment, reaction efficiency, process efficiency, design of products with respect to the environment and with no impact to human health and safety and waste reduction [137]. This method assesses how green a process is using a scale from 0 to 100 where higher values are better. Initially all products and processes are at 100 points and depending on how they score in the evaluated area, the value suffers penalties.

In the paper 81 products are shown to have been evaluated and a specific example is given on the synthesis of vanillyl ethyl ether using different solvents with 1,2-Dichloroethane scoring 23 points, dichloromethane scoring 24 points and toluene scoring 37 points.

1.7.2. Conclusions from Existing Metrics and Methods

Despite the large amount of options to make a greenness assessment, the limited quantitative results and the lack of a holistic approach make it difficult to allow for comparative conclusions to be made. With the need for a context when applying these metrics it becomes clear that while a "perfect" set of metrics is impossible to find, there have yet to appear metrics capable of providing a satisfactory numeric answer to the greenness of a process while taking into account all parts of green chemistry [26].

1.8. Geo Ground Engineering Operations, Lda's green chemistry grid

Geo Ground Engineering Operations, Lda created a green chemistry comparison grid, this grid focuses on each principle one by one and adds 3 additional principles (for a total of 15 principles), turning each into an empiric formula and integrating it between 0 (worst case) and 1 (best case) to allow for a green index to be determined. This normalized index can then be used to determine what process is greener from a purely objective point of view while also giving information on the process' impact on each individual principal.

Principle 1

The first principle of green chemistry focuses on waste reduction and is one of the two principles with an associated formula, the E-factor [24] (Equation 1.1). The E-factor is ideally as low as possible and, in this case, calculated by considering waste all outputs from the process other than the intended product. Lastly, in order to integrate this value from 0 (worst case) to 1 (best case) the E-factor was turned into a percentage using the following expression (Equation 1.12):

Equation 1.12. Integrated E-factor

$$Integrated\ E\text{-}factor = \frac{1}{1 + E\text{-}factor}$$

Principle 2

The second principle of green chemistry aims to maximize the incorporation of all materials used in a synthetic method into the final product. This principle also has an associated formula, the Atom Economy [25] (Equation 1.2). Ideally the Atom Economy should be as high as possible, and its result is a percentage between 0% and 100%, as such it's already integrated between the objective of 0 (worst case) and 1 (best case).

Principle 3

This principles states that substances used and generated in a synthetic method should be as non-toxic as possible to both the human health and the environment. For this principle a formula had to be created from root. Assuming that the total toxicity of a substance can be separated into a human toxicity parcel and an environmental toxicity parcel (as is done in other assessments [138]), the Hazard Index for each substance (Equation 1.13) was considered to be the sum of the Human Toxicity Index and the Environment Toxicity Index for that substance. Due to the extensive nature of toxicology studies, a multidisciplinary approach had to be taken in order to develop the Indexes used in this principle through a collaboration with experts in the fields of Biology, Biochemistry and Chemistry, among others.

Equation 1.13. Hazard Index

$$Hazard\ Index = Human\ Toxicity\ Index + Environment\ Toxicity\ Index$$

The Human Toxicity (Equation 1.14) was considered to be a function of the Exposure time, the Exposure level and either the lethal dose low (LDLo, the minimum dose of a substance required to kill a specimen from a population) or the median lethal dose (LD50, the dose of a substance required to kill, on median, half the specimens from a population), depending on the available data. This data can be taken, for example, from the U.S. National Library of Medicine's TOXNET in the ChemID*plus* database [139]. This database has toxicity information about over 100,000 chemicals.

Equation 1.14. Human Toxicity

$$Human\ Toxicity = \frac{Exposure\ level\ (\frac{mg}{kg\ person})}{LDLo\ /\ LD50\ (\frac{mg}{kg\ person}.day)} * Exposure\ time\ (day)$$

In addition, the Exposure level (Equation 1.15) was considered to be dependent on the mass of chemical used to produce 1 kg of product, the number of people, the average person weight and the person's area of exposure.

Equation 1.15. Exposure level

$$Exposure\ level\ \left(\frac{mg}{kg\ person}\right) = \frac{m_{Chemical}\ (\frac{mg}{Kg\ of\ product})}{Number\ person * Avg\ Weight_{Person}(Kg)} * Exposure_{area}(\%)$$

Lastly, the Human Toxicity was normalized to values between 0 (worst case) and 1 (best case), obtaining the Human Toxicity Index (Equation 1.16).

Equation 1.16. Human Toxicity Index

$$Human\ Toxicity\ Index = \frac{1}{Human\ Toxicity + 1}$$

The determination of the Environment Toxicity Index (Equation 1.17) is done through the use of a substance's Environment Toxicity Rank, a tabled value dependent on the acute aquatic toxicity of the substance.

Equation 1.17. Environment Toxicity Index

$$Environment\ Toxicity\ Index = \frac{1}{Log\ (Environment\ Toxicity\ Rank) + 1}$$

Acute aquatic toxicity is determined separately for algae, bivalves, crustaceans and fish. This division is done because of the characteristics they have and different trophic levels (position in the food chain) that each of them occupy, having different effects in the eco-system and reacting differently to the substances [140]. Algae occupy a position of primary producers [141]; crustaceans are considered the representative group of "standard" primary consumers [141]; bivalves, usually the largest group of filter-feeding organisms in freshwater ecosystems [142], are primary consumers as well; fish are secondary consumers [141].

To allow for the Environment Toxicity Rank to be determined, an aquatic toxicity database was created with joint information from the two different sources:

- United States' ECOTOXicology knowledgebase (ECOTOX) [143], a knowledgebase that integrates three different databases: AQUIRE (aquatic life), PHYTOTOX (terrestrial plants) and TERRETOX (terrestrial wildlife) with information on the toxicity of several different substances.

- European Chemicals Agency's (ECHA) database [144], containing information on over 18,000 unique substances including, for some of them, toxicity information using the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations

Afterwards, using the available data and filtering it based on a priority list (Table 1.16 and Table 1.17) the obtained values are ranked in comparison with all other chemicals in the database, and the final sum and ordering of these rankings is used to determine the substance's Environment Toxicity Rank . The value for the Environment Toxicity Index is between 0 (worst case) and 1 (best case).

Table 1.16. ECOTOX priority list

Priority	Fish Endpoint	Bivalve Endpoint	Crustacean Endpoint	Algae Endpoint	Duration	Concentration
1st	LC 50	LC 50	LC 50	EC 50	4 days (96 hours)	mg/L
2nd	Other LCs	Other LCs	Other LCs	Other ECs	3 days (72 hours)	mmol/L
3rd	LDs	LDs	LDs	LCs	2 days (28 hours)	Blanks
4th	EC 50	EC 50	EC 50	All others	1 day (24 hours)	mg/Kg, mmol/Kg, ml/Kg and %
5th	Other ECs	Other ECs	Other ECs			pH
6th	All others	All others	All others			mCi, mCi/Kg, mCi/L and mCi/mmol

Table 1.17. ECHA priority list

Priority	Fish Endpoint	Bivalve Endpoint	Crustacean Endpoint	Algae Endpoint	Duration	Concentration	Significance level
1st	LC 50	LC 50	LC 50	EC 50	4 days	mg/L	1 or 2
2nd	Other LCs	Other LCs	Other LCs	Other ECs	3 to 5 days	mmol/L	3
3rd	LDs	LDs	LDs	LCs	2 to 6 days	Blanks	4
4th	EC 50	EC 50	EC 50	All others	1 to 7 days	mg/Kg and %	
5th	Other	Other	Other ECs			pH	

6th	ECs EDs, EEs, LLs, ELs, ICs, LRs, LTs, blanks	ECs EDs, EEs, LLs, ELs, ICs, LRs, LTs, blanks	EDs, EEs, LLs, ELs, ICs, LRs, LTs, blanks				

The use of the Human Toxicity Index (between 0 and 1) and the Environment Toxicity Index (between 0 and 1) makes the value for the Hazard Index to be between 0 (worst case) and 2 (best case) for each individual substance, as such to integrate it between 0 (worst case) and 1 (best case) the average of the Hazard Indexes is calculated and divided by 2 (the maximum possible value) (Equation 1.18).

Equation 1.18. Integrated Hazard Index

$$Integrated\ Hazard\ Index = \frac{\sum Hazard\ Index\ of\ individual\ substances}{2 * number\ of\ substances}$$

Principle 4

This principle mainly focuses on reducing the toxicity of the product and has no associated mathematical formula. However, considering this principal similar to principle 3 and having already created the required equations to determine the toxicity of a substance (Equation 1.13, Equation 1.14, Equation 1.15, Equation 1.16, Equation 1.17 and Equation 1.18) those same formulae are used in this principle to determine the toxicity of the product.

Principle 5

The 5th principle of green chemistry aims to reduce the usage of auxiliary substances and/or reducing their associated hazards. Having no associated metric, the Safety Index was proposed to assess it (Equation 1.19).

Equation 1.19. Safety Index

$$Safety\ Index\ (\%) = (1 - \frac{Total\ Index}{16}) * 100$$

This expression is considered to be dependent on the substance's Total Hazard Index, a value between 0 (best case) and 16 (worst case) corresponding to the sum of Health Index, Flammability Index, Stability Index and Special Index (Equation 1.20). These four Indexes values are obtained directly from the related parameters on the substance's Material Safety Data Sheet (MSDS) (Figure 1.4): Health Hazard for Health Index, Fire Hazard for Flammability Index, Instability Hazard for Stability Index and Special Hazards for Special

$$Total\ Index = Health\ Index + Flammability\ Index + Stability\ Index + Special\ Index$$

4 = Can be lethal
3 = Can cause serious or permanent injury
2 = Can cause temporary incapacitation or injury
1 = Can cause significant irritation
0 = No hazard

4 = Will vaporize and readily burn at normal temperature
3 = Can be ignited under almost ambient temperature
2 = Must be heated or high ambient temperature to burn
1 = Must be preheated before ignition can occur
0 = Will not burn

Fire Hazard

Health Hazard

Instability Hazard

OX = Oxidizer
W = Reacts with water
SA = Asphyxiant gas
ACID, ALK = Acid or alkaline
BIO = Biohazard
POI = Poisonous
RAD = Radioactive
CRYO = Cryogenic

Special Hazard

4 = May explode at normal temperatures and pressures
3 = May explode at high temperature or shock
2 = Violent chemical change at high temperatures or pressures
1 = Normally stable. High temperature makes unstable
0 = Stable

Figure 1.4. Hazard Classifications [145] [146]

Equation 1.21. Health Index

$$Health\ Index = Health\ Hazard\ level$$

Equation 1.22. Flammability Index

$$Flammability\ Index = Fire\ Hazard\ level$$

Equation 1.23. Stability Index

$$Stability\ Index = Instability\ Hazard\ level$$

Equation 1.24. Special Index

$$Special\ Index = 0.5 * number\ of\ special\ hazard\ warnings$$

After applying the formulae, the Integrated Safety Index can be calculated, using the average Safety Index of all the auxiliary substances in the process (Equation 1.25). The obtained value is between 0 (worst case) and 1 (best case).

Equation 1.25. Integrated Safety Index

$$Integrated\ Safety\ Index = \frac{\sum Safety\ Index\ of\ individual\ auxiliary\ substances}{number\ of\ auxiliary\ substances}$$

Principle 6

This principle states that energy requirements should be minimized for their economic and environmental impacts and has no formula attached to it. Considering that the total required energy for a process is described as a function of both power and time requirements for all the used equipment, a mathematical expression was proposed (Equation 1.26). Integration of this value between 0 (worst case) and 1 (best case) can then be done through a logarithmic scale (Equation 1.27) allowing for process comparisons.

Equation 1.26. Total Energy Requirements

$$Total\ Energy\ Requirements\ (kWh) = \sum (Power\ (kW) * Time\ (h))$$

Equation 1.27. Integrated Energy Requirements

$$Integrated\ Energy\ Requirements = \frac{1}{Log\ (Total\ Energy\ Requirements(kWh)) + 1}$$

Principle 7

This principle focuses on the renewability of raw materials and no formula is associated to it. The proposed metric considers that a material is either completely renewable or completely non-renewable. As such, it is based on material integration unto the final product and a binary renewability factor (1 for renewable materials like biomass [147], 0 for non-renewable materials like fossil fuels [147]) (Equation 1.28), determining what percentage of the feedstocks is renewable.

Equation 1.28. Feedstock

$$Feedstock = (\frac{mass\ of\ reagent\ (kg)}{mass\ of\ product\ (kg)} * 100) * Renewability\ factor\ (0\ or\ 1)$$

The obtained value for feedstock is between 0% and 100% and integration is done via the feedstock average for all materials (Equation 1.29). The integrated feedstock would ideally be between 0 (worst case, fully non-renewable feedstock) and 1 (best case, fully renewable feedstock), however one of the presented results shows a value of 5.63, outside the intended range.

Equation 1.29. Integrated Feedstock

$$Integrated\ Feedstock = \frac{\sum Feedstocks}{number\ of\ reagents}$$

Principle 8

The 8th principle of green chemistry is about the reduction of derivatization in a process, having no mathematical formula associated to it. Derivatization is the act turning a chemical compound into a similar one by altering its functional groups, for example, using a blocking group, forcing a temporary modification of physical/chemical properties, protection reactions (turning a functional group into a protecting group to increase selectivity) or deprotection reactions (turning a protecting group into a functional group) [148]. Considering this, the metric proposed by Geo Ground Engineering Operations, Lda considers that the downside of derivatization is fully dependant on the required mass of derivatives and not on the technique (in this principle) and is directly integrated into a value between 0 (worst case) and 1 (best case) (Equation 1.30).

Equation 1.30. Integrated Derivatives

$$Derivatives\ Integration = \frac{1}{1 + \sum mass\ of\ derivatives\ required\ to\ produce\ 1\ kg\ of\ product\ (kg)}$$

Principle 9

This principle favours the use of catalytic reagents instead stoichiometric reagents and has no mathematical expression associated to it. In order to assess the use of a catalytic reagent over a stoichiometric one and how selective it is, this metric (Equation 1.31) considered a binary component for the catalyst usage (1 if used, 0 if not used) and the Integrated E-factor from principle 1 (Equation 1.12). The obtained value is between 0 (worst case) and 1 (best case).

Equation 1.31. Integrated Catalyst Metric

$$Integrated\ Catalyst\ Metric = Integrated\ E\text{-}factor * Catalyst\ Usage\ (0\ or\ 1)$$

An exception was considered for this metric's application: If the Integrated E-factor is 1, then the Integrated Catalyst Metric is 1 as well, regardless of using a catalyst or not (Waste could not be further reduced by using a catalyst).

Principle 10

This principle focuses on the degradability of chemical products at the end of their function and has no associated formula. The proposed metric, Half-life Index (Table 1.18), is dependent on the half-life (time required for half of a substance to degrade) of a product or sub product at the end of its function, as is done in other assessments like the environmental impact of alkylphenols [149] with lower half-life values corresponding to better degradability. Another assumption made is that the method of degradation is of no consequence. Integration of the Half-life Index is done by multiplying the Half-life Index of all products and sub products of the process (Equation 1.32), with the obtained value being between 0 (worst case) and 1 (best case).

Table 1.18. Half-life Index

Half-life (days)	Complementary test (% of degradation)	Degradation level	Half-life Index
5	-	High degradability	1
10	-	Medium degradability	0.98
30	≥70%	Low degradability	0.92
100	≥20% and <70%	Residual degradability	0.8
10000	<20%	Non-degradable	0

Equation 1.32. Integrated Half-life Index

$$Integrated\ Half\text{-}life\ Index = \prod Remainder\ chemicals'\ Half\text{-}life\ Index$$

Principle 11

The 11th principle of green chemistry aims prevent pollution through real-time process analysis and has no formula associated to it. Considering that the prevention of pollution is the main message in this principle, the metric chosen is Pollution Prevention (Equation 1.33) and it is calculated for the complete process, being dependant on the mass of each generated substance and their Toxicity Factor (Equation 1.34) representing the risks associated to them through four Indexes. The Health Index (Equation 1.21), Flammability Index (Equation 1.22), Stability Index (Equation 1.23) and Special Index (Equation 1.24) are obtained directly through the use of the associated hazard warnings from the MSDS of the substance (Figure 1.4).

Equation 1.33. Pollution Prevention

$$Pollution\ Prevention = \frac{\sum(mass\ of\ generated\ substance\ (kg) * Toxicity\ Factor)}{mass\ of\ product\ (kg)}$$

Equation 1.34. Toxicity Factor

$$Toxicity\ Factor = Health\ Index + Flammability\ Index + Stability\ Index + Special\ Index$$

Afterwards, this value is integrated (Equation 1.35) between 0 (worst case) and 1 (best case).

Equation 1.35. Integrated Pollution Prevention

$$Integrated\ Pollution\ Prevention = \frac{1}{1 + Pollution\ Prevention}$$

Principle 12

This principle states that substances should be chosen as to minimize the potential for chemical accidents and has no associated mathematical expression. The proposed metric for this principle is the Accident Prevention Index (Equation 1.36), which considers that accident prevention is dependent on three parameters (as stated in the principle [49]): The existence of vapour releases, the risk of fire and the risk of explosion. The choice of these parameters was made based on collaborative efforts with the firemen, who, thanks to their formation in prevention of fires and explosions, helped determine the most critical parameters to analyse.

Equation 1.36. Accident Prevention Index

$$Accident\ Prevention\ Index = Evaporation\ Risk + Fire\ Risk + Explosion\ Risk$$

To calculate the Accident Prevention Index, one of the required parameters is the Evaporation Risk (Equation 1.37). This parameter is binary, with a value of 1 if positive or null and 0 if negative. This is used to define if there exists a risk of vapour releases.

Equation 1.37. Evaporation Risk

$$Evaporation\ Risk\ (1\ if \geq 0;\ 0\ if < 0) = Working\ temperature\ (\underline{o}C) - Melting\ point\ (\underline{o}C)$$

The second parameter is the Fire Risk (Equation 1.38). This parameter is binary and has a value of 1 if positive or null and 0 if negative. This is used to define if there is a risk of fire.

Equation 1.38. Fire Risk

$$Fire\ Risk\ (1\ if \geq 0;\ 0\ if < 0) = Working\ temperature\ (\underline{o}C) - Flash\ point\ (\underline{o}C)$$

The third parameter is the Explosion Risk. This parameter is binary and depends on 3 other binary parameters: The existence of an Ignition Source (Equation 1.39), the Oxygen Content (1 if ≥ 12%, otherwise 0) and the Combustible Concentration (Equation 1.40). These are based off of the explosion triangle (Figure 1.5), showing the required conditions for an explosion to occur [150], and if all of them are 1 the Explosion Risk is considered to be 1, otherwise it is considered to be 0.

Equation 1.39. Ignition Source

$$Ignition\ Source\ (1\ if \geq 0;\ 0\ if < 0)$$
$$= Working\ temperature\ (\underline{o}C) - Minimum\ Ignition\ Temperature\ (\underline{o}C)$$

Equation 1.40. Combustible Concentration

$$Combustible\ Concentration\ (1\ if \geq 0;\ 0\ if < 0)$$
$$= Max\ Vapour\ Concentration\ \left(\frac{mg}{L}\right) - Lower\ Explosion\ Limit(\frac{mg}{L})$$
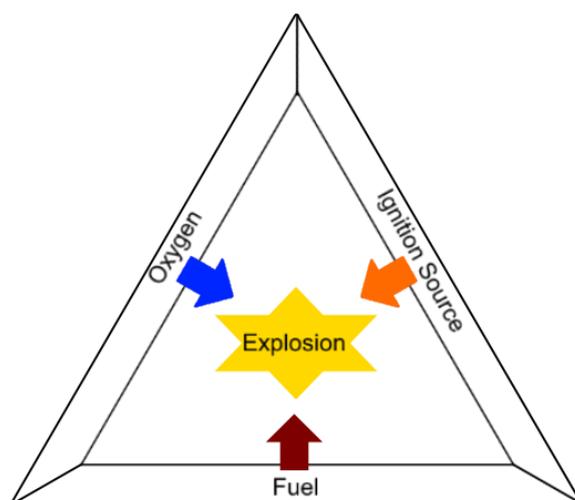
Figure 1.5. Explosion triangle

Lastly, the Accident Prevention Index is integrated (Equation 1.41) to a value between 1 (best case) and 0 (worst case).

Equation 1.41. Integrated Accident Prevention Index

$$Integrated\ Accident\ Prevention\ Index = \frac{1}{1 + \frac{\sum Accident\ Prevention\ Index\ of\ each\ substance}{number\ of\ substances}}$$

Principle 13: Carbon Efficiency

This principle was added for the Geo Ground Engineering Operations, Lda grid considering that carbon analysis isn't taken into account in any other principal despite its importance. It is stated as: "Carbon chemistry is related to some of more hazardous chemical substances in the environment. To that matter, it is important to understand how much of total carbon is incorporated in the desired product.". The chosen metric for it was the Carbon Efficiency (Equation 1.10), which can be directly integrated because its result is between 0% (0, the worst case) and 100% (1, the best case) with the result indicating what percentage of the used carbon was incorporated into the final product.

Principle 14: Reaction Efficiency

Another principle added for the Geo Ground Engineering Operations, Lda grid, the addition of this principle was done under the consideration that another mass-based metric should be used to analyse a reaction's efficiency alongside the atom efficiency (Equation 1.2), stating this principle as : "Design of cleaner reactions with higher yields and incorporation of reactants on final product.". In order to consider only the reactants and the product, the chosen metric was the Curzons Reaction Mass Efficiency (Equation 1.4), as its expression is dependent on the Atom Economy, the yield and the stoichiometric factor of the reaction (Equation 1.5). The final value is also directly integrated between 0 (worst case) and 1 (best case) as it is the percentage of used reagents (including reagents that didn't react and in excess) that were incorporated into the product.

Principle 15: Mass Productivity

The 15th principle of the Geo Ground Engineering Operations, Lda grid is about reduction of all kinds of waste with environmental impact. This principle, not originally belonging to the twelve principles of green chemistry is stated as "Design of processes with lower resources waste. To that matter is important to understand how much resources are used in every step and where is possible to reduce waste.". The chosen metric to determine this was Mass Productivity, also called Generalized Reaction Mass Efficiency (Equation 1.6), were the total mass added into the process were considered to be reactants, reagents, catalysts, solvents, acids, bases, extractions, crystallisations and others. Water was not considered for determination of the Mass Productivity as it has no significant environmental impact. The value returned by this metric is between 0% and 100%, as such it is already integrated between 0 (worst case) and 1 (best case).

2. Materials and Methods

2.1. Computational methods

In order to carry out the assessments, calculations and optimizations proposed in the following sections two different computer programs were used: Microsoft Office Excel and MATLAB (Matrix Laboratory).

2.1.1. Microsoft Office Excel

In Microsoft Office Excel, each principle was initially treated in a different file in order to allow for an in-depth assessment of the proposed formulae and methodologies. For the final Green Chemistry Grid, another file was created with each sheet corresponding to one principle. This allowed for an easier treatment of the data and analysis of the results.

An important part of Microsoft Office Excel is that the regularized incomplete beta function proposed for a few principles can be directly obtained in the program with Equation 2.1 where x is the assessed variable (varying between 0 and 1, otherwise the function returns an error), and α and β are form parameters dependent on the intended use of the function and being determined differently each time:

Equation 2.1. Obtaining the regularized incomplete beta function in Microsoft Office Excel, x is the assessed variable, α and β are form parameters

$$I(x, \alpha, \beta) = BETA.DIST(x, \alpha, \beta, TRUE)$$

2.1.2. MATLAB

MATLAB is a programming language oriented toward numerical computing [151] and was used in order to carry out the proposed optimizations in some principles. The optimizations were made through a genetic algorithm approach using the built-in function with the objective of minimizing the square error of the obtained vs the predicted/intended values (Example code is presented in Annex 1).

To explain the procedure of the genetic algorithm and its choice as the optimization method, a few concepts need to be introduced [152] [153]:

- Individual: An individual is a set of test values for the objective function. For example, if optimization of the arbitrary variables α and β is being carried out, an individual could be $(\alpha, \beta) = (1,1)$.

- Generation: A generation in a genetic algorithm is the name given to a group of test values (called individuals) that are tested independently of each other in order to determine the test values that generate the minimum of the objective function. For example, if a generation had a population of 2 individuals, they could be $(\alpha_{11}, \beta_{11}) = (1,1)$ and $(\alpha_{12}, \beta_{12}) = (1,2)$.

- Cross-over: A cross-over is the creation of a new individual in a generation from two individuals from the previous generation, similiarly to how genes are passed on in a biological context. For example, if generation 1 had individuals $(\alpha_{11}, \beta_{11}) = (1,1)$ and $(\alpha_{12}, \beta_{12}) = (1,2)$ then generation 2 could have an individual from the crossover $(\alpha_{21}, \beta_{21})$.

- Mutation: A mutation is the alteration of an individual, by itself, from a previous generation to the new generation, similiarly to the mutations that occur in biological organisms. For example, if generation 1 had an individual $(\alpha_{11}, \beta_{11}) = (1,1)$, then generation 2 could have the mutated individual $(\alpha_{22}, \beta_{22}) = (2,1)$ (In this case, $\alpha = 1$ mutated to $\alpha = 2$).

Using these concepts the genetic algorithm can be explained step by step as such [152] [153]:

- 1st: A first generation is randomly generated with test values inside the intended range (previsouly defined, dependent on the problem).

- 2nd: All the test values are tested individually in the objective function (previsouly defined, dependent on the problem) and the final result saved.

- 3rd: The final results are compared and the test values that gave the lowest results are considered "elite individuals". The number of elite individuals in a certain generation is previously defined by the user.

- 4th: A new generation is created from the previous one with the "elite individuals" being passed on without change, a certain percentage (defined by the user) being generated by crossovers and the rest being generated from mutations. Individuals outside the test range are ignored and another individual is generated the same way to take its place.

- The 2nd to 4th steps are repeated until the optimization has finished for any given reason defined by the user (several possibilities exist, for example, a certain number of generations passing or a certain number of objective function tests having been made).

- 5th: The individual with the lowest value in the objective function in the final generation is returned to the user as the optimized result.

This algorithm was chosen to carry out the optimizations due to its low memory requirements, as no derivatives or integrals need to be solved, and the possibility to find the absolute minimum of the objective functions in a given interval when multiple minima exist thanks to it's "trial and error" nature (akin to natural selection) [152]. Additionally it has the advantage of being highly costumizable to different situations, for example, through manipulation of the individuals per generation or percentage of crossover [154].

The only downside of this method is it's semi-random nature which can lead to different results for the same optimization. To counter this downside, the genetic algorithms parameters can be customized for a larger number of generations or population at the cost of higher computing times. In order to guarantee that the obtained results were constant or close to each other (considered to be less than a 5% difference), each optimization was carried out 100 times, having obtained the same result every time.

2.2. Green Chemistry Grid

In order to create a Green Chemistry Grid, each of the 12 principles of Green Chemistry and the 3 additional principles proposed in the Geo Ground Engineering Operations, Lda Grid will be treated individually in a first instance (except for the 3rd and 4th and the 5th and 11th due to similarities between them). For all of them the objective will be to propose formulae that end up returning a value between 0 and 1 where 1 corresponds to an ideal process (best-case scenario) and 0 corresponds to the worst-case scenario. This will allow comparison between different principles to be possible (to assess which principles are contributing more or less positively for the final process score) and the final Green Chemistry Grid to be easy to analyse.

Only after having defined the formulae for each individual principle will the Green Chemistry be built and ready to assess the "greenness" of a process according to all of the principles of Green Chemistry.

2.2.1. Principle 1

The first principle of Green Chemistry focuses on the prevention of waste [22]. A mathematical formula already exists to analyse a process according to this principle, the E-factor. The E-factor is defined as the total mass of generated waste per mass of product in a process (Equation 2.2) [24].

Equation 2.2. E-factor

$$E\ factor\ (\frac{kg}{kg\ of\ product}) = \frac{\sum mass\ of\ waste\ (kg)}{mass\ of\ product\ (kg)}$$

When using the above expression (Equation 2.2) all waste is considered to have the same impact no matter how dangerous it may be [24]. In order to determine how much cleaning up is required for the generated waste, the Q factor was also created. This factor is used to give an idea of how dangerous or environmentally malign the waste is (Equation 2.3) [24].

Equation 2.3. E-factor calculation using the Q factor

$$E\ factor\ (\frac{kg}{kg\ of\ product}) = \frac{\sum mass\ of\ waste\ (kg) * Q\ factor}{mass\ of\ product\ (kg)}$$

Despite allowing the E-factor to consider the degree of danger of the generated waste, this is not the 1st principle's main focus, being instead discussed in other principles. Additionally, the Q factor is defined semi arbitrarily as being "low" for less malign substances and higher for more dangerous ones (for example, sodium chloride can be assigned a value of 1 and a heavy metal salt a value between 100 and 1000) [24]. As a result, it was decided the Q-factor would not be used to determine the 1st principle's rating for the Green Chemistry grid.

Water is also not considered as waste when being disposed of as a pure current as it can inflate the E-factors and it has no environmental impact or requires cleaning up [24]. When mixed with impurities it is, however, proposed to be considered for the calculation of the E-factor.

Having analysed the existing formulae (Equation 2.2 and Equation 2.3) and deciding which to implement for the 1st principle in the Green Chemistry grid (Equation 2.2), it becomes necessary to determine how to implement it.

The E factor (Equation 2.2) has a value between 0 (when no waste is generated) and $+\infty$. This range of values can make comparison with other principles and determination of an overall green index for the process complicated. In order to allow all principles to be treated and analysed in the same light, integration of these values to a common range (chosen to be between 0 and 1 for the Green Chemistry grid), as was discussed in Section 2.2, is critical. This integration is considered to have 1 as the best scenario (no waste is generated) and 0 as the worst scenario (as waste reaches higher values). With these considerations, a first attempt at the integration of the E factor was proposed using the following expression (Equation 2.4):

Equation 2.4. E factor integration; first attempt

$$Integrated\ E\ factor\ = \frac{1}{1 + E\ factor\left(\frac{kg}{kg\ of\ product}\right)}$$

This attempt (Equation 2.4), however, treats the E-factor as being the same regardless of the process, not considering that different sectors may have different characteristics that affect waste (for example, the pharmaceutical industry requires extremely high purity products and detailed impurity profiles [155] while producing low volumes, which causes high kg of waste per kg of product). As additional information about the E factor in the industry exists [24] [72], an attempt to integrate the E-factor according to the industry averages (Table 2.1) was made.

Table 2.1. E-factor industry averages, the annual generated waste tonnage is calculated with the minimum being the lowest annual production multiplied by the lowest E-factor and the maximum being the highest annual product tonnage multiplied by the highest E-factor for the industry segment

Industry segment	Annual product tonnage (tonnes of product)	E-factor (ton of waste per ton of product)	Annual generated waste tonnage (tonnes of waste)
Oil refining [24]	$10^6 - 10^8$	0.1	$10^5 - 10^7$
Bulk chemicals [24]	$10^4 - 10^6$	$< 1 - 5$	$10^4 - (5 * 10^6)$
Fine chemicals [24]	$10^2 - 10^4$	$5 - > 50$	$(5 * 10^2) - (5 * 10^5)$
Pharmaceuticals [24]	$10 - 10^3$	$25 - > 100$	$(2.5 * 10^2) - 10^5$
Nanomaterials [72]	$0.1 - 1$	$100 - 100,000$	$10 - 10^6$

In order to have a smooth and continuous profile for the integration of the E-factor, a function with the following characteristics was desired:

- A domain equal to the E-factor's domain ($x = [0; +\infty[$);

- Easy to adapt to different means and/or medians;

- Fits the defined integration objectives of:
    - $E\ factor\ =\ 0\ \rightarrow\ Integrated\ E\ factor\ =\ 1$
    - $E\ factor\ \approx\ +\infty\ \rightarrow\ Integrated\ E\ factor\ \approx\ 0$

- As lower E-factors correspond to a "greener" process according to the principle, the integration function should be strictly decreasing (for example, integration of an E-factor of 2 should always return higher values than integration of an E-factor of 3)

Considering the previous characteristics, the exponential distribution's probability density function (Equation 2.5) was chosen. This function belongs to the exponential family of functions which have common applications in Biology (for example, for the exponential growth phase of a cell population [156]) and Physics/Chemistry (for example, for the radioactive decay of a substance [157]).

Equation 2.5. Exponential distribution's probability density function

$$f(x;\ \beta) = e^{-\frac{x}{\beta}}$$

In order to define the chosen equation, a β parameter needs to be determined. This parameter corresponds to the mean value of the function (Equation 2.6).

Equation 2.6. β determined from a mean value

$$\beta = \mu\ (mean)$$

In an exponential distribution's probability density function, when the β parameter is the same as the test value (x), the equation returns e^{-1} which is approximately 0.37. To have an integration of 0.50 for a chosen value, this value should be treated as a median instead, with β being determined as follows (Equation 2.7).

$$\beta = \frac{median}{\ln(2)}$$

In order to test and evaluate previous equations in the context of this principle, a few test profiles were made (Figure 2.1, Figure 2.2 and Figure 2.3) in order to study potential parameter values to be used.
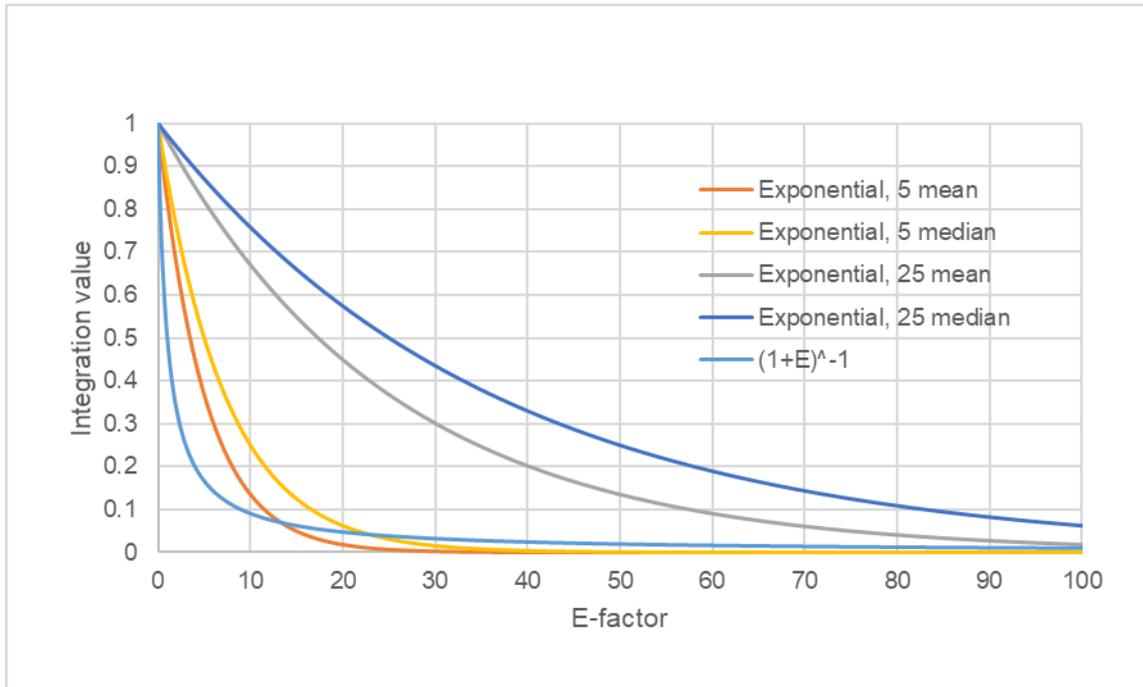
Figure 2.1. Integration profile for the E-factor

From Figure 2.1 it can be seen that the exponential profile promotes a smooth integration that reaches values of approximately 0 when the test value (E-factor) is above a certain limit (dependent on the choice of β). To decide if integration should be made differently for each industry segment or a single expression can be used two of the profiles were compared (Figure 2.2).
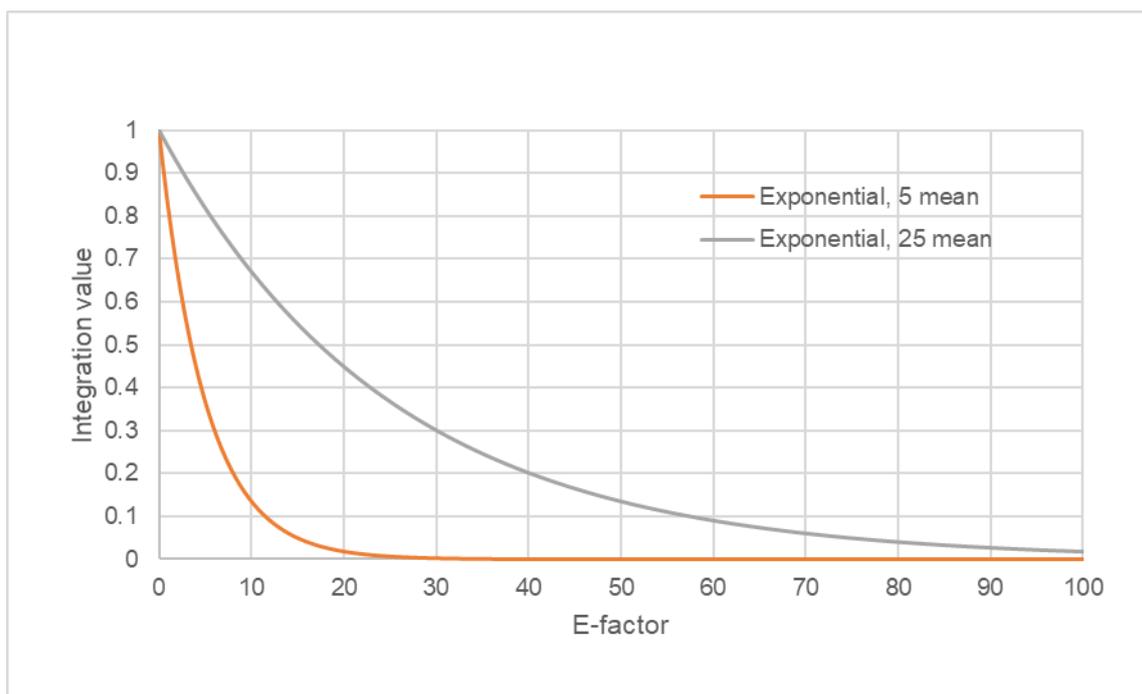
Figure 2.2. Effect of different means on the Integrated E-factor

As it can be seen from Figure 2.2, altering the β parameter from 5 (representative of the fine chemicals industry) to 25 (representative of the pharmaceutical industry) (Figure 2.2) has a major effect on the integration, with 0.50 being reached at an approximate E-factor of 3.50 and 17.50, respectively. Comparing both of these approaches for Pfizer's synthesis of sildenafil citrate [127], considered to be "green" due to its low E factor in the pharmaceutical industry, the results are as follows (Table 2.4):

Table 2.2. Example for the effects of different means on the Integrated E-factor

Process	Industry	E-factor (kg/kg of product)	Integration value using a 25 mean	Integration value using a 5 mean
Pfizer's synthesis of sildenafil citrate target [127]	Pharmaceuticals	6.00	0.79	0.30

From the above example (Table 2.2), the effect of the median on the integration is clear. On one hand, the "green" method for the production of sildenafil citrate has a result of 0.79 when using a β parameter of 25 (representative of the pharmaceutical industry), as expected from a method considered "green". On the other hand, when using a β parameter of 5 (representative of the fine chemicals industry) the obtained integrated value is of 0.30, which can hardly be considered "green". Considering these results and the different characteristics of each industry, the β parameter is chosen to be calculated differently for each industry segment.

Having concluded this, it becomes necessary to choose if the β parameter for each industry segment is calculated considering the average values from the industry as the mean of the integration (causing an integrated value of 0.37 for the average industry value) or the median of the integration (causing an integrated value of 0.50 for the average industry value) (please check Figure 2.3)
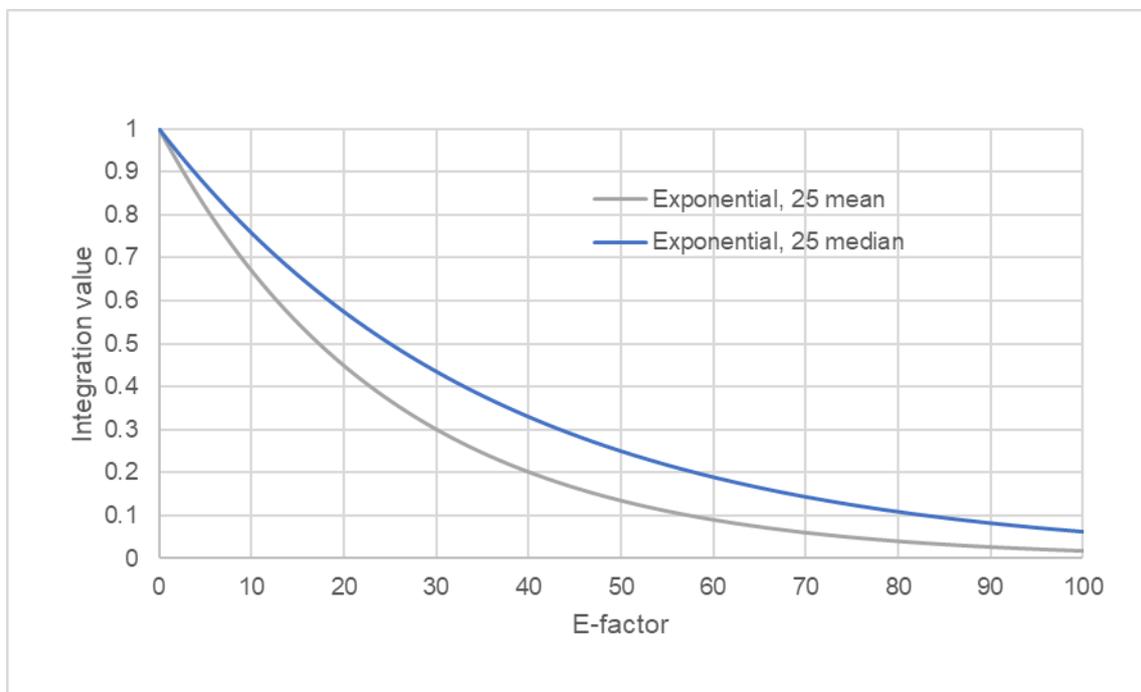
Figure 2.3. Effect of using mean or median on the Integrated E-factor

From Figure 2.3, it is possible to observe that the impacts of considering the average industry values as a mean or a median for the integration has, at most, an absolute difference of approximately 0.15. In order to decide which values to use, the standard process for the synthesis of sildenafil citrate [127] was tested using both approaches (Table 2.3)

Table 2.3. Example of the effects of using the mean or median

Process	Industry	E-factor (kg/kg of product)	Integration value using a 25 mean	Integration value using a 25 median
Synthesis of sildenafil citrate (1997, commercial route) [127]	Pharmaceuticals	22.00	0.41	0.54

From the results in Table 2.3, it can be seen that the integration of the process considered "standard" has values closer to an average integration (0.5) when the β parameter is calculated by treating the average industrial values (Table 2.1) as a median. Considering how the objective of this integration is for the average industrial values to correspond to the average value on the scale from 0 to 1 (which is 0.5), they are considered to be, for purposes of determining the β parameter, the median of the integration.

As a result , 5 profiles were made, one for each industry segment (Figure 2.4, Figure 2.5, Figure 2.6, Figure 2.7, Figure 2.8):

$$f(x; \beta) = e^{-\frac{x}{\beta}} \; ; \; \beta = \frac{0.1}{\ln(2)}$$ for the oil refining industry segment (the desired product is derived from petroleum, for example, kerosene) (Figure 2.4).
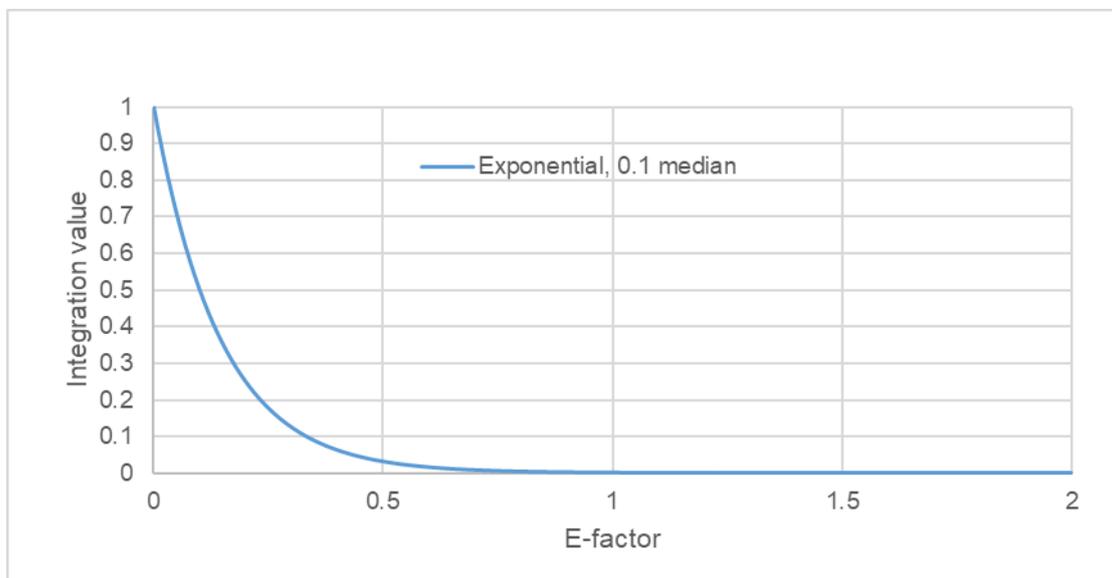
Figure 2.4. Integration values for oil refining

$$f(x; \beta) = e^{-\frac{x}{\beta}}; \; \beta = \frac{1}{\ln(2)}$$ for the bulk chemicals industry segment (the desired product is produced on a large scale, usually through continuous processes and can be used without further modification, for example, acetone), as the lower bound for the bulk chemicals was considered to be 10^4 tonnes / year [24], processes with a production larger than that should be treated as bulk chemicals due to production similarities (with the exception of those belonging to the oil refining industry segment) (Figure 2.5).
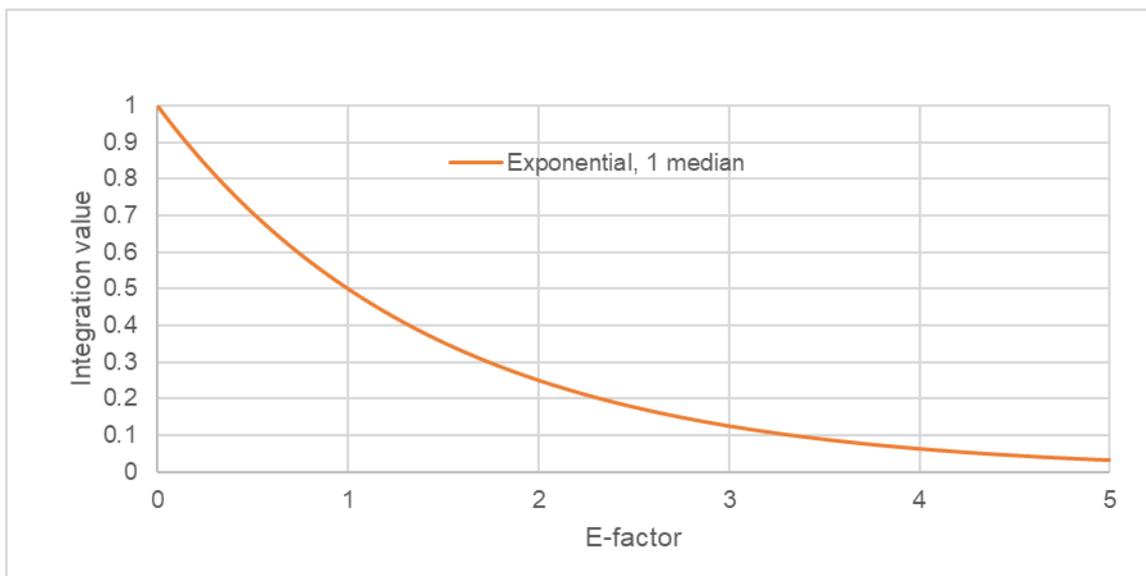
Figure 2.5. Integration values for bulk chemicals

$f(x; \beta) = e^{-\frac{x}{\beta}}; \beta = \frac{5}{\ln(2)}$ for the fine chemicals industry (the desired product is produced on a small scale, usually through batch processes and is used in the production of other products, for example, additives), as the higher bound was considered to be 10^4 tonnes / year [24], processes with a production lower than that should be treated as fine chemicals due to production similarities (with the exception of those belonging to the pharmaceuticals industry or nanomaterials) (Figure 2.6).
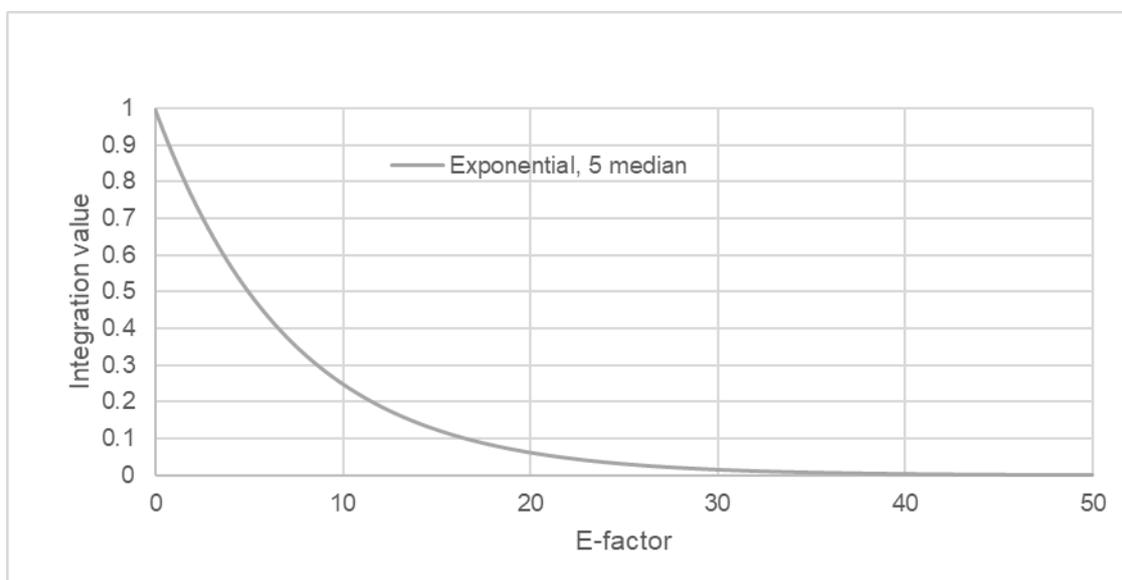
Figure 2.6. Integration values for fine chemicals

$f(x; \beta) = e^{-\frac{x}{\beta}}; \beta = \frac{25}{\ln(2)}$ for the pharmaceuticals industry (the desired product is an Active Pharmaceutical Ingredient) (Figure 2.7).
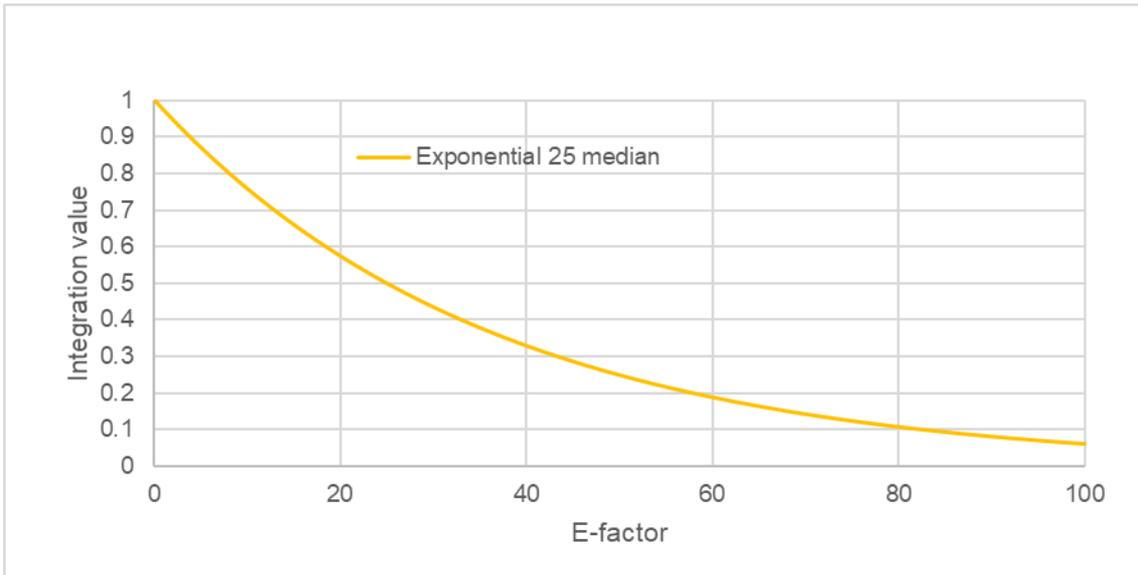
Figure 2.7. Integration values for pharmaceuticals

$f(x; \beta) = e^{-\frac{x}{\beta}}; \beta = \frac{100}{\ln(2)}$ for the nanomaterials industry (the desired product is a nanomaterial) (Figure 2.8).
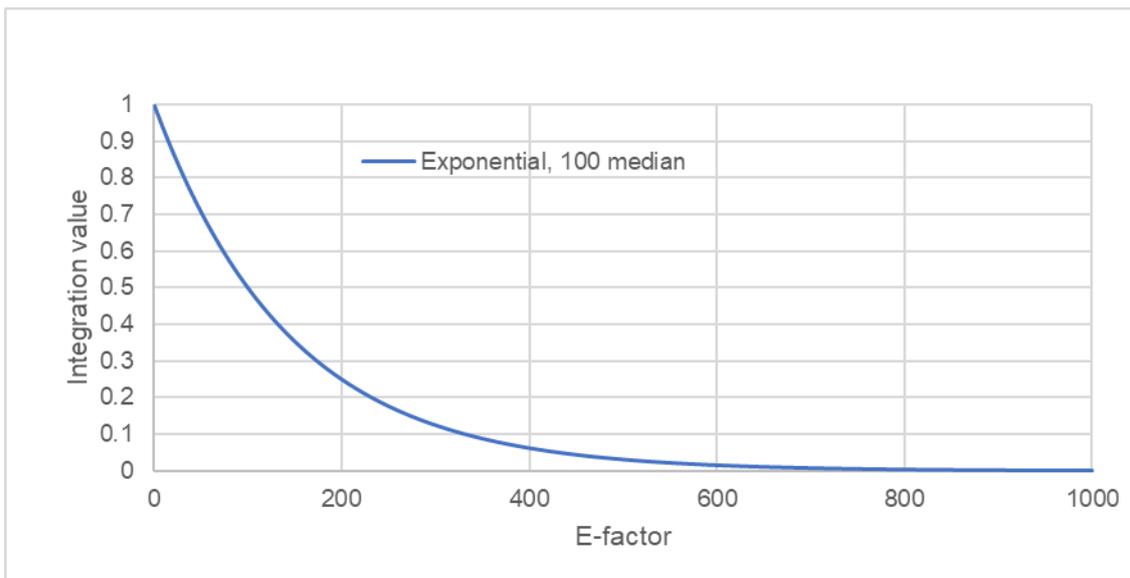
Figure 2.8. Integration values for nanomaterials

A few examples using the final integration profiles (Figure 2.4, Figure 2.5, Figure 2.6, Figure 2.7 and Figure 2.8) follow:

Table 2.4. Integration examples

Process	Industry	E-factor (kg/kg of product)	Integration value
Pfizer's synthesis of sildenafil citrate target [127]	Pharmaceuticals	6.00	0.85
Synthesis of sildenafil citrate (1997, commercial route) [127]	Pharmaceuticals	22.00*	0.54
Optimised medicinal chemistry (1994) [127]	Pharmaceuticals	100.00*	0.06

*The E-factors for the synthesis of sildenafil citrate (1997, commercial route) and the optimised medicinal chemistry (1994) only include organic wastes

As can be seen from the test results (Table 2.4), the integration classifies the optimised medicinal chemistry processes from 1994 as "non-green" for today's standards (with a 0.06 integration), while classifying the standard commercial route for the synthesis of sildenafil citrate "average" (with a 0.54 integration) and the method proposed by Pfizer as the clear "green" alternative (with an integrated value of 0.85). These results are as expected, with a clear differentiation between the three syntheses methods allowing them to be compared in the light of the current paradigm of the industry.

2.2.2. Principle 2

The 2nd principle states that "synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product" [22]. Atom Economy (Equation 2.8) is a measure associated to the principle that calculates the percentage of reagents that is incorporated into the product by dividing the molar weight of the product (P) with the molar weight of the reagents.

Equation 2.8. Atom Economy [25]

$$Atom\ Economy\ of\ P\ (\%) = \frac{molar\ weight\ of\ P\ (kg/mol)}{\sum molar\ weight\ of\ reagents\ (kg/mol)} * 100$$

The Atom Economy varies between 0% and 100%, therefore, to integrate this principle in values between 0 and 1 is easy and it can be done linearly (Equation 2.9).

Equation 2.9. Linear integration of the Atom Economy

$$Integrated\ Atom\ Economy = Atom\ Economy$$

However, following a linear integration, can be a disadvantage as it leads to considering an increase from 1% to 2% atom economy the same as an increase from 49% to 50% or 99% to 100% (Figure 2.9).
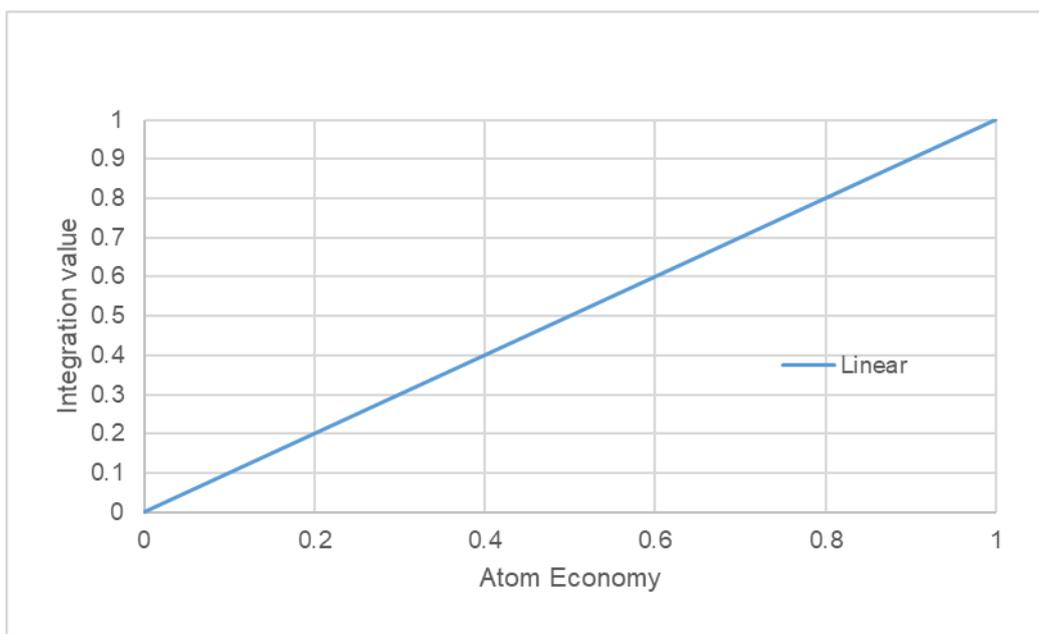
Figure 2.9. Linear integration profile for Atom Economy

A proposed solution is to change the integration to a double bounded, strictly increasing (higher values for the Atom Economy are always better, according to this principle), non-linear function (to allow for differentiation between value ranges) and a large variation near a median value (meaning that changes near the median are considered more relevant than changes far from it). An example of a function with these characteristics is the regularized incomplete beta function (Equation 2.10), which has a representation on a double bounded domain of $x = [0,1]$.

Equation 2.10. Regularized incomplete beta function

$$I(x, \alpha, \beta) = \frac{B(x, \alpha, \beta)}{B(1, \alpha, \beta)}$$

Where B is the incomplete beta function (Equation 2.11), α and β are form parameters (positive real numbers) and x is the test value.

Equation 2.11. Incomplete beta function

$$B(x, \alpha, \beta) = \int_{a}^{x} t^{\alpha-1} * (1 - t)^{\beta-1} dt$$

Although the test value x needs to be between 0 and 1, a transformation can turn any variable in a double bounded interval into it (Equation 2.12).

Equation 2.12. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

The median (0.5 integration) of the regularized incomplete beta function for a double bounded variable y (in this case, the Atom Economy) can be determined from the α and β parameters using the following equation (Equation 2.13):

Equation 2.13. Regularized incomplete beta function median

$$median \cong lower\ bound + \frac{\alpha - \frac{1}{3}}{\alpha + \beta - \frac{2}{3}} * (upper\ bound - lower\ bound)$$

In order to determine the effects of the α parameter in the integration, a test was conducted. First, the β parameter was set to an arbitrary value (2 was chosen) and three different values for the α parameter were chosen (arbitrarily as well, chosen to be 2, 3 and 4). Afterwards the profiles of the function when the chosen parameters were used ($I(x, 2,2)$, $I(x, 3,2)$ and $I(x, 4,2)$) were compared (Figure 2.10).
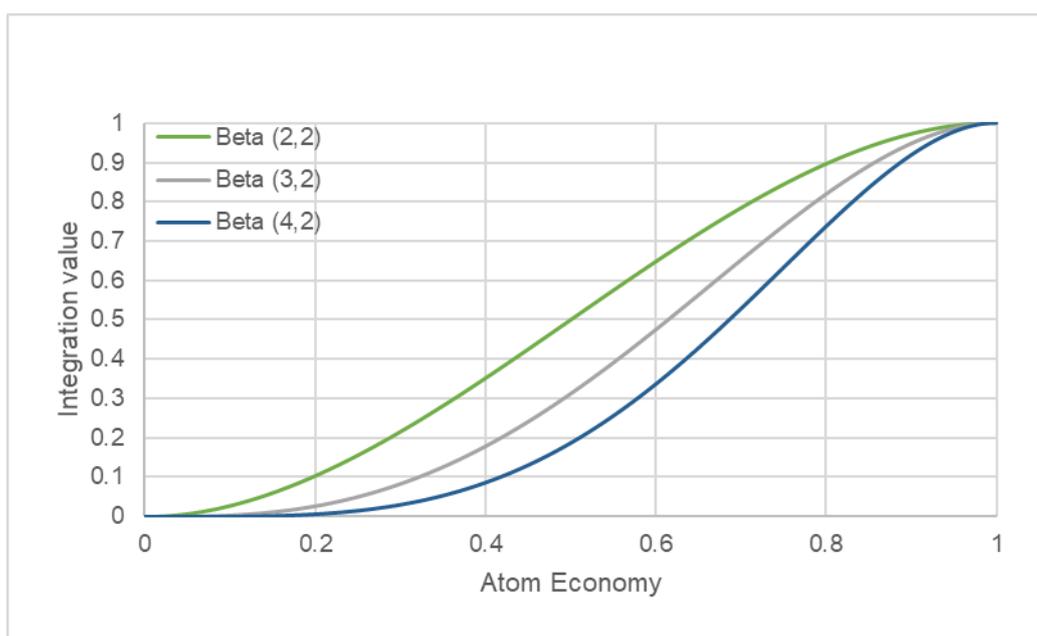
Figure 2.10. Effect of the alfa parameter on the integration value of Atom Economy

From Figure 2.10 it is possible to see that a higher α parameter shifts the growth curve to higher test values, causing the integrated value to stay lower in a larger range (for $I(x, 2,2)$ a 0.1 integration is reached at a test value of 0.2; on the other hand, for $I(x, 4,2)$ a 0.1 integration is only reached at a test value of approximately 0.42). This means that the α form parameter can be seen as defining how many integration values are close to 0.

After evaluation of the effects of the α parameter, a similar test was made to determine the effects of the β parameter. First the α value was set to 2 (in order to mirror the previous test) and β was chosen to be 2, 3 and 4 (mirroring the previous test as well). Afterwards the profiles of the $I(x, 2,2)$, $I(x, 2,3)$ and $I(x, 2,4)$ functions were compared (Figure 2.11).
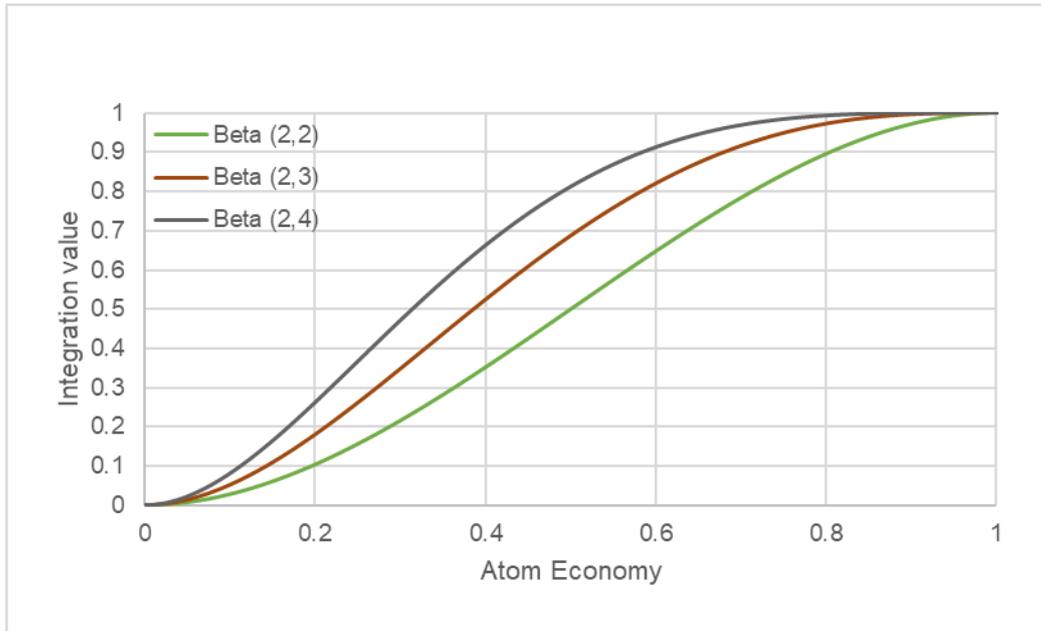
Figure 2.11. Effect of the beta parameter on the integration value of Atom Economy

From Figure 2.11 it is possible to conclude that a higher β parameter shifts the curve to lower values, causing the integrated value to stay at higher values in a larger range (for $I(x, 2,2)$ a 0.9 integration is reached at a test value of 0.8; on the other hand, for $I(x, 2,4)$ a 0.9 integration is reached at a test value of approximately 0.58). This means that the β form parameter can be seen as defining how many integration values are close to 1.

Although the regularized incomplete beta function has the desired characteristics, the mathematical expression used to describe isn't simple, with an integral that needs to be solved (Equation 2.10 and Equation 2.11).

Another function with the desired characteristics (double bounded, strictly increasing, non-linear with a large variation near a median value) for the integration of the Atom Economy is Kumaraswamy distribution's cumulative distribution function, which has a simple mathematical representation and is commonly used in hydrological studies (Equation 2.14) [158] [159] and other simulation models [160]. This function is defined by two form parameters (α and β), where x is the test value.

Equation 2.14. Kumaraswamy distribution's cumulative distribution function

$$F(x; \alpha, \beta) = 1 - (1 - x^\alpha)^\beta$$

Graphically, this equation is similar to the regularized incomplete beta function, being double bounded with $x = [0,1]$, but with lower values for the same α and β parameters (Figure 2.12).
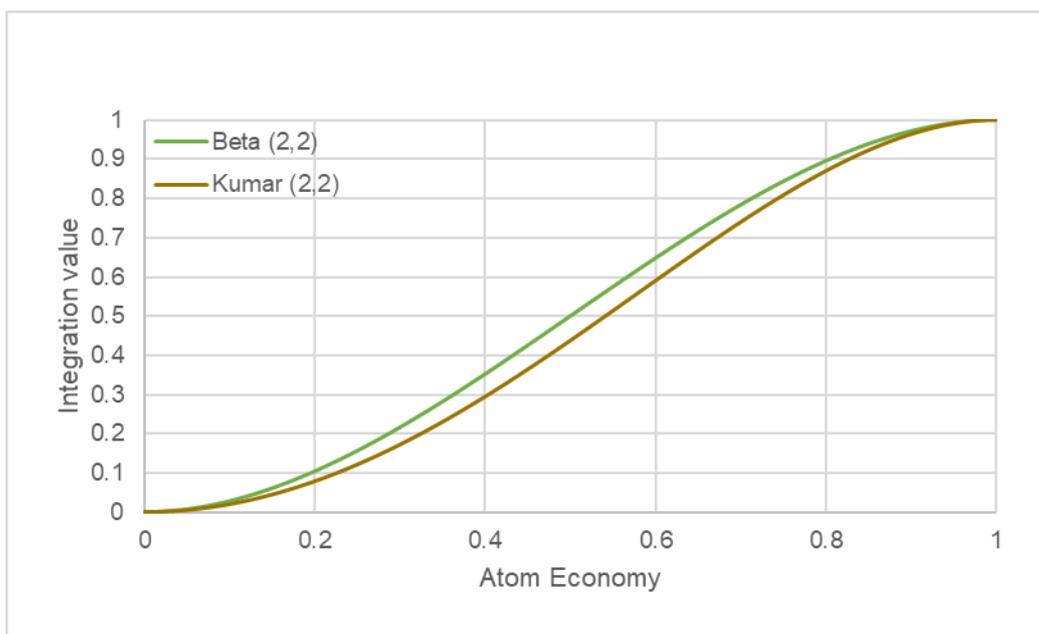
Figure 2.12. Comparison between Kumaraswamy and Beta for the same α and β parameters

As with the regularized incomplete beta function, normalizing the Atom Economy using Equation 2.12 allows a lower bound different from 0 and an upper bound different from 1 to be used.

Moreover, herein, it is suggested that the average Atom Economy depends on the type of chemical process (Table 2.5), as such the alfa and beta parameters, as well as the lower and upper bounds of the function, were chosen to represent those tendencies.

Table 2.5. Average atom economy per reaction type [125]

Chemistry type (1)	Atom Economy (%)	Chemistry type (2)	Atom Economy (%)
Acid salt	100	Epoxidation	83
Base salt	100	Borohydride	75
Hydrogenation	84	Iodination	89
Sulfonation	89	Cyclisation	77
Decarboxylation	77	Amination	87
Esterification	91	Lithal	76
Knoevenagel	89	Base hydrolysis	81
Cyanation	77	C-Acylation	81
Bromination	84	Acid hydrolysis	76
N-Acylation	86	Chlorination	74
S-Alkylation	84	Elimination	72
C-Alkylation	88	Grignard	76
N-Alkylation	73	Resolution	99
O-Arylation	85	N-Dealkylation	64

In order to represent the tendencies in Table 2.5, a statistical analysis of the data is done. In this analysis, the parameters under study will be the lower bound of the data sample, the lower quartile (middle value between the lower bound and median of the data), the median (middle value of the data) and the upper quartile (middle value between the median and upper bound of the data).

First, the lower bound was chosen to represent the lowest value on the table (64%) and the upper bound was considered to be 100% (as this is the objective of the principle). Afterwards, the lower quartile (76%, meaning that 25% of the data is between 64%-76%), median (83.5%, meaning that 50% of the data is between 64%-83.5%) and upper quartile (88.25%, meaning that 75% if the data is between 64%-88.25%) of the data were determined. Lastly, the alfa and beta parameters were calculated via MATLAB through a genetic algorithm approach by minimizing the quadratic error for the lower quartile (set as a 0.25 integration at 76%), the median (set as a 0.5 integration at 83.5%) and the upper quartile (set as a 0.75 integration at 88.25%) of the function (Figure 2.13 and Figure 2.14).

```
                                Best           Mean        Stall
Generation      Func-count      f(x)           f(x)      Generations
   121            36600        0.001874       0.001874       43
   122            36900        0.001874       0.001874       44
   123            37200        0.001874       0.001874       45
   124            37500        0.001874       0.001874       46
   125            37800        0.001874       0.001874       47
   126            38100        0.001874       0.001874       48
   127            38400        0.001874       0.001874       49
   128            38700        0.001874       0.001874       50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 2.10
 Beta parameter estimation = 1.96
```

Figure 2.13. Genetic algorithm results for the regularized incomplete beta function from MATLAB

As can be seen from Figure 2.13 the genetic algorithm optimization for the regularized incomplete beta function obtained results for $\alpha = 2.10$ and $\beta = 1.96$ with a minimized square error of approximately 0.0019.

```
                                Best           Mean        Stall
Generation      Func-count      f(x)           f(x)      Generations
   211            63600         0.00175        0.00175        49
   212            63900         0.00175        0.00175        50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 1.93
 Beta parameter estimation = 2.08
```

Figure 2.14. Genetic algorithm results for the Kumaraswamy distribution's cumulative distribution function

Figure 2.14 shows the results of the genetic algorithm optimization for the Kumaraswamy distribution's cumulative distribution function. The optimized parameters from the algorithm are $\alpha = 1.93$ and $\beta = 2.08$, with the minimized square error of approximately 0.002.

Once optimized with the genetic algorithm the alfa and beta parameters for both functions to fit the data, an error analysis was conducted in order to determine the best method (Table 2.6).

Table 2.6. Error analysis for the regularized incomplete beta function integration

Parameter	Predicted	Obtained	Absolute	Percentage	Absolute

	value	value	error	error (%)	percentage error (%)
Minimum	0.00	0.00	0.00	0.00	0.00
Q1	0.25	0.23	0.02	-6.93	6.93
Median	0.50	0.53	0.03	6.42	6.42
Q3	0.75	0.73	0.02	-3.16	3.16
Maximum	1.00	1.00	0.00	0.00	0.00

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to an Atom Economy of 64%, the lower quartile (Q1) corresponds to an Atom Economy of 76%, the median corresponds to an Atom Economy of 83.5%, the upper quartile (Q3) corresponds to an Atom Economy of 88.25% and the maximum corresponds to an Atom Economy of 100%

From the regularized incomplete beta function's integration error analysis (Table 2.6) it is possible to conclude that the maximum error is of 6.9% for the lower quartile integration (Q1).

Table 2.7. Error analysis for the Kumaraswamy distribution's cumulative distribution function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.00	0.00	0.00	0.00	0.00
Q1	0.25	0.23	0.02	-6.78	6.78
Median	0.50	0.53	0.03	6.47	6.47
Q3	0.75	0.73	0.02	-2.78	2.78
Maximum	1.00	1.00	0.00	0.00	0.00

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to an Atom Economy of 64%, the lower quartile (Q1) corresponds to an Atom Economy of 76%, the median corresponds to an Atom Economy of 83.5%, the upper quartile (Q3) corresponds to an Atom Economy of 88.25% and the maximum corresponds to an Atom Economy of 100%

From the Kumaraswamy distribution's cumulative distribution function integration error analysis (Table 2.7) the maximum error is of 6.8% for the lower quartile integration (Q1).

Comparing both error analyses, it is possible to conclude that, overall, Kumaraswamy distribution's cumulative distribution function integration has lower errors closer to the integration limits with a 6.8% error for the lower quartile (Q1) and 2.8% error for the upper quartile (Q3). When compared to the regularized incomplete beta function's integration which has, respectively, 6.9% and 3.2% errors it appears to be superior. For the median however, the regularized incomplete beta function integration has an error of 6.4%, slightly lower than the Kumaraswamy distribution's cumulative distribution function integration which has an error of 6.5%.

Overall, both methods proved to have an acceptable error and have a similar profile (Figure 2.15)
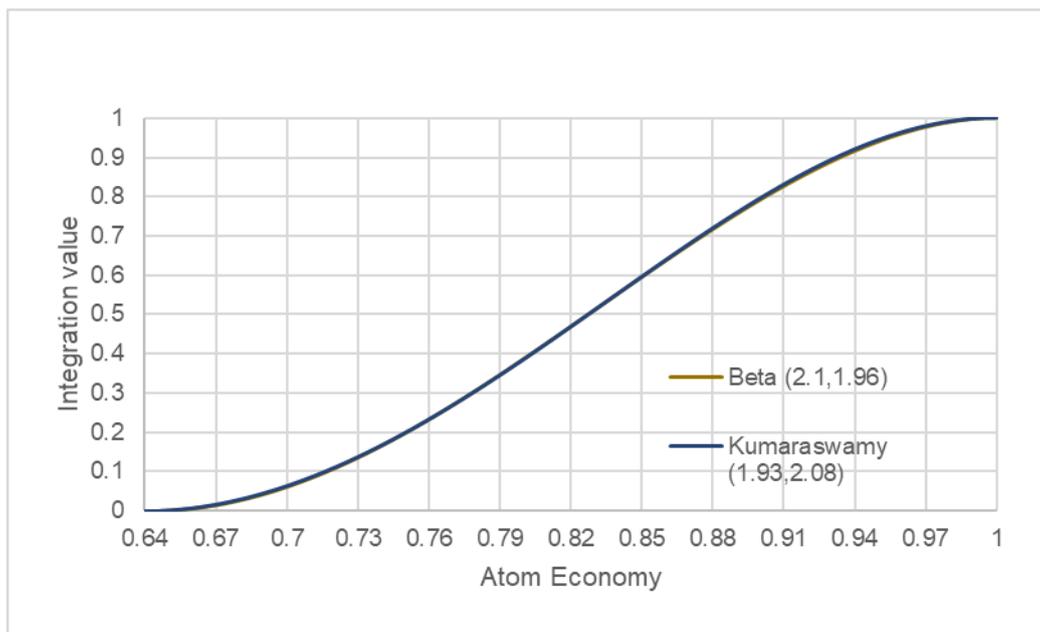
Figure 2.15. Atom Economy integration profiles using the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function

As a result of the error analyses, the choice for integration function is Kumaraswamy distribution's cumulative distribution function (Figure 2.16) due to an overall lower error (less 0.1% for Q1 and 0.4% for Q3, with a 0.1% increase for the median) and increased precision near the integration limits.
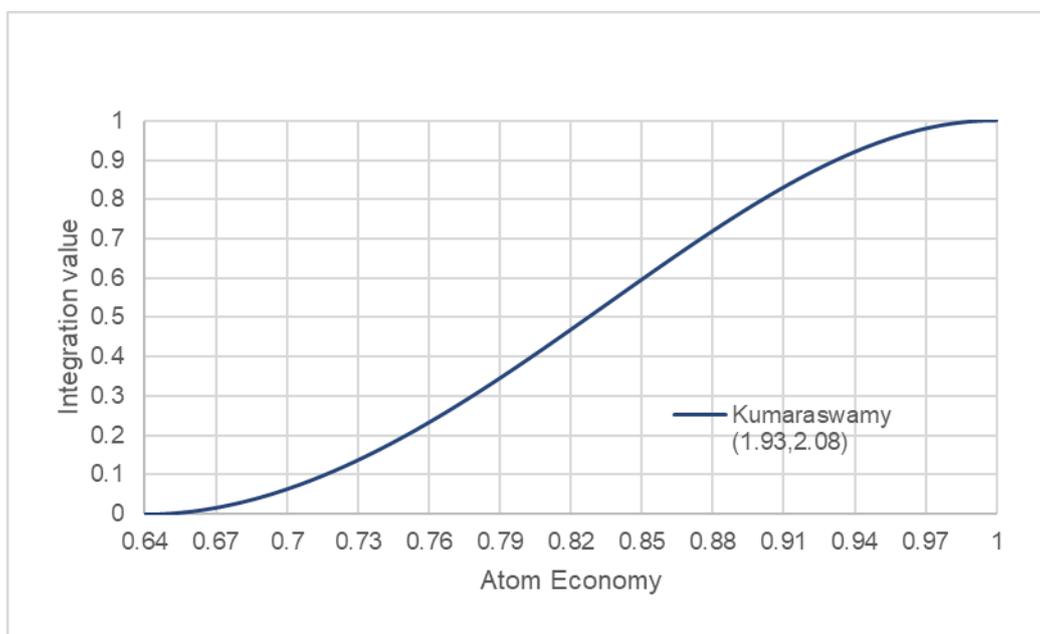
Figure 2.16. Integration profile for Atom Economy, values for the Atom Economy below 0.64 are considered to have an integrated value of 0

In order to test the proposed method, an example on the synthesis of benzoic hydrazide by two different processes is carried out. The two methods under study are a conventional synthesis and a "green" synthesis using microwave radiation (Table 2.8).

Table 2.8. Atom Economy example for the synthesis of benzoic hydrazide

Process	Atom Economy	Integrated value
Conventional synthesis of benzoic hydrazide	62.30 [27]	0.00
Greener synthesis of benzoic hydrazide	79.10 [27]	0.35

From Table 2.8, the integrated value for the "greener" synthesis of benzoic hydrazide (0.35) is higher than the conventional method which has an integrated value of 0.00. These results are in accordance with what was the predicted as, according to this principle, the "greener" synthesis of benzoic hydrazide is considered superior to the conventional synthesis.

2.2.3. Principles 3 and 4

The 3rd principle of Green Chemistry focuses on the reduction of the toxicity of used and generated substances [22]. The 4th principle of Green Chemistry focuses on the reduction of the toxicity of chemical products while maintaining efficacy [22]. Neither of these principles has any associated mathematical expression.

As both the 3rd and 4th principle focus on the toxicity of substances a single expression can be proposed for usage in both, in the case of the 3rd principle for the assessment of reagents and in the case of the 4th principle for the assessment of products. In order to propose a metric for these principles, experts from different fields of science (for example, Biology and Chemistry) had to work together having considered the need to take into account both the toxicity to humans and the toxicity for the environment on the proposed metric (Equation 2.15).

Equation 2.15. Hazard Index, the average of an environmental parcel and a human parcel is made in order to give equal importance to each

$$Hazard\ Index = \frac{Human\ Tolerability\ Index + Environment\ Toxicity\ Index}{2}$$

In order to apply the proposed formula (Equation 2.15), both a Human Tolerability Index and an Environment Toxicity Index need to de defined for each substance.

The proposed method to determine the Human Tolerability Index is to consider the toxicity of the substance using the LD50 (the required dosage of the substance to, on average, kill half the population in study) or LDLo (the minimum required dosage of a substance to kill an individual of the population in study) and the exposure that the people related to the process have to it (Equation 2.16).

Equation 2.16. Human Tolerability, LDLo is preferably used but if no information on it exists or if it is incomplete, the LD50 can be used

$$Human\ Tolerability$$
$$= Exposure\ time\ \left(\frac{day}{kg\ of\ product}\right) * \frac{Exposure\ level\ \left(\frac{mg}{Kg\ of\ product.Kg\ of\ person}\right)}{LDLo\ /\ LD50\ \left(\frac{mg}{Kg\ of\ person}.day\right)}$$

Determination of the Exposure level is proposed to be done based on the mass of each substance that the people related to the process are exposed to, in order to produce 1 kg of product per the total weight of the people exposed to it (Equation 2.17).

Equation 2.17. Exposure level

$$Exposure\ level\ (\frac{mg}{Kg\ of\ product.Kg\ of\ person})$$
$$= \frac{m_{Chemical}\ (\frac{mg}{Kg\ of\ product})}{Number\ of\ people\ \times Avg\ Weight_{Person}(kg\ of\ person)} \times Exposure_{area}\ (\%)$$

Another proposed method for the determination of the Exposure level is in a "per day" basis instead of "per kg of product" by using Equation 2.18, since time is a major factor on the effects of a substance on the organism.

Equation 2.18. Exposure level alternative; compared to Equation 2.17 the mass of the substance under study is in mg/day instead of mg/kg of product

$$Exposure\ level\ (\frac{mg}{day.Kg\ of\ person})$$
$$= \frac{m_{Chemical}\ (\frac{mg}{day})}{Number\ of\ people\ \times Avg\ Weight_{Person}(kg)} \times Exposure_{area}\ (\%)$$

The above expression (Equation 2.18) however, considers timeframes of exposure, and would require further information on the acute and chronic toxicity of the substance (as the mass of substance the people are exposed to could vary over time). Furthermore, information on the biological half-life (time required for the organism to degrade half of the mass of a substance) would be required to determine if the substance would be accumulating on the organism along the day or over different days.

As the above parameters can be extremely variable and these principles focus mainly on the toxicity of the used substances and products on the chemical process and not on the operational procedures, Equation 2.17 was chosen to determine the Exposure level.

In order to facilitate a direct comparison of the Human Tolerability (Equation 2.16) with the Environmental Toxicity (as was proposed in Equation 2.15, the Hazard Index) normalization of it into an Index between 0 and 1 (where 1 is the best case scenario and 0 the worst case, as proposed in section 2.2) can be useful. A first attempt at this normalization was made through a logarithmic expression (Equation 2.19).

Equation 2.19. Human Tolerability Index, logarithmic normalization

$$Human\ Tolerability\ Index = \frac{1}{Log(Human\ Tolerability) + 1}$$

To test the proposed logarithmic normalization (Equation 2.19) a graphical analysis is carried out (Figure 2.17):
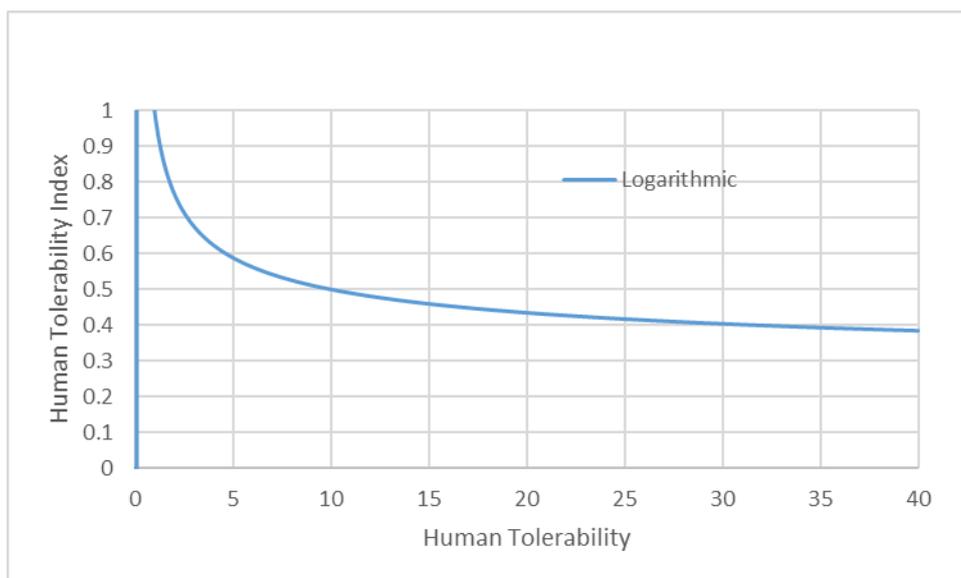
Figure 2.17. Human Tolerability Index profile for the logarithmic expression

From Figure 2.17 it can be seen that the proposed logarithmic expression (Equation 2.19) does not fulfil the criteria of having the Human Tolerability index limited between 0 and 1. Additionally, it requires a large value for the Human Tolerability to reach an index closer to 0.

For example, if the Human Tolerability is 1 it means that for each kg of product the LDLo/LD50 of the substance was reached. In this case the logarithmic expression gives an Index of 1 (the best value it can return). Even at values 10 times higher than the necessary mass of a substance to reach the LD50 (Human Tolerability = 10) the logarithmic expression still presents an Index of 0.5 (a median value for the Index).

As such, another alternative was proposed for the normalization of the Human Tolerability, with the following desired characteristics:

- A double bounded domain of $[0; 1]$, since the Human Tolerability reaches a "critical" value at 1 where human life has reached a clear danger, values above it are considered to have an automatic integration of 0 (worst-case scenario).
- Fits the normalization objective of:
    o $Human\ Tolerability = 0 \rightarrow Human\ Tolerability\ Index = 1$
    o $Human\ Tolerability \geq 1 \rightarrow Human\ Tolerability\ Index = 0$
- As lower Human Tolerability values correspond to "greener" processes according to the principles, the normalization function should be strictly decreasing.

Considering the desired characteristics, the chosen function is the regularized incomplete beta function, previously used for principle 2 (see section 2.2.2) due to its ease of use in limited domains (Equation 2.20), where x is the test value (in this case highest Human Tolerability (Equation 2.16) among the tested substances) and α and β are form parameters between 0 and $+\infty$ responsible for the shape that the function takes.

$$I(x, \alpha, \beta) = \frac{B(x, \alpha, \beta)}{B(1, \alpha, \beta)}$$

In order to define the regularized incomplete beta function, the α and β form parameters (responsible for the shape that the integration function takes, see section 2.2.2) need to be determined. As an exponential expression can be used to describe several types of biological processes [156] [157], the alfa parameter is set as 1, in order to simulate such a profile. Afterwards, the median of the integration function was proposed to be $0.(3)$ to reduce the risk for human health (the 0.5 integration will happen when the mass of the substance is at a third of the "critical" value) (Figure 2.18).

With both the alfa parameter and the median taking the assumed values, the beta parameter can be calculated using the following approximation (Equation 2.21):

Equation 2.21. Determination of β parameter from the median and α parameter

$$\beta \cong \frac{1}{3} + \frac{(1 - median) * (\alpha - \frac{1}{3})}{median}$$

From Equation 2.21 the obtained value for the beta parameter is 1.67. From this, the normalization profile can be built using $\alpha = 1$ and $\beta = 1.67$ (Figure 2.18):
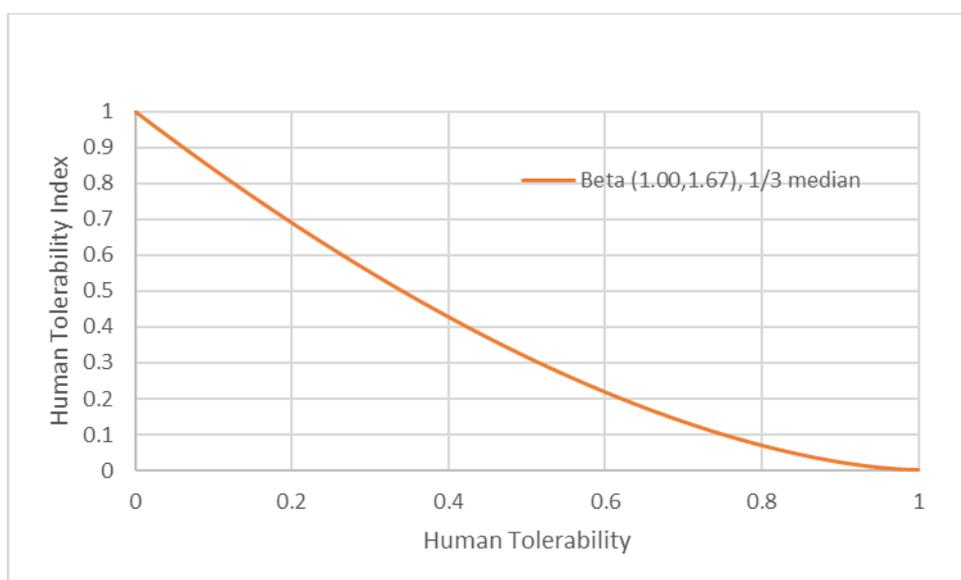
Figure 2.18. Human Tolerability Index normalization profile, values for the Human Tolerability above 1 are considered to have a Human Tolerability Index of 0

Using the methodology proposed above (Equation 2.16, Equation 2.17 and Figure 2.18), the Human Tolerability Index can be determined. Following this, a method to calculate the Environment Toxicity Index needs to be proposed as well.

The proposed method to determine the Environment Toxicity Index is to consider the Acute aquatic toxicity of the substances (determined for algae, bivalves, crustaceans and fish).This information can be found, for example, in the ECOTOX [143] and ECHA [144] databases. Afterwards, a ranking can be made where the first position corresponds to least toxic substance that has been studied and the last position to the most toxic substance that has been studied. Currently, this ranking has assessed 5418 different substances.

From the position on the ranking, the Environment Toxicity Index is proposed to be determined by using a logarithmic function (Equation 2.22), with the objective of being normalized between 0 (worst case scenario) and 1 (best case scenario).

Equation 2.22. Environment Toxicity Index, logarithmic approach

$$Environment\ Toxicity\ Index = \frac{1}{Log\ (Environment\ Toxicity\ Rank) + 1}$$

Using the above function (Equation 2.22) to create the normalization profile, the following graphic is obtained (Figure 2.19):
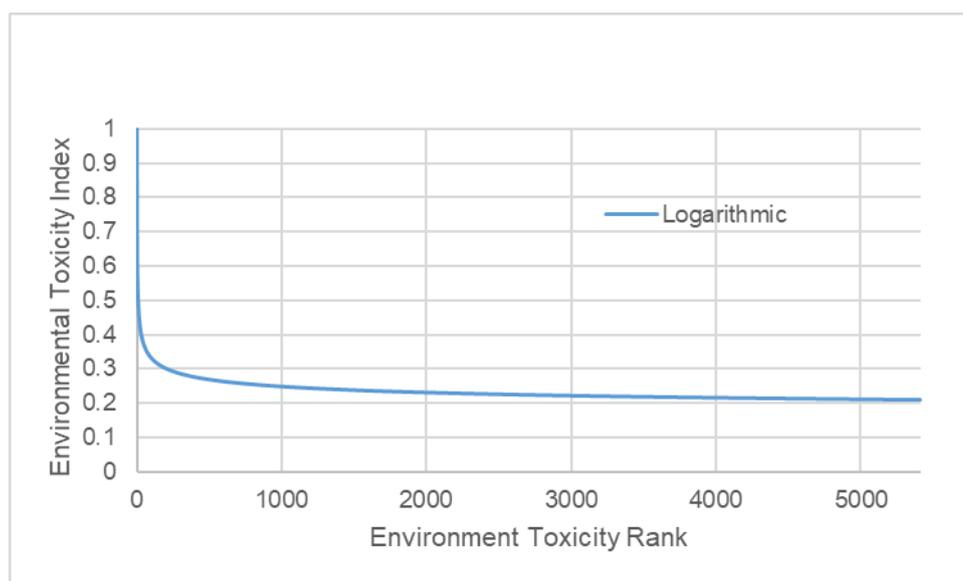
Figure 2.19. Environment Toxicity Index integration profile for the logarithmic expression

The proposed profile (Figure 2.19), however, does not consider the mass of used/formed substances and is not normalized between 0 and 1 for the currently listed substances (5418 different substances).

The proposed alternative to the logarithmic approach, considering how the list is bound to grow as new substances are synthesized or analysed, is to use a linear expression to normalize the Environment Toxicity Rank (Equation 2.23).

$$Normalized\ Environment\ Toxicity\ Rank = 1 - \frac{Environment\ Toxicity\ Rank\ of\ substance - 1}{Number\ of\ listed\ substances - 1}$$

From Equation 2.23 the objective of obtaining a normalized value between 0 and 1 for each of the assessed substances is achieved with the possibility of easily adjusting the value as new substances are added to the list.

Addition of a mass parcel to the Environment Toxicity Index is proposed to be done by considering the mass percentage of each when compared to the total mass of substances under study for the principle (Equation 2.24).

Equation 2.24. Pondered Environmental Toxicity for each substance

$$Pondered\ Environmental\ Toxicity = Normalized\ Environment\ Toxicity\ Rank$$
$$* \frac{mass\ of\ substance\ (kg)}{total\ mass\ of\ substances\ under\ study\ for\ the\ principle\ (kg)}$$

Lastly the Environment Toxicity Index is calculated for the process using the sum of the Pondered Environment Toxicity for each of the considered substances (Equation 2.25).

Equation 2.25. Environmental Toxicity Index alternative

$$Environmental\ Toxicity\ Index = \sum Pondered\ Environmental\ Toxicity$$

The obtained result of the Hazard Index calculation (Equation 2.15) is set between the average of the returned values of the Human Tolerability Index and the Environment Toxicity Index. As both of these Indexes were normalized between 0 and 1 in order to allow their unbiased sum for the Hazard Index the average of both is set between 0 and 1 as well. This results in no further integration being required as was proposed in section 2.2 in order to facilitate data treatment and comparison.

2.2.4. Principles 5 and 11

The 5th principle of Green Chemistry focuses on reducing the usage of auxiliary substances and making them innocuous [22]. The 11th principle of Green Chemistry focuses on monitoring processes in order to reduce the formation of hazardous substances [22]. Neither of these principles has an associated mathematical expression.

As both the 5th and 11th are about reducing the usage (principle 5) and formation (principle 11) of hazardous substances, the same metric will be proposed for usage with both. In the case of the 5th principle the inputs will be analysed while for the 11th principle the outputs will be analysed. In order to assess how hazardous a substance is, the National Fire Protection Association's method can be considered. This method considers that there are four hazard types (Figure 2.20):

Figure 2.20. Hazard Classifications [145] [146]

- The Health Hazard (blue diamond) which assesses the dangers to human health of the substance. Ranked 0 to 4, where 0 is an innocuous substance and 4 represents a possibly lethal substance;
- The Fire Hazard (red diamond) which assesses the danger of a fire breaking out due to the substance. Ranked 0 to 4, where 0 is a non-flammable substance and 4 is a substance that can ignite by itself at normal temperature;
- The Instability Hazard (yellow diamond) which assesses the danger of explosion of the substance. Ranked 0 to 4, where 0 is a stable substance and 4 is a substance that easily explodes;
- The Special Hazard (white diamond) which assess other possible hazardous conditions or characteristics. No ranking is made for these hazards, only the warning is given.

In order to consider that all hazard types assessed by the National Fire Protection Association (NFPA) (Figure 2.20) have an equal importance, it is proposed that the Special Hazard be normalized between 0 and 4 as the other hazards (Health, Fire and Instability). Currently up to 8 types of Special Hazards that can coexist exist, as a result, each of them will be considered to have the same value of 0.5 so the maximum sum of them is 4 (Table 2.9).

Table 2.9. Special hazard values

Notation	Definition	Value
OX	Oxidizer	0.5
W	Reacts with water	0.5
SA	Simple asphyxiant gas	0.5
AC, AL	Strong acid (AC) or base (AL)	0.5
BIO	Biological hazard	0.5
POI	Poisonous	0.5
RA, RAD	Radioactive	0.5
CYL, CRIO	Cryogenic	0.5

From Table 2.9, the possible total Special hazard is seen to vary between 0 (when no hazard is present) and 4 (when all hazards are present). By having the proposed value of 0.5 for all hazards, however, it isn't being considered that each of them can have a different impact on human and environmental health and safety. In order to take that into account, the existing special hazards are proposed to be divided into 3 categories depending on the possible impacts of each:

- Category 1 includes oxidizers, substances that react with water, simple asphyxiant gases, strong acids or bases and cryogenic substances. All of the considered hazards for this category either have a highly limited range of action (for example, only the user or the laboratory where they are used) or require high concentrations to pose a danger. The special hazards of this category are proposed to have, in a first approach, a special hazard value of 0.1 (Table 2.10). Values for the other proposed danger categories will be calculated using this value as a basis.

- Category 2 includes poisonous substances. Substances that are classified with the "poisonous" hazard require low concentrations to kill an average human with symptoms appearing in less than 1 hour (for example, strychnine [161]) and may sometimes transmit from one to another through contact or proximity (for example through dust). The special hazard in this category is proposed to have a special hazard value equal to the sum of the category 1 special hazards (Equation 2.26) (Table 2.10). This value is proposed as it allows a poisonous substance to be considered the same (in terms of special hazard value) as a substance with all the danger category 1 hazards.

Equation 2.26. Category 2 special hazard calculation

$$Category\ 2\ special\ hazard = \sum Category\ 1\ special\ hazards$$

- Category 3 includes biological hazards and radioactive substances. Both of these types of substances can have long-term impacts on the human health and eco-system while easily spreading and being possibly complicated to control (for example, the Ebola virus [162]). The special hazards in this category are proposed to have a value that makes the sum of all hazards 4, as was previously proposed in order to have all hazard types in Figure 1.4 have the same value range (0 to 4) (Equation 2.27) (Table 2.10). The obtained value should also be higher the category 2 special hazard (Equation 2.26) as this category poses a higher danger

Equation 2.27. Category 3 special hazard calculation

$$Category\ 3\ hazard = \frac{4 - \sum Category\ 1\ and\ 2\ special\ hazards}{2\ (as\ there\ are\ 2\ special\ hazards\ in\ this\ category)}$$

Considering the proposed division by danger categories, a second version of the special hazard values is created (Table 2.10):

Table 2.10. Special hazard values considering danger categories

Notation	Definition	Danger Category	Value
OX	Oxidizer	1	0.1
W	Reacts with water	1	0.1
SA	Simple asphyxiant gas	1	0.1
AC, AL	Strong acid (AC) or base (AL)	1	0.1
BIO	Biological hazard	3	1.5 (Equation 2.27)
POI	Poisonous	2	0.5 (Equation 2.26)
RA, RAD	Radioactive	3	1.5 (Equation 2.27)
CYL, CRIO	Cryogenic	1	0.1

From Table 2.10 it is possible to conclude that the proposed division of Special hazard values based on the danger category still fits the criteria of varying between 0 (when no special hazard exists) and 4 (when all special hazards are considered to exist). The choice of values for each category, as previously described, also appears to be working as intended, with the danger category 2 hazard being considered as dangerous as the sum of all category 1 hazards and the category 3 hazards having a high value (superior to a value of 1, as they can spread over large areas and have long lasting consequences for the biosphere).

After having all hazard values defined, the Total Hazard Index of the substance is proposed to be calculated as the sum of them (Equation 2.28).

Equation 2.28. NFPA Total Hazard Index for each substance

$$Total\ Hazard\ Index = Health\ Hazard + Fire\ Hazard + Instability\ Hazard + Special\ Hazard$$

Lastly, the process' Total Hazard Index is proposed to be determined from the pondered sum of each of the assessed substances based on their mass percentage (Equation 2.29):

Equation 2.29. Process Total Hazard Index

$$Process\ Hazard\ Index = \sum Total\ Hazard\ Index * \frac{mass\ of\ substance\ (kg)}{total\ mass\ of\ assessed\ substances\ (kg)}$$

Current legislation does not force the NFPA notation to be used in a substance's MSDS. The Globally Harmonized System of Classification and Labelling of Chemicals (GHS), however, is in transition to be legally required in a substance's MSDS [163]. As such, in cases where the NFPA diamond isn't represented, a list with the GHS Hazard Warnings is proposed to be used instead by classifying each of the warning phrases as a number between 1 and 4 for each specific hazard type. The Hazard Indexes were proposed by following the "Classification criteria" and "Decision logic and guidance" used in the GHS document [163] and comparing it with the NFPA fire diamond notations in order to determine the closest equivalence (Table 2.11). Due to the lack of equivalence to the "Special hazards", "Environmental hazards" are proposed to be used instead, in order to maintain four different hazard types.

Table 2.11. GHS Hazard Indexes. The Hazard Index column was proposed by following the "Classification criteria" and "decision logic and guidance" sections in the GHS document [163] and comparing it with the NFPA fire diamond

Hazard Code	Hazard Statement [163]	Hazard Index
H200	Unstable explosive	4 in Instability Hazard
H201	Explosive; mass explosion hazard	4 in Instability Hazard
H202	Explosive; severe projection hazard	4 in Instability Hazard
H203	Explosive; fire, blast or projection hazard	4 in Instability Hazard
H204	Fire or projection hazard	3 in Instability Hazard
H205	May mass explode in fire	3 in Instability Hazard
H206	Fire, blast or projection hazard; increased risk of explosion if desensitizing agent is reduced	2 in Instability Hazard
H207	Fire or projection hazard; increased risk of explosion if desensitizing agent is reduced	2 in Instability Hazard
H208	Fire hazard; increased risk of explosion if desensitizing agent is reduced	2 in Instability Hazard
H220	Extremely flammable gas	4 in Fire Hazard
H221	Flammable gas	3 in Fire Hazard
H222	Extremely flammable aerosol	4 in Fire Hazard
H223	Flammable aerosol	3 in Fire Hazard
H224	Extremely flammable liquid and vapour	4 in Fire Hazard
H225	Highly flammable liquid and vapour	3 in Fire Hazard
H226	Flammable liquid and vapour	2 in Fire Hazard
H227	Combustible liquid	1 in Fire Hazard
H228	Flammable solid	2 in Fire Hazard
H229	Pressurized container: May burst if heated.	1 in Instability Hazard
H230	May react explosively even in the absence of air	4 in Instability Hazard
H231	May react explosively even in the absence of air at elevated pressure and/or temperature	3 in Instability Hazard
H232	May ignite spontaneously if exposed to air	4 in Fire Hazard
H240	Heating may cause an explosion	2 in Instability Hazard
H241	Heating may cause a fire or explosion	2 in Instability Hazard and 2 in Fire Hazard
H242	Heating may cause a fire	2 in Fire Hazard
H250	Catches fire spontaneously if exposed to air	4 in Fire Hazard
H251	Self-heating; may catch fire	3 in Fire Hazard
H252	Self-heating in large quantities; may catch fire	2 in Fire Hazard
H260	In contact with water releases flammable gases which may ignite spontaneously	2 in Instability Hazard and 4 in Fire Hazard
H261	In contact with water releases flammable gas	2 in Instability Hazard and 2

		in Fire Hazard
H270	May cause or intensify fire; oxidizer	2 in Instability Hazard and 2 in Fire hazard
H271	May cause fire or explosion; strong oxidizer	3 in Instability Hazard and 3 in Fire Hazard
H272	May intensify fire; oxidizer	1 in Instability Hazard and 1 in Fire Hazard
H280	Contains gas under pressure may explode if heated	2 in Instability Hazard
H281	Contains refrigerated gas; may cause cryogenic burns or injury	2 in Health Hazard
H290	May be corrosive to metals	1 in Health Hazard
H300	Fatal if swallowed	4 in Health Hazard
H301	Toxic if swallowed	3 in Health Hazard
H302	Harmful if swallowed	2 in Health Hazard
H303	May be harmful if swallowed	1 in Health Hazard
H304	May be fatal if swallowed and enters airway	4 in Health Hazard
H305	May be harmful if swallowed and enters airway	2 in Health Hazard
H310	Fatal in contact with the skin	4 in Health Hazard
H311	Toxic in contact with the skin	3 in Health Hazard
H312	Harmful in contact with the skin	2 in Health hazard
H313	May be harmful in contact with the skin	1 in Health Hazard
H314	Causes severe skin burns and eye damage	4 in Health Hazard
H315	Causes skin irritation	3 in Health Hazard
H316	Causes mild skin irritation	2 in Health Hazard
H317	May cause an allergic skin reaction	1 in Health Hazard
H318	Causes serious eye damage	3 in Health Hazard
H319	Causes serious eye irritation	2 in Health Hazard
H320	Causes eye irritation	1 in Health hazard
H330	Fatal if inhaled	4 in Health Hazard
H331	Toxic if inhaled	3 in Health Hazard
H332	Harmful if inhaled	2 in Health Hazard
H333	May be harmful if inhaled	1 in Health Hazard
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled	1 in Health Hazard
H335	May cause respiratory irritation	1 in Health Hazard
H336	May cause drowsiness or dizziness	2 in Health Hazard
H340	May cause genetic defects	4 in Health Hazard
H341	Suspected of causing genetic defects	4 in Health Hazard
H350	May cause cancer	4 in Health Hazard
H351	Suspected of causing cancer	4 in Health Hazard
H360	May damage fertility or the unborn child	4 in Health hazard
H361	Suspected of damaging fertility or the unborn child	4 in Health Hazard
H362	May cause harm to breast-fed children	4 in Health Hazard
H370	Causes damage to organs	4 in Health Hazard
H371	May cause damage to organs	3 in Health Hazard
H372	Causes damage to organs through prolonged or repeated exposure	2 in Health Hazard
H373	May cause damage to organs through prolonged or repeated exposure	2 in Health Hazard
H300 + H310 + H330	Fatal if swallowed, in contact with skin or if inhaled	4 in Health Hazard
H400	Very toxic to aquatic life	4 in Environmental Hazard
H401	Toxic to aquatic life	3 in Environmental Hazard
H402	Harmful to aquatic life	1 in Environmental Hazard
H410	Very toxic to aquatic life with long lasting effects	4 in Environmental Hazard
H411	Toxic to aquatic life with long lasting effects	4 in Environmental Hazard
H412	Harmful to aquatic life with long lasting effects	3 in Environmental Hazard
H413	May cause long lasting effects to aquatic life	2 in Environmental Hazard
H420	Harms public health and the environment by destroying ozone in the upper atmosphere	2 in Environmental Hazard

After using Table 2.11 to turn the hazard warnings into the associated hazard indexes, the Total Hazard Index is proposed to be calculated as the sum of the highest obtained hazard warnings of each type (Equation 2.30).

Equation 2.30. GHS Total Hazard Index

$$Total\ Hazard\ Index$$
$$= Maximum\ Health\ Hazard + Maximum\ Fire\ Hazard$$
$$+ Maximum\ Instability\ Hazard + Maximum\ Environmental\ Hazard$$

Lastly, the Process Hazard Index is calculated as the pondered sum of the Total Hazard Index of all assessed substances (Equation 2.31):

Equation 2.31. Process Hazard Index

$$Process\ Hazard\ Index = \sum Total\ Hazard\ Index * \frac{mass\ of\ substance\ (kg)}{total\ mass\ of\ assessed\ substances\ (kg)}$$

For the determination of the Process Hazard Index, either by the NFPA method (Figure 2.20 , Equation 2.28 and Equation 2.29) or the GHS method (Table 2.14, Equation 2.30 and Equation 2.31) the mass of used/generated substances wasn't considered. This is because, although principle 5 mentions reducing the usage of auxiliary substances [22], this same parameter is analysed in other principles (for example, principle 1 (see section 2.2.1)) in higher detail and, as such, it was considered that its analysis for these principles would not give further information on the "greenness" of the process. Further details on how to use both methods and comparison of their results are demonstrated through an example ahead, starting on Table 2.13.

Lastly, the obtained value for the Process Hazard Index (Equation 2.31) is proposed to be integrated between 0 and 1, where 0 is the worst-case scenario and 1 is the best-case scenario (as described in section 2.2), to facilitate further data treatment and comparison with the results of other principles or methodologies. In order to carry out the integration the following characteristics are required for the chosen function:

- Has a double-bounded domain of $[0; 16]$, the same as the Process Hazard Index;
- Fits the defined integration objectives of:
  - $Process\ Total\ Index\ = 0 \rightarrow Integrated\ Total\ Index\ = 1$
  - $Process\ Total\ Index = 16 \rightarrow Integrated\ Total\ Index = 0$
- According to the principles, lower hazard values (lower Process Hazard Index) are considered "greener"- As such, the chosen function should be strictly decreasing

Considering the desired characteristics, the regularized incomplete beta function, already analysed and used for the 2nd principle (please see section 2.2.2), was chosen (Equation 2.32).

Equation 2.32. Integrated Process Hazard proposed expression

$$Integrated\ Process\ Hazard = 1 - I(x;\ \alpha, \beta)$$

In Equation 2.32, x needs to be a value between 0 and 1. In order to turn the value range of the Process Hazard Index ($[0; 16]$) into the desired range of $[0; 1]$, Equation 2.33 can be used, where y is the Process Hazard Index and x is the input value for the Integrated Process Hazard (Equation 2.32).

Equation 2.33. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Lastly, the α and β form parameter need to be determined. As no information exists to allow the α and β parameters to be mathematically determined, they will be chosen based on the following considerations:

- The median value of the Process Hazard Index is 8. As the Process Hazard Index varies between 0 and 16 it can be assumed that the median value of the integration (corresponding to a 0.5 integration) is the median value that the Process Hazard Index can take.
- It is symmetric in respect to the median point (in this case, proposed to be (8.0,0.5)). This means that altering the value of the Process Hazard Index from 0 to 1 will have the same impact on the integrated value as altering it from 15 to 16. In an incomplete beta function this results in $\alpha =$.
- Values from the Process Hazard Index closer to the limits are also close to the limits of the integration as they can be considered to already be on a "very bad" or "very good" range. More specifically, it will be assumed that the lower quartile of possible values for the Process Hazard Index (4) will have a 0.9 integration and the higher quartile of possible values for the Process Hazard Index (12) will have a 0.1 integration.

With the above considerations in mind, the α and β parameters are optimised using MATLAB's genetic algorithm with the objective of reducing the total square error for the proposed integration objectives (Figure 2.21):

- A Process Hazard Index of 0 has an integrated value of 1
- A Process Hazard Index of 4 has an integrated value of 0.9
- A Process Hazard Index of 8 has an integrated value of 0.5
- A Process Hazard Index of 12 has an integrated value of 0.1
- A Process Hazard Index of 16 has an integrated value of 0

```
                      Best          Mean       Stall
Generation    Func-count     f(x)          f(x)    Generations
    61          18600     1.452e-06     1.452e-06      41
    62          18900     1.452e-06     1.452e-06      42
    63          19200     1.452e-06     1.452e-06      43
    64          19500     1.452e-06     1.452e-06      44
    65          19800     1.452e-06     1.452e-06      45
    66          20100     1.452e-06     1.452e-06      46
    67          20400     1.452e-06     1.452e-06      47
    68          20700     1.452e-06     1.452e-06      48
    69          21000     1.452e-06     1.452e-06      49
    70          21300     1.452e-06     1.452e-06      50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa and beta parameter estimations = 3.09
```

Figure 2.21. MATLAB results for the genetic algorithm optimization of the α and β parameters

From Figure 2.21 it is seen that the obtained values for the α and β parameter from the MATLAB optimization are of 3.09 with the associated square error of approximately $1.45 * 10^{-6}$. In order to confirm these results an error analysis is conducted (Table 2.12):

Table 2.12. Error analysis for determination of the alfa and beta parameters for the regularized incomplete beta function

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	1.0000	1.0000	0.0000	0.0000	0.0000
Q1	0.9000	0.9006	0.0006	0.0677	0.0677
Median	0.5000	0.5009	0.0009	0.1905	0.1905
Q3	0.1000	0.0999	0.0001	-0.0876	0.0876
Maximum	0.0000	0.0000	0.0000	0.0000	0.0000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Process Hazard Index of 0, the lower quartile (Q1) corresponds to a Process Hazard Index of 4, the median corresponds to a Process Hazard Index of 8, the upper quartile (Q3) corresponds to a Process Hazard Index of 12 and the maximum corresponds to a Process Hazard Index of 16

From the error analysis of the optimization of the α and β to fit the previous considerations, it can be seen to be working as intended with the absolute percentage error never being superior to 0.1905%. As such, the integration profile is built for the Process Hazard Index using $I(x; 3.09,3.09)$, where x is the normalized variable defined by Equation 2.12 (Figure 2.22).
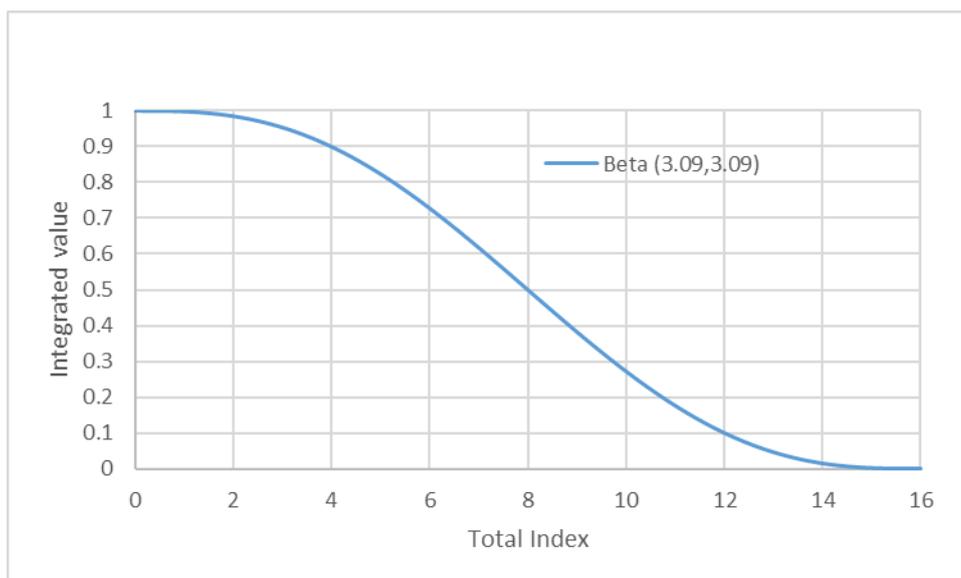
Figure 2.22. Integration profile for the Process Hazard Index

In order to test both methodologies proposed above (Determining the Process Hazard Index through the NFPA's fire diamond or through GHS' Hazard warnings), a comparison of the results for the Integrated value obtained by both will be conducted. The chosen substances to carry out the test are sodium hydroxide (a commonly used strong base), hydrochloric acid (a commonly used strong acid), mercury (a dangerous compound for the environment), ammonia (used in the synthesis of several products), propane (used as fuel) and acrylamide (used for the production of polymers or in molecular biology). As such, the results for the proposed substances used the NFPA fire diamond follow (Table 2.13):

Table 2.13. Integrated Process Hazard of different substances and mixtures calculated through the NFPA fire diamond

Substance/ Mixture	Health Hazard	Fire Hazard	Instability Hazard	Special Hazard	Process Hazard Index (Equation 2.28 and Equation 2.29)	Integrated Process Hazard (Figure 2.22)
Sodium Hydroxide 1.0M	3 [164]	0 [164]	1 [164]	0 [164]	4	0.90
Hydrochloric Acid 1.0M	3 [165]	0 [165]	1 [165]	0 [165]	4	0.90
Mercury, 1000 ppm	3 [166]	0 [166]	0 [166]	0 [166]	3	0.95
Ammonia	3 [167]	1 [167]	0 [167]	0 [167]	4	0.90
Propane	2 [168]	4 [168]	0 [168]	0 [168]	6	0.73
Acrylamide Solution, 40%	3 [169]	2 [169]	2 [169]	0 [169]	7	0.62

In the above table (Table 2.13) the results for the Process Hazard Index of the tested substances and mixtures is seen only have values below the median value that it can take. This can be explained by the fact that the Special Hazard warnings are mostly optional to use, and, in the case of the tested substances and mixtures, it was always 0 (no warnings). Following this, the same mixtures and substances were tested using the GHS hazard warnings as previously proposed. The first step of the proposed method is identifying the GHS hazard warnings for the substance/mixture (Table 2.14).

Table 2.14. GHS hazard warnings of different substances and mixtures

Substance/ Mixture	Hazard warnings
Sodium Hydroxide 1.0M	H314, H318, H402 [164]
Hydrochloric Acid 1.0M	H302, H314, H318, H335, H402 [165]
Mercury, 1000 ppm	H272, H290, H300, H310, H314, H318, H330, H373, H400, H402, H410, H412 [166]
Ammonia	H280, H314, H332 [167]
Propane	H220, H280 [168]
Acrylamide Solution, 40%	H301, H313, H315, H317, H332, H340, H350, H361, H373 [169]

Following the identification of the hazard warnings (Table 2.14), the Health, Fire, Instability and Environmental are considered to be the highest value associated to those warnings according to the proposed table (Table 2.11). This results in the following table (Table 2.15):

Table 2.15. Integrated Process Hazard of different substances and mixtures calculated through the GHS hazard warnings. The Health Hazard, Fire Hazard, Instability Hazard and Environmental Hazard are determined by considering the highest values in Table 2.11 for the hazard warnings in Table 2.14

Substance/ Mixture	Health Hazard	Fire Hazard	Instability Hazard	Environmental Hazard	Process Hazard Index (Equation 2.30 and Equation 2.31)	Integrated Process Hazard (Figure 2.22)
Sodium Hydroxide 1.0M	4	0	0	1	5	0.82
Hydrochloric Acid 1.0M	4	0	0	1	5	0.82
Mercury, 1000 ppm	4	1	1	4	10	0.27
Ammonia	4	0	2	0	6	0.73
Propane	0	4	2	0	6	0.73
Acrylamide Solution, 40%	4	0	0	0	4	0.90

From Table 2.15 it can be seen that the Process Hazard Index has values ranging from 4 to 10 for the assessed substances and mixtures. These results are in the area of highest variation in the integration (between 4 and 12) and the proposed environmental impact has a large impact in the case of mercury, showing that considering it can be important. Comparing the results for the Process Hazard Index and Integrated Process Hazard obtained from the NFPA fire diamond (Table 2.13) and the GHS hazard warnings (Table 2.15) using Table 2.16:

Table 2.16. Results for the Process Hazard Index and Integrated Process Hazard determined through the NFPA fire diamond (Table 2.13) and through the GHS hazard statements (Table 2.15)

Substance/ Mixture	Process Hazard Index (NFPA method, Table 2.13)	Integrated Process Hazard (NFPA method, Table 2.13)	Process Hazard Index (GHS method, Table 2.15)	Integrated Process Hazard (GHS method, Table 2.15)
Sodium Hydroxide 1.0M	4	0.90	5	0.82
Hydrochloric Acid 1.0M	4	0.90	5	0.82
Mercury, 1000 ppm	3	0.95	10	0.27
Ammonia	4	0.90	6	0.73
Propane	6	0.73	6	0.73
Acrylamide Solution, 40%	7	0.62	4	0.90

From the comparison of the obtained results for both methods (Table 2.16), it can be seen that the Integrated Process Hazard calculated from either method can generate different results, mostly obtaining a lower or equal integrated value when considering the GHS method (the only exception is acrylamide). This can be due to taking into account the environmental impact on the GHS method (reducing the integrated value when present). Additionally, the types of dangers presented by either method deviate largely in the cases of mercury and acrylamide.

In the case of mercury, while the GHS hazard warnings mention the possibility of intensifying fires (H272 [166]); the NFPA fire diamond describes it as a completely non-flammable under standard fire conditions (0 in Fire Hazard [166]). The Environmental Hazard also presents a major impact on the Process Hazard Index calculated via the GHS method as it has a value of 4 due to being very toxic for aquatic life (H400 [166]) with long lasting effects (H412 [166]); a factor that is not considered in the NFPA method.

In the case of acrylamide, the NFPA method presents a higher Process Hazard Index (lower integrated value) due to considering the existence of both Instability Hazard (with a value of 2 [169]) and a Fire Hazard (a value of 2 as well [169]). On the other hand, the GHS hazard warnings for that same mixture are only related to health warnings (H301, H313, H315, H317, H332, H340, H350, H361, H373 [169]).

In conclusion, both the proposed methods can be used as there are no guarantees, at the time of writing, that the Material Safety Data Sheet of the used substance or mixture will have both. However, as legislation is moving towards the necessity of having the GHS hazard warnings, this method is recommended when possible. This method, although presenting lower integrated results, is also closer to the objectives of the principle as it considers the environmental impact of the substances as well.

2.2.5. Principle 6

The 6th principle is about minimizing the energy requirements considering environmental and economic costs [22] and has no metrics directly associated to it. Considering this, a metric is proposed based on the energy requirements of each equipment used in the process (Equation 2.34).

Equation 2.34. Total Energy Requirements

$$Total\ Energy\ Requirements = \sum Energy\ Requirements\ for\ each\ equipment\ (kWh)$$

The Total Energy Requirements obtained from Equation 2.34 vary between 0 and $+\infty$. In order to facilitate data treatment and interpretation in a global green chemistry grid, an integration between 0 and 1, was performed. The integration formula proposed is represented by Equation 2.35.

Equation 2.35. Integrated Energy Requirements

$$Integrated\ Energy\ Requirements = \frac{1}{Log\ (Total\ Energy\ Requirements(kWh)) + 1}$$

This approach, however, ends up not considering the effects of the economic and environmental costs of energy, which is one of the principle's objectives. In order to attempt this, the impact of the used energy can be considered to be divided into economic costs and environmental costs (as stated in the principle).

Considering the above, another formula is proposed, the Energy Index (Equation 2.36). This Index is considered to be the average of a normalized economic parcel and a normalized environmental parcel (by using the average of a normalized value both are considered to be equally important).

Equation 2.36. Energy Index

$$Energy\ Index = \frac{Economic\ Cost\ Index + Environmental\ Cost\ Index}{2}$$

The economic parcel of the Energy Index (Economic Cost) can be calculated as the price of all energy required per kg of product in the process, using the following proposed equation (Equation 2.37):

Equation 2.37. Economic Cost

$$Economic\ Cost\ (\frac{€}{kg\ of\ product}) = \sum Energy\ Requirement\ \left(\frac{kWh}{kg\ of\ product}\right) * Energy\ Price\ \left(\frac{€}{kWh}\right)$$

The above expression (Equation 2.37), however, returns a value between 0 and $+\infty$, which goes against the objective of having a normalized value between 0 and 1 for the Economic Cost Index. Integration to an index between 0 and 1 can be done using an expression with the following characteristics:

- A domain equal to Economic Cost's value range ($x = [0; +\infty[$);
- Fits the defined integration objectives of:
    - $Economic\ Cost\ =\ 0\ \rightarrow\ Economic\ Cost\ Index\ =\ 1$
    - $Economic\ Cost\ \approx\ +\infty\ \rightarrow\ Economic\ Cost\ Index\ \approx\ 0$
- As a lower Economic Cost corresponds to a "greener" process according to the principle, the integration function should be strictly decreasing (Higher values of the Economic Cost always have lower integrated values).

As the desired characteristics are like the desired characteristics of the integration function used for the 1st principle (please check section 2.2.1), the chosen expression was the exponential distribution's probability density function as well (Equation 2.38).

Equation 2.38. Exponential distribution's probability density function

$$f(x;\ \beta) = e^{-\frac{x}{\beta}}$$

In order to use the above equation (Equation 2.38) a β parameter needs to be defined. Determination of the β parameter was done considering, as with the 1st principle, the median value (Equation 2.39).

Equation 2.39. β determined from a median value

$$\beta = \frac{median}{\ln(2)}$$

For calculation of the β parameter using Equation 2.39 the median was considered to be 0.30 €/kg of product (2.69 kWh/kg, the average energy intensity for the chemical industry in 2015 [170] [171] multiplied by 0.11 €/kWh, the average cost of energy in Europe in 2017 [172]). As a result, the integration profile for the Economic Cost Index was built with $f(x;\ \beta) = e^{-\frac{x}{\beta}}$; $\beta = \frac{0.30}{\ln(2)}$ (Figure 2.23).
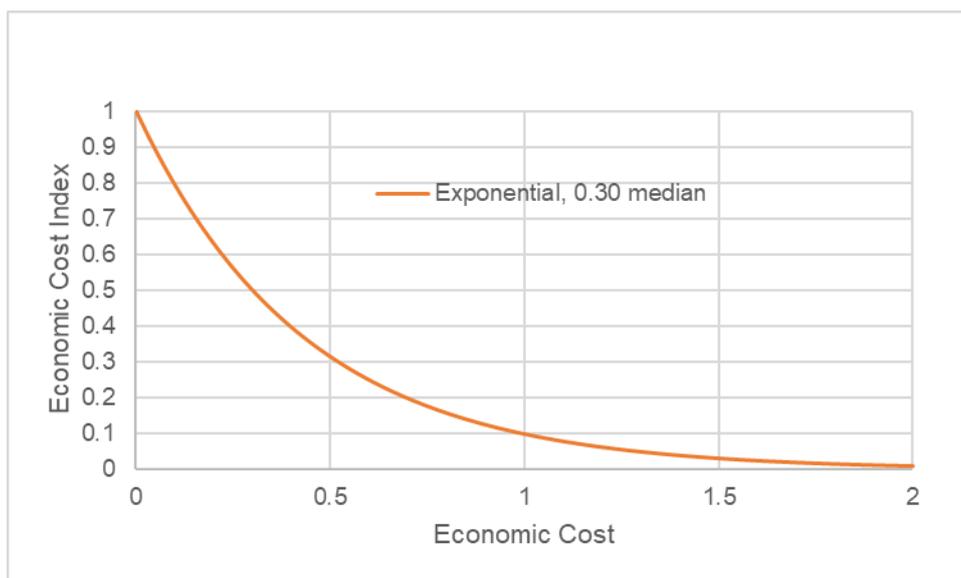
Figure 2.23. Economic Cost Index

Looking at the above graphic (Figure 2.23) it is possible to conclude that the characteristics considered necessary for the integration of the Economic Cost into an Index have been achieved. In order to evaluate the integration, two methods for the synthesis of benzoic hydrazide, a conventional one and a greener one using microwave radiation, have been compared:

Table 2.17. Economic Cost Index example for the synthesis of hydrazides

Process	Energy Requirements (kWh) [27]	Energy Price (€) [173]	Economic Cost (Equation 2.37)	Economic Cost Index (Figure 2.23)
Conventional synthesis of benzoic hydrazide [27]	9.00	0.11*	0.990	0.10
Greener synthesis of benzoic hydrazide [27]	0.05	0.11*	0.006	0.99

*As the energy price is dependent on time and location it was assumed, for the purposes of this comparison, that it was the average cost of energy in Europe in 2015 *[173]*

From an analysis of Table 2.17 it can be concluded that the greener method for the synthesis of benzoic hydrazide has a larger Economic Cost Index value than the conventional method (0.99 vs 0.10). These results are as expected due to the large difference in Energy Requirements for both methods (the greener method requires 180 times less energy [27]).

Having defined how the Economic Cost Index is determined (Equation 2.37 and Figure 2.23) it becomes necessary to define the Environmental Cost Index as well.

Implementation of environmental costs can be made using an arithmetic factor, for example, based on the CO_2 releases of the energy source, since CO_2 releases or CO_2 equivalent releases are commonly used metrics in environmental assessments [174]. By multiplying that value with the % of energy that comes from the associated source and summing them, the result is the predicted CO_2 emissions/kWh in the process. Lastly, by multiplying this value with the energy requirements of the process, the CO_2 emissions from energy per kg of product are obtained (Equation 2.40).

Equation 2.40. Environmental Cost

$$Environmental\ Cost\ \left(\frac{g\ of\ CO_2}{kg\ of\ product}\right)$$

$$= Energy\ Requirements\ \left(\frac{kWh}{kg\ of\ product}\right)$$

$$* \sum \left(CO2\ emission\ of\ source\ \left(\frac{g\ of\ CO_2}{kWh}\right) * Energy\ from\ source(\%)\right)$$

To apply the above equation (Equation 2.40) data on the CO_2 emissions from different energy sources (in g of CO_2/kWh) is required. This information can be found in the table below (Table 2.18 [175] [176]).

Table 2.18. CO$_2$ emissions from different energy sources

Energy Source	CO$_2$ emission (g/kWh)
Coal [175]	955
Oil [175]	818
Natural gas [175]	430
Diesel [175]	772
Hydro [175]	9
Wind [175]	9
Solar photovoltaic [175]	167
Solar thermal electric [175]	38
Biomass (Energy crops) [175]	27
Geothermal [175]	9
Nuclear [176]	130

The values obtained from the proposed expression (Equation 2.40 and Table 2.18) are between 0 (if no energy is required or an ideal zero emissions energy source is used) and $+\infty$ (for increasingly high energy requirements). As the objective is to have the Environmental Cost normalized between 0 and 1 an integration expression with the following characteristics is required:

- A domain equal to the Environmental Cost's value range ($x = [0; +\infty]$);
- Fits the defined integration objectives of:
  - $Environmental\ Cost\ =\ 0\ \rightarrow\ Environmental\ Cost\ Index\ =\ 1$
  - $Environmental\ Cost\ \approx\ +\infty\ \rightarrow\ Environmental\ Cost\ Index\ \approx\ 0$
- As a lower Economic Cost corresponds to a "greener" process according to the principle, the integration function should be strictly decreasing (Higher values of the Economic Cost always have lower integrated values).

As these criteria are similar to the criteria defined for the integration of the Economic Cost previously done, the same approach for the integration will be made (Equation 2.41).

Equation 2.41. Exponential distribution's probability density function

$$f(x;\ \beta) = e^{-\frac{x}{\beta}}$$

In order to use Equation 2.41, a β parameter needs to be defined. As with the Economic Cost, its determination was done using a median value for the integration (Equation 2.42).

Equation 2.42. β determined from a median value

$$\beta = \frac{median}{\ln(2)}$$

For Equation 2.42, the median was determined by calculating the Environmental Cost with the following considerations:

- In Europe, approximately 30% of the energy is sourced from natural gas, 10% from petroleum and 60% from other energies, which mainly include renewables [173].
- In Europe, the average energy intensity of the chemical industry in 2015 was of 2.69 kWh/kg of product [170] [171].

With these considerations in mind, the average Environmental Cost of energy in Europe was determined (Table 2.19):

Table 2.19. Determination of the Environmental Cost of energy in Europe, the CO_2 emissions of a process are the sum total of the product of the Energy from Source and the associated CO_2 emissions. The Energy Requirements and the Environmental Cost are only applicable to the process total.

Energy Source	Energy from Source (%) [173]	CO_2 emissions (g of CO_2/ kWh) [175]	Energy Requirements (kWh/g of product) [170]	Environmental Cost (g CO_2/g of product) (Equation 2.40)
Natural Gas	30	430	N.A.	N.A.
Petroleum	10	818	N.A.	N.A.
Other energies (mostly renewables)	60	9[1]	N.A.	N.A.
Process total	100	216.20[2]	2.69	581.58

[1]As there is no indication to what renewable energies are used, they were considered to be Hydro, Wind or Geothermal, which have the lowest CO_2 emissions (9 g/kWh) in Table 2.18. [2] The CO_2 emissions of the process are the pondered total of the CO_2 emissions of the individual energy sources. N.A.: Not available

As can be seen in Table 2.19, the average Environmental Cost of energy in Europe is, at best, of approximately 581.58 g CO_2 /g of product. By substituting this value in Equation 2.42 as the median (in order to have a 0.50 integration), the β parameter is obtained ($\beta = \frac{581.58}{\ln(2)}$) and the integration profile for the Environmental Cost Index is built (Figure 2.24).
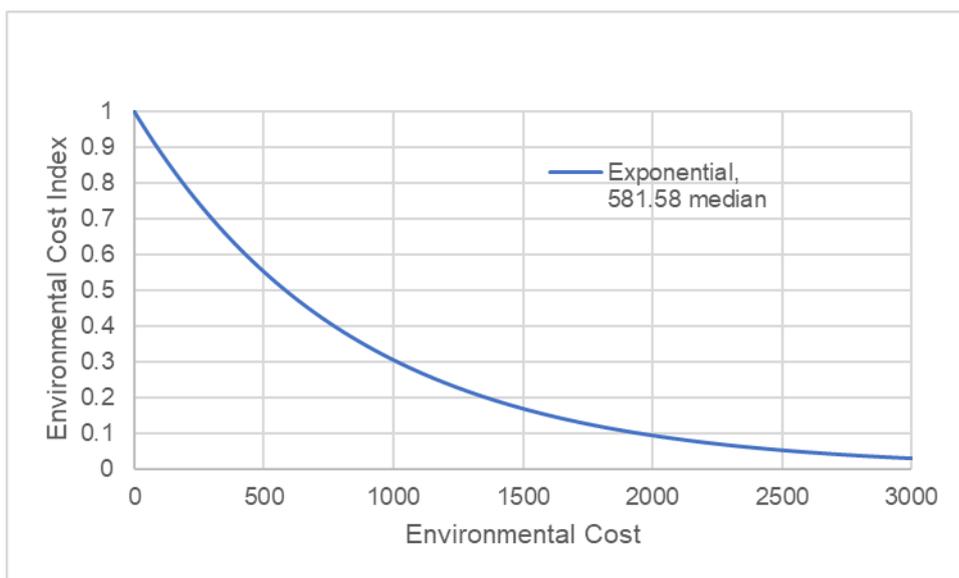
Figure 2.24. Environmental Cost Index

From the above figure (Figure 2.24) it can be concluded that the desired characteristics for the Environmental Cost Index have been followed. In order to test the integration, the same two methods for the synthesis of benzoic hydrazide tested for the Economic Cost, a conventional one and a greener one using microwave radiation, have been compared:

Table 2.20. Environmental Cost Index example for the synthesis of hydrazides

Process	Energy Requirements (kWh) [27]	CO_2 emissions of process (g CO_2/ kWh) (Table 2.19)	Environmental Cost (Equation 2.40)	Environmental Cost Index (Figure 2.24)
Conventional synthesis of benzoic hydrazide [27]	9.00	216.2*	1945	0.10
Greener synthesis of benzoic hydrazide [27]	0.05	216.2*	11	0.99

*As the source of energy is dependent on the energy provider, for the purposes of this comparison it was considered to be the average CO_2 emissions of a process in Europe (Table 2.19)

From an analysis of the above comparison (Table 2.20) it can be concluded that the greener method for the synthesis of benzoic hydrazide has a larger Environmental Cost Index value than the conventional method (0.99 vs 0.10). This large difference can be explained due to the greener process requiring 180 times less energy [27].

Having defined a calculation method for both the Economic Cost Index (Equation 2.37 and Figure 2.23) and the Environmental Cost Index (Equation 2.40 and Figure 2.24) the Energy Index can be calculated (Equation 2.43).

Equation 2.43. Energy Index

$$Energy\ Index = \frac{Economic\ Cost\ Index + Environmental\ Cost\ Index}{2}$$

As both the Economic Cost Index and the Environmental Cost Index are normalized between 0 and 1, the average of both is between 0 and 1 as well. Consequently, no further integration needs to be done for the Energy Index.

Continuing with the example of the two synthesis methods of benzoic hydrazide previously presented (Table 2.17 and Table 2.20), the final Energy Index for these two processes can be determined (Table 2.21)

Table 2.21. Energy Index example for the synthesis of benzoic hydrazide

Process	Economic Cost Index (Table 2.17)	Environmental Cost Index (Table 2.20)	Energy Index (Equation 2.43)
Conventional synthesis of benzoic hydrazide [27]	0.10	0.10	0.10
Greener synthesis of benzoic hydrazide [27]	0.99	0.99	0.99

From Table 2.21 it can be observed that the Energy Index for the conventional synthesis of benzoic hydrazide is lower than the Energy Index of the method considered "greener". These results also appear to be extremely expressive, with the Energy Index of the green method being 9.9 times higher than that of the conventional method. This is in accordance with the referenced study on the synthesis of hydrazides, which shows the green method to have 180 to 400 times less energy requirements than the conventional method [27].

Another characteristic from the presented results is that the Economic Cost Index and the Environmental Cost Index have the same value. This is the due to having been assumed that both, the energy price (Table 2.17) and CO_2 emissions (Table 2.20) of the considered process were average, due to lack of data. This caused the Economic Cost (Equation 2.37) and Environmental Cost (Equation 2.40) to vary from the average only in terms of energy requirements of the processes and have the same integration value.

2.2.6. Principle 7

The 7th principle of Green Chemistry states that the raw materials of feedstocks should be renewable when technically and economically practicable [22]. No mathematical formula has been associated to it.

In order to analyse this principle a metric is proposed based on the required mass of each reagent per mass of product and if it is renewable or not through a binary "Renewability factor" (considered to be 1 for renewable materials and 0 for non-renewable materials) (Equation 2.44).

Equation 2.44. Feedstock

$$Feedstock = (\frac{mass\ of\ reagent\ (kg)}{mass\ of\ product\ (kg)} * 100) * Renewability\ factor\ (0\ or\ 1)$$

Using Equation 2.44 returns a value between 0 and $+\infty$. This range of values can generate complications when interpreting or comparing with other data due to not being a double-bounded interval. To solve this, integration between 0 and 1 (as proposed for all principles in the Green Chemistry Grid in section 2.2) can be done. A first attempt at integration was performed by dividing the obtain Feedstock (Equation 2.44) by the number of reagents in the process (Equation 2.45):

Equation 2.45. Integrated Feedstock

$$Integrated\ Feedstock = \frac{\sum Feedstocks}{number\ of\ reagents}$$

Using Equation 2.45, however, does not guarantee an integration between 0 and 1 which is the proposed objective. Instead, it returns a value between 0 (for example, when no renewable feedstocks are used) and $+\infty$ (for example, if a large mass ($\approx \infty$) of a single reagent are required). In order to fulfil that criteria, alterations to the proposed formulae were made.

The proposed alteration is to change the mass of product in Equation 2.44 to the total mass of used reagents (Equation 2.46).

Equation 2.46. First alteration to Feedstock

$$Feedstock = \left(\frac{mass\ of\ reagent\ (kg)}{\sum mass\ of\ reagents\ (kg)}\right) * Renewability\ factor\ (0\ or\ 1)$$

Performing the above alteration, the proposed Feedstock metric (Equation 2.46) now represents the percentage of renewable material feedstocks into the process. This expression however, still has the downside of assessing renewability in a simple fashion using a binary value. This leads to considering all renewable materials as equally good and all non-renewable materials as equally bad, which may not represent the truth, for example, due to different years of reserves (considered, for example, in BASF's Eco-efficiency method to assess a process's greenness [61]).

A solution for this is to change the binary "Renewability factor" into a continuous factor capable of describing the inherent differences between different types of renewable and non-renewable materials (as can be seen in BASF's Eco-efficiency method [61] or the European Commission's Report on Critical Raw Materials and the Circular Economy [40]). This factor will be called the "Sustainability factor" (Equation 2.47).

Equation 2.47. Second alteration to Feedstock

$$Feedstock = \left(\frac{mass\ of\ reagent\ (kg)}{\sum mass\ of\ reagents\ (kg)}\right) * Sustainability\ Factor$$

Determination of the suggested Sustainability Factor can be done by considering the report on critical raw materials published by the European Commission [40] [177] [178]. In this report, materials are assessed for their "Supply Risk", which is calculated based on the material's worldwide consumption and reserves (indicative of "how renewable" it is), and "Economic Importance", which is calculated based on the material's impact on the economy (indicative of the negative impact it would have for the economy if depleted). Afterwards if both the Supply Risk is superior to 1 [40] [177] [178] and the Economic Importance is superior to 2.8 [40] [177] [178] the material is deemed "critical", otherwise it is considered "non-critical".

The objective of the proposed Sustainability Factor is for it to be a continuous factor. As such, the values given to the Supply Risk and Economic Importance on the report on critical raw materials [40] [177] [178] will be considered instead of the final binary conclusion of "critical" or "non-critical".

In order to give the same weight to both the Supply Risk and Economic Importance (as the principle considers both the renewability and the technical and economic practicability) these values will first be normalized as they have different ranges for critical/non-critical in the report [40] [177] [178] (Equation 2.48 and Equation 2.49).

Equation 2.48. Normalized Supply Risk

$$Normalized\ Supply\ Risk = \frac{Supply\ Risk}{Supply\ Risk\ critical\ threshold\ (at\ the\ time\ of\ study, 1.00)}$$

By using Equation 2.48 the Supply Risk is normalized, changing its non-critical range to $[0; 1]$ and critical range to $[1; +\infty]$. At the time of study, however, the Supply Risk was already set for the objective ranges and, as a result, the normalized variable is the same as the original variable. Regardless, Equation 2.48 is proposed as the Supply Risk critical threshold can be subject to change. In order to test the proposed equation, three different materials will be analysed (Table 2.22): Magnesium (a critical raw material [40] [177]), gold (a non-critical raw material [40] [178]) and molybdenum (a non-critical raw material close to the threshold of becoming critical [40] [178]).

Table 2.22. Example of the determination of the Normalized Supply Risk

Material	Supply Risk	Normalized Supply Risk (Equation 2.48)
Magnesium	4.00 [177]	4.00
Gold	0.20 [178]	0.20
Molybdenum	0.90 [178]	0.90

Continuing the same line of thought for the Economic Importance the following equation is proposed (Equation 2.49):

Equation 2.49. Normalized Economic Importance

$$Normalized\ Economic\ Importance = \frac{Economic\ Importance}{Supply\ Risk\ critical\ threshold\ (at\ the\ time\ of\ study, 2.80)}$$

Using Equation 2.49 the Economic Importance, which originally was considered non-critical for values in the $[0.0; 2.8]$ range and critical in the $[2.8; +\infty]$ range becomes normalized. This normalized variable is considered non-critical for values in the $[0; 1]$ range and critical in the $[1; +\infty]$ range. An example of this is represented in Table 2.23 using the same materials:

Table 2.23. Example of the determination of the Normalized Economic Importance

Material	Economic Importance	Normalized Economic Importance (Equation 2.49)
Magnesium	7.10 [177]	2.54
Gold	2.00 [178]	0.71
Molybdenum	5.20 [178]	1.86

After normalized, both the Supply Risk (Equation 2.48) and Economic Importance (Equation 2.49), the Sustainability Factor can be determined. Determination of the Sustainability Factor is proposed to be done as the average of both the Normalized Supply Risk and Normalized Economic Importance in order to give equal importance to both (as the principle does not give explicit priority to one or the other) (Equation 2.50).

Equation 2.50. Sustainability Factor

$$Sustainability\ Factor = \frac{Normalized\ Supply\ Risk + Normalized\ Economic\ Importance}{2}$$

Using the examples of magnesium, gold and molybdenum, which already had the Normalized Supply Risk (Table 2.22) and the Normalized Economic Importance (Table 2.23) calculated, the determination of the Sustainability Factor is represented in Table 2.24:

Table 2.24. Example of the determination of the Sustainability Factor

Material	Normalized Supply Risk (Table 2.22)	Normalized Economic Importance (Table 2.23)	Sustainability Factor (Equation 2.50)
Magnesium	4.00	2.54	3.27
Gold	0.20	0.71	0.46
Molybdenum	0.90	1.86	1.38

From Table 2.24 it can be concluded that differentiation between magnesium (which is critical with high values for both the Supply Risk and Economic Importance), gold (which is non-critical) and molybdenum (which is non-critical but close to the critical threshold) has been achieved. The sustainability factor was, as expected, closest to 0 for gold (0.46) and highest for magnesium (3.27). On the other hand, molybdenum, which is considered by the report on critical raw materials, non-critical [40] [178] had a value above 1.00.

This is due to, in the report, a material being considered critical when both the Supply Risk and Economic Importance are above the threshold. However, in the proposed expression (Equation 2.50) a material reaches a sustainability factor equivalent to being critical when the average of both normalized parameters is above 1. In the case of molybdenum, the Normalized Supply Risk is of 0.9 (very close to the threshold) and the Normalized Economic Importance is of 1.86 (far above the threshold) led to a sustainability factor of 1.38.

As the definition of critical/non-critical isn't being considered for the assessment of this principle due to its binary nature, instead being used quantitative values for "how renewable" (Supply Risk) and "how economically important" (Economic Importance), this error is considered acceptable with. In case of the critical/non-critical definition being necessary, the one presented in the report on critical raw materials [40] [177] [178] will be used (both the Supply Risk and Economic Importance above their respective thresholds), unless noted.

Following the above conclusions, the Sustainability Factor can now be determined for other substances (Table 2.25) in the same way as was done for magnesium, gold and molybdenum.

Table 2.25. Sustainability Factor for raw materials present in the report on critical raw materials [40] [177] [178]. Values for the Economic Importance and Supply Risk are obtained from source [177] if the material is considered critical by the report and source [178] if the material is considered non-critical by the report [40]. In case of substances that appear multiple times, the individual assessment should be used (for example, rhodium appears individually and as part of the Platinum-group metals)

Substance	Economic Importance (EI)	Supply Risk (SR)	Normalized EI (Equation 2.49)	Normalized SR (Equation 2.48)	Sustainability Factor (Equation 2.50)
Aggregates[1]	2.30	0.20	0.82	0.20	0.51
Aluminium	6.50	0.50	2.32	0.50	1.41
Antimony	4.30	4.30	1.54	4.30	2.92
Baryte	2.90	1.60	1.04	1.60	1.32
Bauxite	2.60	2.00	0.93	2.00	1.46
Bentonite	2.10	0.30	0.75	0.30	0.53
Beryllium	3.90	2.40	1.39	2.40	1.90
Bismuth	3.60	3.80	1.29	3.80	2.54
Borates	3.10	3.00	1.11	3.00	2.05
Chromium	6.80	0.90	2.43	0.90	1.66
Cobalt	5.70	1.60	2.04	1.60	1.82
Coking coal	2.30	1.00	0.82	1.00	0.91
Copper	4.70	0.20	1.68	0.20	0.94
Diatomite	3.80	0.30	1.36	0.30	0.83
Feldspar	2.40	0.70	0.86	0.70	0.78
Fluorspar	4.20	1.30	1.50	1.30	1.40
Gallium	3.20	1.40	1.14	1.40	1.27
Germanium	3.50	1.90	1.25	1.90	1.58
Gold	2.00	0.20	0.71	0.20	0.46
Gypsum	2.20	0.50	0.79	0.50	0.64
Hafnium	4.20	1.30	1.50	1.30	1.40
Heavy rare earth elements (HREEs)[2]	3.70	4.80	1.32	4.80	3.06
Helium	2.80	1.60	1.00	1.60	1.30
Indium	3.10	2.40	1.11	2.40	1.75
Iridium	4.30	2.80	1.54	2.80	2.17
Iron ore	6.20	0.80	2.21	0.80	1.51
Kaolin	2.30	0.50	0.82	0.50	0.66
Lead	3.70	0.10	1.32	0.10	0.71
Light rare earth elements (LREEs)[3]	3.60	4.90	1.29	4.90	3.09
Limestone	2.50	0.10	0.89	0.10	0.50
Lithium	2.40	1.00	0.86	1.00	0.93
Magnesite	3.70	0.70	1.32	0.70	1.01
Magnesium	7.10	4.00	2.54	4.00	3.27
Manganese	6.10	0.90	2.18	0.90	1.54
Molybdenum	5.20	0.90	1.86	0.90	1.38

Natural cork	1.50	1.10	0.54	1.10	0.82
Natural graphite	2.90	2.90	1.04	2.90	1.97
Natural rubber	5.40	1.00	1.93	1.00	1.46
Natural teak wood	2.00	0.90	0.71	0.90	0.81
Nickel	4.80	0.30	1.71	0.30	1.01
Niobium	4.80	3.10	1.71	3.10	2.41
Palladium	5.60	1.70	2.00	1.70	1.85
Perlite	2.10	0.40	0.75	0.40	0.58
Phosphate rock and white phosphorus	5.10	1.00	1.82	1.00	1.41
Platinum	4.90	2.20	1.75	2.20	1.98
Platinum-group metals (PGMs)[4]	5.00	2.50	1.79	2.50	2.14
Potash	4.80	0.70	1.71	0.70	1.21
Rhenium	2.00	1.00	0.71	1.00	0.86
Rhodium	6.60	2.50	2.36	2.50	2.43
Ruthenium	3.50	3.40	1.25	3.40	2.33
Sapele wood	1.30	1.40	0.46	1.40	0.93
Scandium	3.70	2.90	1.32	2.90	2.11
Selenium	4.50	0.40	1.61	0.40	1.00
Silica sand	2.60	0.30	0.93	0.30	0.61
Silicon metal	3.80	1.00	1.36	1.00	1.18
Silver	3.80	0.50	1.36	0.50	0.93
Sulphur	4.60	0.60	1.64	0.60	1.12
Talc	3.00	0.40	1.07	0.40	0.74
Tantalum	3.90	1.00	1.39	1.00	1.20
Tellurium	3.40	0.70	1.21	0.70	0.96
Tin	4.40	0.80	1.57	0.80	1.19
Titanium	4.30	0.30	1.54	0.30	0.92
Tungsten	7.30	1.80	2.61	1.80	2.20
Vanadium	3.70	1.60	1.32	1.60	1.46
Zinc	4.50	0.30	1.61	0.30	0.95

[1]crushed stone, gravel, granules, pebbles, sand; [2]dysprosium, erbium, gadolinium, holmium, lutetium, ytterbium, thulium, samarium, terbium, yttrium; [3]cerium, europium, lanthanum, neodymium, praseodymium; [4]platinum, palladium, rhodium, ruthenium, iridium, osmium

Table 2.25 only contains substances assessed on the report on critical raw materials published by the European Commission [40] [177] [178]. Substances that were not assessed on the report are considered to have a Sustainability Factor of 0, as they were not considered to be potentially critical, possibly due to an extremely low Supply Risk or Economic Importance.

Following the determination of the Sustainability Factor the proposed Feedstock metric can now be calculated using Equation 2.51:

Equation 2.51. Feedstock metric

$$Feedstock = \sum \left[\left(\frac{mass\ of\ reagent\ (kg)}{\sum mass\ of\ reagents\ (kg)} \right) * Sustainability\ factor \right]$$

The Feedstock metric calculated using Equation 2.51 returns a value corresponding to the pondered average of the Sustainability Factor of each reagent used in the process. As a result, this value is set on the range of $x = [0; +\infty[$, where 0 is obtained for when only completely "green" reagents are used and higher values as larger amounts of reagents with a high Sustainability Factor are used.

As the proposed objective is to have an output for the metric integrated between 0 and 1, where 0 is the worst-case scenario and 1 is the ideal process, an integration formula needs to be created with the following characteristics:

- A domain equal to the Feedstock value range ($x = [0; +\infty[$);
- Fits the defined integration objectives of:
  - $Feedstock = 0 \rightarrow Integrated\ Feedstock = 1$
  - $Feedstock \approx +\infty \rightarrow Integrated\ Feedstock \approx 0$
- As a lower Feedstock value corresponds to a "greener" process according to the principle, the integration function should be strictly decreasing (Higher values of the Feedstock always have lower integrated values).

Taking these characteristics into consideration, which are similar to the ones desired for the integration of the E-factor in the 1st principle (see section 2.2.1), the exponential distribution's probability density function (Equation 2.52).

Equation 2.52. Exponential distribution's probability density function

$$f(x;\ \beta) = e^{-\frac{x}{\beta}}$$

To use the exponential distribution's probability density function (Equation 2.52) a β parameter needs to be defined. As with the 1st principle, the β parameter was chosen to be defined based on a median value for the integration (Equation 2.53).

Equation 2.53. β determined from a median value

$$\beta = \frac{median}{\ln(2)}$$

The median value for the integration was considered to be the value for the Feedstock metric when all used materials are, on average, on the critical threshold. This means that the sustainability factor for all used reagents is considered to be 1, leading to a Feedstock value of 1 as well. As such the integration profile for the Feedstock metric is built using $f(x;\ \beta) = e^{-\frac{x}{\beta}}$; $\beta = \frac{1}{\ln(2)}$ (Figure 2.25).
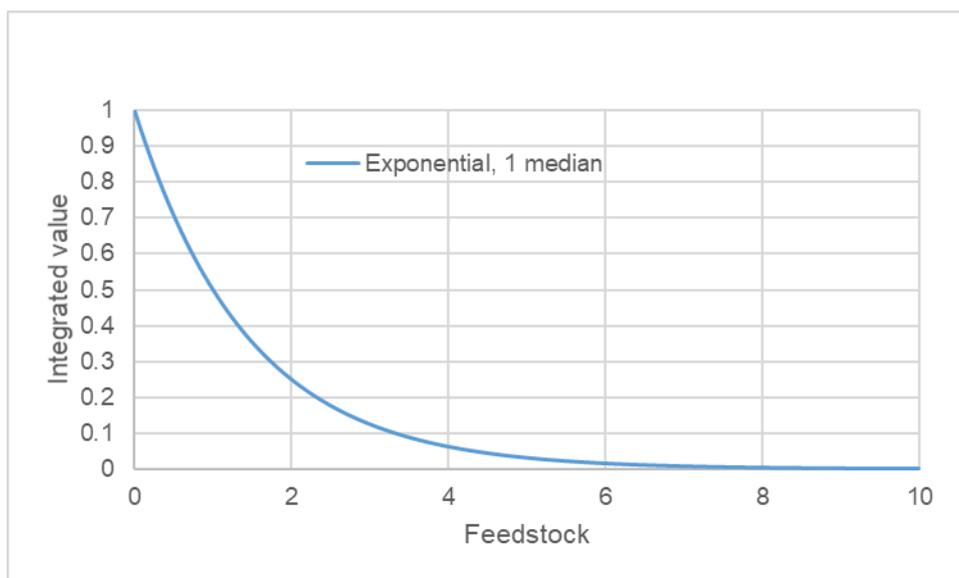
Figure 2.25. Integration profile for feedstocks

In order to analyse the proposed integration (Figure 2.25), three hypothetical processes using only a single reagent are tested: One using only magnesium, one using only gold and one using only molybdenum (Table 2.26).

Table 2.26. Example of Integrated Feedstock calculation for 3 hypothetical single reagent processes

Reagent	Sustainability Factor (Equation 2.50)	Feedstock (Equation 2.51)	Integrated Feedstock (Figure 2.25)
Magnesium	3.27	3.27*	0.10
Gold	0.46	0.46*	0.73
Molybdenum	1.38	1.38*	0.38

*Feedstock is equal to the Sustainability Factor due to the process having only 1 reagent

Analysing Table 2.26 it is possible to see that the Integrated Feedstock has a clear differentiation between the "greenest" hypothetical process in study (gold, with a 0.73 integration) and the less "green" option (magnesium, with a 0.10 integration). This differentiation isn't as noticeable at higher values of Feedstock as can be seen when comparing magnesium (3.27 feedstock with a 0.10 integration) and molybdenum (1.38 feedstock with a 0.38 integration), however, this was to be expected as the chosen function is an exponential. As an example of application to a process with multiple reagents a hypothetical reaction of 0.7 kg of gold reaction with 0.3 kg of magnesium was analysed (Table 2.27):

Table 2.27. Example of Integrated Feedstock calculation for a hypothetical multiple reagent process

Reagent	Mass of reagent / Total mass of reagents (kg/kg)	Sustainability Factor (Equation 2.50)	Feedstock (Equation 2.51)	Integrated Feedstock (Figure 2.25)
Magnesium	0.3	3.27	1.30	0.41
Gold	0.7	0.46		

From Table 2.27 it is possible to conclude that both the proposed metric and its integration are working as desired, with the hypothetical process achieving a Feedstock value of 1.30 and an integration of 0.41. These results are as expected when compared with Table 2.26, as gold has a Feedstock of 0.46 and integration of 0.73 when alone and magnesium a Feedstock of 3.27 and integration of 0.10 and the hypothetical reaction of both in Table 2.27 results in-between.

2.2.7. Principle 8

The 8th principle of Green Chemistry focuses on the avoidance of derivatization steps [22]. No mathematical expression currently exists to quantify this principle. As no mathematical expression exists, in order to quantify this principle for the Green Chemistry grid a metric is proposed based on the mass of derivatives required per kg of product (Equation 2.54)

Equation 2.54. Derivatives metric

$$Derivatives\ metric\ \left(\frac{kg}{kg\ of\ product}\right) = \frac{\sum mass\ of\ derivatives\ (kg)}{mass\ of\ product\ (kg)}$$

Using the above expression (Equation 2.54) the obtained result corresponds to the mass of waste generated from derivatives, similarly to the E-factor (please see section 2.2.1).

The obtained value, however, is set between 0 and $+\infty$, which goes against the proposed objective of having a value between 0 and 1 for each principle in order to facilitate data interpretation and treatment (please see section 2.2). As such, an attempt at the integration of the Derivatives metric was proposed the same way as for the 1st principle (Equation 2.55).

Equation 2.55. Derivatives Integration, first attempt

$$Derivatives\ Integration = \frac{1}{1 + Derivatives\ metric\ \left(\frac{kg}{kg\ of\ product}\right)}$$

This function (Equation 2.55) is set in the desired range of values (between 0 and 1, with 0 being the worst case and 1 the best case). However, the required Derivatives metric to reach lower integration values is high, for example, to have an integrated value of 0.05 the Derivatives metric needs to be 19 kg /kg of product (meaning 19 kg of derivatives are used for 1 kg of product). In order to change this another integration method with the following characteristics herein is proposed:

- A domain equal to the Derivatives metric domain ($x = [0; +\infty[$);
- Easy to adapt to different values;
- Fits the defined integration objectives of:
  - $Derivatives\ metric\ = 0 \rightarrow Derivatives\ Integration\ = 1$
  - $Derivatives\ metric\ \approx +\infty \rightarrow Derivatives\ Integration \approx 0$
- As a lower Derivatives metric correspond to a "greener" process according to the principle, the integration function should be strictly decreasing (Higher values of the Derivatives metric always have lower integrated values).

With these characteristics in mind the proposed method to integrate the Derivatives metric is to use the exponential distribution's probability density function (Equation 2.56), as was similarly done for the 1st principle (please see section 2.2.1).

Equation 2.56. Exponential distribution's probability density function

$$f(x; \beta) = e^{-\frac{x}{\beta}}$$

To use this equation the β parameter needs to be defined. As this parameter has a direct effect on both the integration function's profile (see section 2.2.1) and median (Equation 2.57), it will be chosen considering a median value of 1 (meaning a 0.5 integration occurs when the required mass of derivatives is the same as the generated product)

Equation 2.57. Relation between β and median

$$\beta = \frac{median}{\ln(2)}$$

Applying Equation 2.7 and the above consideration, $\beta = \frac{1}{\ln(2)}$. Having determined β, the profile for the integration using the exponential distribution's probability density function (Equation 2.56) can be built as $f(x; \beta) = e^{-\frac{x}{\beta}}; \beta = \frac{1}{\ln(2)}$. In order to determine what approach to use (Equation 2.55 or Equation 2.56), both profiles are now compared (Figure 2.26).
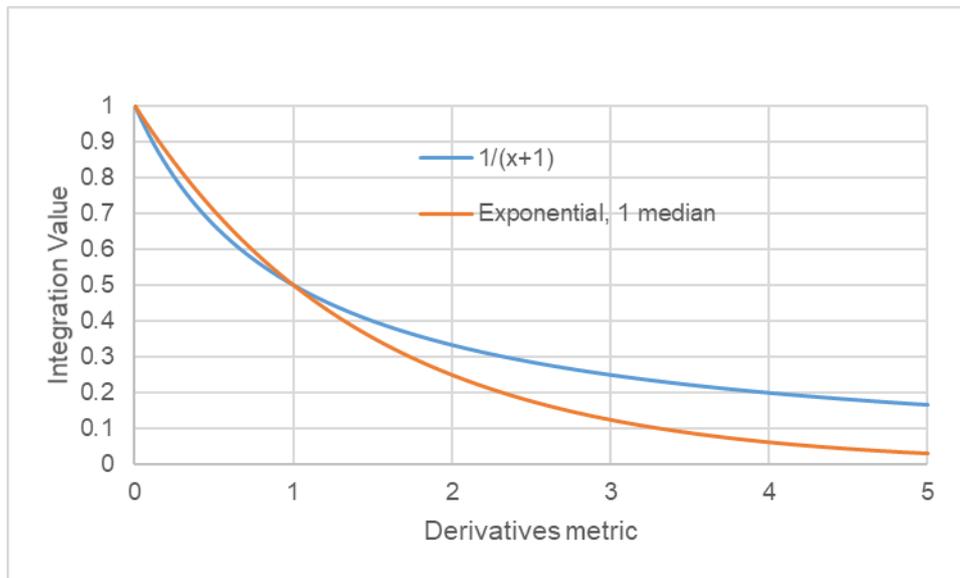
Figure 2.26. Integration profile for derivatives, both proposed methods presented for comparison

From Figure 2.26 it can be observed that for lower values integration using Equation 2.55 or Equation 2.56 the profiles are very similar. On the other hand, for an integration of values above a derivatives metric of 1, the difference between both methods becomes noticeable with the exponential approach (Equation 2.56), faster reaching lower values for the integration.

For example, an integration of 0.2 is reached at a Derivatives metric of 2.32 using Equation 2.56 while it is reached at 4 using Equation 2.55. Based on these differences, the chosen approach for the integration is the one which uses Equation 2.56 as it allows for a larger range of integration values to be reached quicker. With these considerations, the integration profile for the Derivatives metric can be built (Figure 2.27).
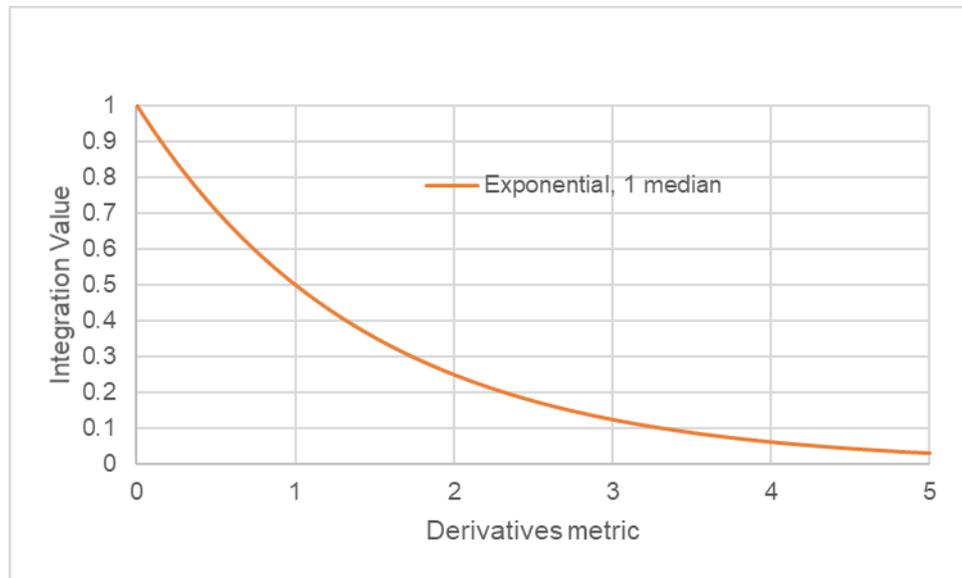
Figure 2.27. Integration profile for the Derivatives metric

From Figure 2.27 the integration of the Derivatives into a value between 0 and 1 appears to be working as intended. In order to test the application of the proposed formula for the Derivatives (Equation 2.54) and the integration (Figure 2.27), three hypothetical processes are tested in Table 2.28:

- One where 0.3 kg of derivatives are used to produce 1 kg of product;

- One where 0.7 kg of derivatives are used to produce 1 kg of product;
- One where 1.5 kg of derivatives are used to produce 1 kg of product

Table 2.28. Example of derivatives integration for the three hypothetical processes described above

Mass of derivatives (kg)	Mass of product (kg)	Derivatives metric (kg/kg)	Derivatives integration
0.30	1.00	0.30	0.81
0.70	1.00	0.70	0.62
1.50	1.00	1.50	0.35

As it can be seen from Table 2.28, the integration function is working as expected with higher differentiation at lower values of the Derivatives metric. Using the above example, the "greenest" process according to this principle would be the one where 0.3 kg of derivatives are used, with a 0.81 integration. On the other hand, and the "least green" process would be the one where 1.5 kg of derivatives are used with a 0.35 integration.

2.2.8. Principle 9

This principle states that catalytic reagents (as selective as possible) are superior to stoichiometric ones [22]. However no mathematical expression currently exists to assess it. In order to analyse this principle in the Green Chemistry grid, the proposed metric was considered to depend on the usage of a catalyst and the yield from the chemical process (Equation 2.58).

Equation 2.58. Catalyst Metric, catalyst usage is a binary factor considered 1 if a catalyst is used and 0 if a catalyst is not used

$$Catalyst\ Metric = Catalyst\ Usage\ (0\ or\ 1) * Reaction\ Yield\ (\%)$$

The output of the above equation (Equation 2.58), due to using the reaction Yield for calculations, is set between 0 and 1 contemplates four possible scenarios (Table 2.29):

Table 2.29. Catalyst Metric calculation possible scenarios

Catalyst Usage	Yield (%)	Catalyst Metric
1	≠ 100	Yield
1	100	Yield
0	≠ 100	0
0	100	1*

*Although Equation 2.58 returns a value of 0, the catalyst metric is considered to be 1 as the yield can't be further improved from using a catalyst

Below, the scenarios represented in Table 2.29 are explained

- A catalyst is used (catalyst usage is 1) and the yield is different from 100%. In this case, the output corresponds to the Yield.

- A catalyst is used (catalyst usage is 1) and the yield is 100%. In this case the output is the yield (In this scenario, 1).

- A catalyst isn't used (catalyst usage is 0) and the yield isn't 100%. In this case the output is 0.

- A catalyst isn't used (catalyst usage is 0) and the yield is 100%. In this case, according to Equation 2.58, the output is 0. However, as this scenario corresponds to a case where the yield is already 100% and, as a result, no further optimization in this front could be done through the use of catalysts, the output is automatically considered to be 1 (the highest value Equation 2.58 can have).

The principle also states that the selectivity of the used catalysts is important, however, selectivity isn't completely intrinsic to the catalyst / reaction and can be highly dependent on the operating conditions [179] (for example, temperature and concentration). Additionally, the selectivity of the catalyst has an influence on the reaction yield, as less selective catalysts will have lower yields. As a result, after investigating this issue, it was decided to leave that factor out of the proposed expression (Equation 2.58).

With the previous considerations in mind, the proposed Catalyst metric has a range of values from 0 to 1, where 1 corresponds to the best scenarios (100% reaction yield) and 0 the worst scenario (no catalyst is used, and yield can still be improved or an inadequate catalyst is used and the reaction yield is 0%). This means that no further alterations to the catalyst metric are required (Equation 2.59) to obtain an integrated value in order to facilitate data treatment and interpretation.

Equation 2.59. Integrated Catalyst Metric

$$Integrated\ Catalyst\ Metric = Catalyst\ Metric$$

By considering Equation 2.59, the integration profile for this principle ends up being the same as the proposed metric's profile (Equation 2.58). The proposed metric's profile is, in turn, linear between 0 and 1 when a catalyst is used; automatically 0 when a catalyst isn't used, and the yield isn't 100%; and 1 when a catalyst isn't used but the yield can't be further improved (already at 100%) (Table 2.29).

2.2.9. Principle 10

The 10th principle of Green Chemistry is about reducing the degradation time of the products at the end of their function [22], and no mathematical formula is associated to it. In order to assess this principle for the Green Chemistry grid, the half-life of the products was considered to be the key factor. The half-life of a substance is the amount of time required for, on average, the mass of that substance to reduce to half its value. A first approach for the proposed metric was the creation of a table considering the half-life of a substance, % of degradation collected by complementary biodegradability tests and its degradation level. Afterwards, a value between 0 and 1, designated by half-life index, was given according to those factors as shown in Table 2.30.

Table 2.30. Half-life Index table

Half-life (days)	Complementary test (% of degradation)	Degradation level	Half-life Index
5	-	High degradability	1
10	-	Medium degradability	0.98
30	≥70%	Low degradability	0.92
100	≥20% and <70%	Residual degradability	0.8
10000	<20%	Non-degradable	0

However, the above table, does not allow a continuous range of values, with substances in the same range of values having the same Half-life Index. For example, using two hypothetical substances A and B:

- Substance A has a Half-life of 2 days. Using Table 2.30 it is given a Half-life Index of 1.
- Substance B has a Half-life of 4 days. Using Table 2.30 it is given a Half-life Index of 1.

Considering the presented example, substance A is, according to the principle, "greener" than substance B as it has a lower Half-life and, as a result, a lower degradation time.

In order to allow for a continuous value for the Half-life Index, it is proposed to be calculated through a continuous function. Furthermore, as the threshold for the half-life of a substance to be considered degradable is, according to the EPA [180] and the REACH regulation for marine water [181], 60 days, the chosen function should be limited to that interval. To summarize, the desired function is proposed to have the following characteristics:

- A domain in the range of $[0,60]$ days. This range of values is desired as it corresponds to the range at which a substance is considered degradable according to the EPA [180] and the REACH regulation for marine water [181].
- Resemblance or relation to an exponential function, as the decay profile of a substance tends to follow an exponential profile (Equation 2.60) [157].

Equation 2.60. Example of an exponential function, more specifically the Exponential Distribution's probability density function used for the 1st principle (please see section YY)

$$f(x;\ \beta) = e^{-\frac{x}{\beta}}$$

- As a lower half-life corresponds to a "greener" substance, according to the principle, the chosen function should be strictly decreasing.
- In order to have no further need to integrate the obtained value between 0 and 1, where 1 is the best-case scenario and 0 the worst (as was proposed in section 2.2); it should preferably fit that criteria.

Considering the previous requirements, the chosen function is, similarly to the 2nd principle's integration function, a regularized incomplete beta function (see section 2.2.2). In this case, unlike the 2nd principle, lower values are considered "greener" and, as a result, the proposed function for the Half-life Index is obtained by subtracting the regularized incomplete beta function to 1 (Equation 2.61).

Equation 2.61. Half-life Index expression

$$Half\ life\ Index = 1 - I(x;\ \alpha, \beta)$$

In the above equation (Equation 2.61), *x* needs to be a value between 0 and 1. As the half-life of a biodegradable substance is considered to be set between 0 and 60 according to the EPA [180] and REACH regulations for marine water [181] (with values above being considered non-biodegradable and, as such, being given a Half-life Index of 0), it first needs to be normalized using Equation 2.62, where y is the half-life of the substance in days.

Equation 2.62. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Lastly, to use Equation 2.61 the α and β form parameters need to be determined. In order to have the desired exponential profile, the α parameter is considered to be 1. Moreover, the median value of the function (corresponding to a 0.5 integration on a scale from 0 to 1) is considered to be 15 days, as this value represents the maximum half-life for a substance to be considered readily biodegradable, according to the European Centre for Ecotoxicology and Toxicology of Chemicals [182].

In order to determine the β parameter the approximate relation between it, the function bounds, the median value of the integration function (value at which the function has a 0.5 integration) and the α parameter can be considered (Equation 2.63):

Equation 2.63. Determination of β parameter from bounds, median and α parameter

$$\beta \cong \frac{1}{3} + \frac{(upper\ bound - median) * (\alpha - \frac{1}{3})}{(median - lower\ bound)}$$

As a result of applying the above approximation (Equation 2.21), β was determined as 2.33. As Equation 2.63 corresponds to an approximation, an error analysis (Table 2.31) was conducted for the objective of a 0.5 Half-life Index value for the considered median and 1 and 0 for the lower and upper bounds, respectively.

Table 2.31. Error analysis carried out via Microsoft Office Excel for the beta function with the β parameter calculated through Equation 2.21

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	1.00	1.00	0.00	0.00	0.00
Median	0.50	0.51	0.01	2.17	2.17
Maximum	0.00	0.00	0.00	0.00	0.00

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Half-life of 0 days, the median corresponds to a Half-life of 15 days and the maximum corresponds to a Half-life of 60 days.

As can be seen in Table 2.31, the obtained error for the median in the approximation was of 2.17% with the bounds having an error of 0.00%.

In order to further reduce the obtained error of the approximation another attempt was made estimating the β parameter. This attempt was conducted through MATLAB's genetic algorithm with the objective of minimizing the error for the median (Figure 2.28).

```
                                  Best           Mean        Stall
Generation      Func-count        f(x)           f(x)        Generations
    61            18600         2.96e-11       5.919e-10       36
    62            18900         2.96e-11       4.777e-10       37
    63            19200         2.96e-11       4.128e-10       38
    64            19500         2.96e-11       4.285e-10       39
    65            19800         2.96e-11       4.987e-10       40
    66            20100         2.96e-11       4.661e-10       41
    67            20400         2.96e-11        4.98e-10       42
    68            20700         2.96e-11       5.207e-10       43
    69            21000         2.96e-11       5.081e-10       44
    70            21300         2.96e-11       6.155e-10       45
    71            21600         2.96e-11       6.055e-10       46
    72            21900         2.96e-11       5.472e-10       47
    73            22200         2.96e-11       5.395e-10       48
    74            22500         2.96e-11       5.278e-10       49
    75            22800         2.96e-11       5.153e-10       50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

Beta parameter estimation = 2.41
```

Figure 2.28. MATLAB's optimization results for the estimation of the beta parameter

As can be seen from Figure 2.28, the MATLAB optimization returned a value for β of 2.41. In order to determine which value for the β parameter is used, an error analysis for this method was conducted (Table 2.32).

Table 2.32. Error analysis for the beta function with the β parameter calculated through MATLAB

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	1.0000	1.0000	0.0000	0.0000	0.0000
Median	0.5000	0.4999*	0.0000	0.0167	0.0167
Maximum	0.0000	0.0000	0.0000	0.0000	0.0000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Half-life of 0 days, the median corresponds to a Half-life of 15 days and the maximum corresponds to a Half-life of 60 days.

For the MATLAB optimization the absolute percentage error was of 0.0000% for the bounds (the same value as the approximation using Equation 2.63) and 0.0167% for the median value, which is considerably lower than the obtained error value of 2.1700% when calculating β using Equation 2.63.

As a result, the chosen value for the β parameter is of 2.41 (the value obtained through the MATLAB optimization).

Having considered a value for both α (=1) and β (=2.41), the Half-life Index's profile can be built (Figure 2.29).
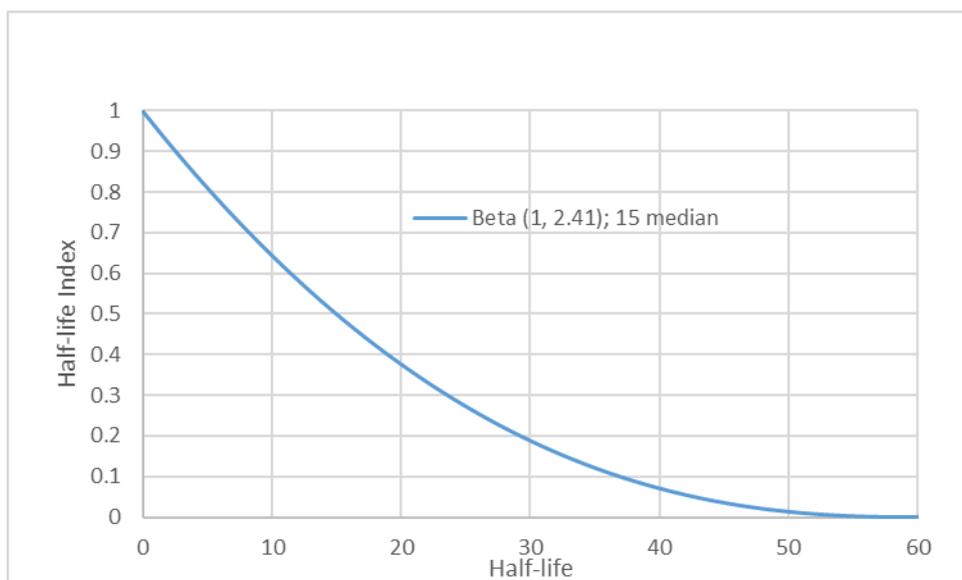
Figure 2.29. Half-life Index function profile

As can be seen from the above figure (Figure 2.29), the proposed function (Equation 2.61) appears to fit all the desired criteria as it is double bounded between 0 and 60 with a Half-life Index of 1 and 0, respectively (meaning no further integration is required, as proposed in section 2.2), and an approximately exponential profile form. In order to determine if the proposed method is usable, examples for three substances were investigated (Table 2.33):

Table 2.33. Half-life Index calculation for phenol, naphthalene and plastic wastes

Product	Half-life (days)	Normalized half-life (Equation 2.12)	Half-life Index (Equation 2.32)
Phenol	2.00 [182]	0.00(3)	0.92
Naphthalene	11.40 [182]	0.19	0.60
Polyethylene	50 years [183]	More than 1	0.00*

*As the half-life of polyethylene is over the predicted range for biodegradable substances, the half-life Index is considered to be 0 (worst case scenario)

From Table 2.33 it is possible to see that the proposed Half-life Index is working as intended with the value for the Half-life Index of phenol (the "greenest" option according to this principle) being higher than the other options. In the case of polyethylene, the half-life is 50 years [183] which means that it is outside the range of substances considered biodegradable and, as such, is considered to have an automatic Half-life Index of 0.

2.2.10.   Principle 12

The 12th principle states that substances and their form should be chosen to minimize the potential of accidents, including releases, explosions and fires [22] and there is no mathematical formula associated to it. In order to assess this principle for the Green Chemistry grid, a metric is proposed based on the three hazard examples given on the principle: The risk of releases, the risk of explosions and the risk of fires (Equation 2.64).

Equation 2.64. Accident Prevention metric

$$Accident\ Prevention = Evaporation\ Risk + Fire\ Risk + Explosion\ Risk$$

The proposed parameters (Evaporation Risk, Fire Risk and Explosion Risk) are considered to be binary with the following rules:

- If the working temperature is higher than the melting point, the Evaporation Risk is considered to be 1, otherwise it is considered to be 0;
- If the working temperature is higher than the flash point, the Fire Risk is considered to be 1, otherwise it is considered to be 0;
- The Explosion Risk is considered to be dependent on 3 factors deemed necessary by firemen for an explosion to occur:
  - The Ignition Source, which is considered to be 1 if the working temperature is higher than the ignition temperature, otherwise it is considered to be 0;
  - The Oxygen Content, which is considered to be 1 if the oxygen concentration is higher than 12%, otherwise it is considered to be 0;
  - The Combustible Concentration, which is considered to be 1 if the maximum vapour concentration is higher than the lower explosion limit).
  - If the three factors above (Ignition Source, Oxygen Content and Combustible Concentration) are 1, then the Explosion Risk is considered to be 1 as well, otherwise if even one of the factors is 0 then the Explosion Risk is 0.

With the Accident Prevention metric defined by the above rules for each individual substance, it needs to be defined for the process in the whole. In order to do this, the average of the Accident Prevention values for all substances is considered (Equation 2.65):

Equation 2.65. Accident Prevention Index

$$Accident\ Prevention\ Index = \frac{\sum Accident\ Prevention\ of\ each\ substance}{number\ of\ substances}$$

The proposed method using Equation 2.64 and Equation 2.65 considers the risk of each individual substances, however, it fails to consider the possible interactions between substances. An example of this shortcoming is demonstrated considering a hypothetical process where substances A, B and C are used at the same time (Table 2.34):

Table 2.34. Characteristics of substances A, B and C in a hypothetical process

Substance	Ignition Source	Oxygen Content	Combustible Concentration	Explosion Risk	Evaporation Risk	Fire Risk
A	1	0	0	0	0	0
B	0	1	0	0	0	0
C	0	0	1	0	0	0

Considering the above substances (Table 2.34) it can be seen that for all of them the Explosion Risk, Evaporation Risk and Fire Risk are 0 and, as a result, using Equation 2.64 the Accident Prevention metric is 0 for each substance and using Equation 2.65 the Accident Prevention Index for the process is 0 as well. However, when it is considered that all of them are in contact with each other, the following analysis can be done according to Table 2.35:

Table 2.35. Analysis of the hypothetical process P

Process	Ignition Source	Oxygen Content	Combustible Concentration	Explosion Risk	Evaporation Risk	Fire Risk
P*	1 (Due to substance A)	1 (Due to substance B)	1 (Due to substance C)	1	0	0

*Process P is a hypothetical reaction between substances A, B and C from Table 2.34

From Table 2.35 it can be seen that although each individual substance in Table 2.34 presents no risks, when all of them are together there is an Explosion Risk and, as a result, when applying Equation 2.64 to the process the Accident Prevention metric has a value of 1. This result demonstrates that a simple analysis of each individual substance is not enough. As such, an alteration to Equation 2.65 in order to consider the possible interactions in the process is proposed:

Equation 2.66. Accident Prevention Index considering possible interactions between substances

$$Accident\ Prevention\ Index \\ = \frac{\sum Accident\ Prevention\ of\ each\ substance}{number\ of\ substances} \\ + Accident\ Prevention\ Index\ of\ the\ process$$

The result of the above equation (Equation 2.66) can be seen to vary between 0 (the best-case scenario, when none of the assessed hazards are considered to exist) and 6 (the worst-case scenario, when all hazards being assessed are considered to exist). As a result, integration of this range into a scale from 0 to 1, where 0 is the worst case and 1 is the best case can be useful for further treatment of the data for the Green Chemistry grid (as was proposed in section 2.2). To do this, a first attempt was made at the integration using Equation 2.67:

Equation 2.67. Accident Prevention Integration, first attempt

$$Integrated\ Accident\ Prevention = \frac{1}{1 + \dfrac{\sum Accident\ Prevention\ of\ each\ substance}{number\ of\ substances}}$$

The approach proposed in Equation 2.67, however, was made considering Equation 2.65 and Equation 2.64. Due to the alteration proposed in Equation 2.66 another method for the integration of the Accident Prevention Index is desired with the following characteristics:

- A domain in the range of the Accident Prevention Index ($[0,6]$).
- As a lower Accident Prevention Index corresponds to a "greener" process, the chosen function should be strictly decreasing

Considering the above factors, the chosen integration method was through the regularized incomplete beta function due to it being a double-bounded function with a large degree of adaptability. In order to be strictly decreasing the same approach that was used for principle 10 was used here (please see section 2.2.9) (Equation 2.68).

Equation 2.68. Integrated Accident Prevention

$$Integrated\ Accident\ Prevention = 1 - I(x;\ \alpha, \beta)$$

For the above equation (Equation 2.68), x needs to be a value between 0 and 1. Normalization of the Accident Prevention Index can be done using Equation 2.69, where y is the Accident Prevention Index:

Equation 2.69. Normalization of a double-bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Lastly, the α and β form parameters needs to be determined. Considering a mirrored treatment above and below the median value the α parameter should be the same as the β parameter. In order to have an approximately linear variation between the Accident Prevention Index values of 2 (obtained, for example, if all substances have the same single risk) and 4 (obtained, for example, if all substances have two of the same risks), the α and β parameters were considered to be 3.

With the previous considerations, the integration profile for the Accident Prevention Index can be built according to Figure 2.30:
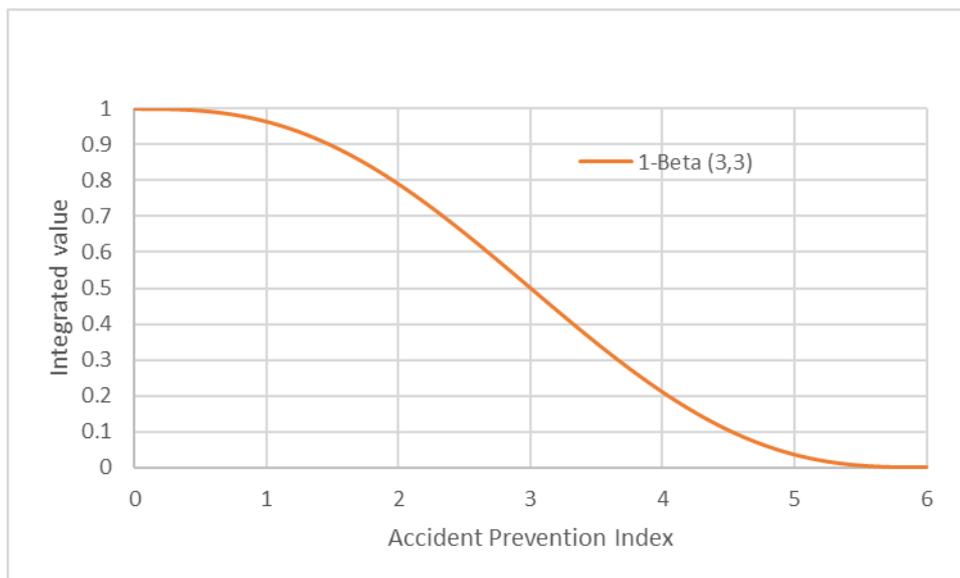
Figure 2.30. Integration profile of the Accident Prevention Index

As can be seen from Figure 2.30, the integration is, as intended, approximately linear in the middle range of values (between an Accident Prevention Index of 2 and 4) with approximately exponential profiles near the extremes (between 0 and 2 and between 4 and 6). The median value of the integration can also be seen to be 3. This value is considered acceptable for the 0.5 integration as it corresponds to a situation where the average Accident Prevention of the substances is 1 (which means, on average, every substance has a single risk) and the Accident Prevention of the process is 2 (which means two different risks are present in the process).

Using the example from Table 2.34 and Table 2.35 for the hypothetical reaction (P) with the altered Accident Prevention Index (Equation 2.66) and the integration profile from Figure 2.30, the results are as follows (Table 2.36):

Table 2.36. Accident Prevention of substances A, B and C in a hypothetical process

Substance	Explosion Risk (Table 2.34)	Evaporation Risk (Table 2.34)	Fire Risk (Table 2.34)	Accident Prevention (Equation 2.64)
A	0	0	0	0
B	0	0	0	0
C	0	0	0	0

From Table 2.36 it can be observed that the Accident Prevention of each of the considered substances is 0. As such, in Equation 2.66, the parcel associated to individual substances has a value of 0. Continuing the analysis for the process in general (Table 2.37):

Table 2.37. Accident Prevention of the hypothetical process P

Process	Explosion Risk (Table 2.35)	Evaporation Risk (Table 2.35)	Fire Risk (Table 2.35)	Accident Prevention (Equation 2.64)
P*	1	0	0	1

*Process P is a hypothetical reaction between substances A, B and C from Table 2.36

From Table 2.37 the Accident Prevention of the hypothetical process P can be seen to be 1. As a result, the parcel associated to the process interactions of the Accident Prevention Index (Equation 2.66) is 1 as well.

Having conducted the analysis of the Accident Prevention (Equation 2.64) of each individual substance, the Accident Prevention Index (Equation 2.66) can be calculated. The obtained value for it in the presented example is of 1.

Lastly, the integrated value for the Green Chemistry grid can be obtained through Figure 2.30. In the given example the obtained integrated value is of 0.96, which allows to be concluded that this hypothetical process is, according to this principle, "green".

2.2.11.   Principle 13

For the Green Chemistry Grid, a 13th principle was proposed, Carbon Efficiency. This principle is stated as "Carbon chemistry is related to some of more hazardous chemical substances in the environment. To that matter, it is important to understand how much of total carbon is incorporated in the desired product". This proposed principle has the Carbon Efficiency metric associated to it (Equation 2.70).

Equation 2.70. Carbon Efficiency [125]

$$Carbon\ Efficiency\ (\%) = \frac{Amount\ of\ carbon\ in\ the\ product\ (mol)}{Amount\ of\ carbon\ in\ the\ reagents\ (mol)} * 100$$

The Carbon Efficiency (Equation 2.70) varies between 0% and 100%. As such, integration to an index between 0 and 1 for the Green Chemistry grid (as was proposed in section 2.2 in order to facilitate interpretation of each principle and comparison between them) can be done linearly (Equation 2.71).

Equation 2.71. Linear integration of the Carbon Efficiency

$$\text{Integrated Carbon Efficiency } = \text{ Carbon Efficiency}$$

As with the 2nd principle (please see section 2.2.2), a linear integration can be considered a disadvantage due to a change from 1% to 2% having the same impact as a change from 49% to 50% or 99% to 100%.

Herein, the proposed solution is the usage of a function with the following characteristics:

- Must represent a double-bounded interval;
- Strictly increasing since, according to the principle, higher values of the Carbon Efficiency are better;
- Adaptable to different medians of the Carbon Efficiency with a large variation near the considered Carbon Efficiency's median value.

Considering the above characteristics, two very similar functions fit the criteria: (i) the regularized incomplete beta function and (ii)Kumaraswamy distribution's cumulative distribution function.

As was performed for the 2nd principle (section 2.2.2), in order to decide which one to use, an integration profile will be built for both functions by taking into account the average carbon efficiency in different types of chemical processes (Table 2.38).

Table 2.38. Average Carbon Efficiency [125]

Chemistry type (1)	Carbon Efficiency (%)	Chemistry type (2)	Carbon Efficiency (%)
Acid salt	83	Epoxidation	74
Base salt	89	Borohydride	70
Hydrogenation	74	Iodination	96
Sulfonation	85	Cyclisation	70
Decarboxylation	74	Amination	71
Esterification	68	Lithal	76
Knoevenagel	75	Base hydrolysis	77
Cyanation	83	C-Acylation	60
Bromination	87	Acid hydrolysis	76
N-Acylation	67	Chlorination	83
S-Alkylation	78	Elimination	58
C-Alkylation	68	Grignard	55
N-Alkylation	76	Resolution	32
O-Arylation	69	N-Dealkylation	43

Using the data from Table 2.38, the minimum value was determined to be 32%, the lower quartile was determined to be 68%, the median was determined to be 74% and the higher quartile was determined to be 79.25%. Afterwards, the bounds for the functions were considered to be the minimum value (32%) and 100% (the objective of the principle is to maximize carbon efficiency).

With these considerations in mind, the profile for the integration using the regularized incomplete beta function (Equation 2.72) can be built.

Equation 2.72. Regularized incomplete beta function, B (x, α, β) is the beta function calculated for the value of x with parameters α and β

$$I(x, \alpha, \beta) = \frac{B(x, \alpha, \beta)}{B(1, \alpha, \beta)}$$

In order to use the above equation (Equation 2.72) the Carbon Efficiency first needs to be normalized to a value range between 0 and 1. Therefore, Equation 2.73 can be used where y is the Carbon Efficiency, the lower bound is considered to be 32% (Table 2.38) and the upper bound is considered to be 100%.

Equation 2.73. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Having a method to normalize the Carbon Efficiency (Equation 2.73), the α and β parameters must be determined. This can be performed through a genetic algorithm approach in MATLAB by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 68.00%), the median (set as a 0.50 integration for 74.00%) and the upper quartile (set as a 0.75 integration for 79.25%). The results of the optimization were as follows (Figure 2.31):

```
                              Best          Mean       Stall
Generation      Func-count     f(x)          f(x)    Generations
   211            63600      5.348e-05     5.348e-05      34
   212            63900      5.348e-05     5.348e-05      35
   213            64200      5.348e-05     5.348e-05      36
   214            64500      5.348e-05     5.348e-05      37
   215            64800      5.348e-05     5.348e-05      38
   216            65100      5.348e-05     5.348e-05      39
   217            65400      5.348e-05     5.348e-05      40
   218            65700      5.348e-05     5.348e-05      41
   219            66000      5.348e-05     5.348e-05      42
   220            66300      5.348e-05     5.348e-05      43
   221            66600      5.348e-05     5.348e-05      44
   222            66900      5.348e-05     5.348e-05      45
   223            67200      5.348e-05     5.348e-05      46
   224            67500      5.348e-05     5.348e-05      47
   225            67800      5.348e-05     5.348e-05      48
   226            68100      5.348e-05     5.348e-05      49
   227            68400      5.348e-05     5.348e-05      50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

Alfa parameter estimation = 9.77
Beta parameter estimation = 6.23
```

Figure 2.31. Genetic algorithm results for the regularized incomplete beta function optimization from MATLAB

As can be seen from Figure 2.31, the optimization of the regularized incomplete beta function obtained results for $\alpha=9.77$ and $\beta=6.23$ with the minimized total square error of approximately $5.348 * 10^{-5}$. Having carried out the optimization, the error analysis is conducted (Table 2.39).

Table 2.39. Error analysis for the regularized incomplete beta function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.000	0.000	0.000	0.000	0.000
Q1	0.250	0.247	0.003	-1.381	1.381
Median	0.500	0.507	0.007	1.395	1.395
Q3	0.750	0.746	0.004	-0.479	0.479
Maximum	1.000	1.000	0.000	0.000	0.000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Carbon Efficiency of 32%, the lower quartile (Q1) corresponds to a Carbon Efficiency of 68%, the median corresponds to a Carbon Efficiency of 74%, the upper quartile (Q3) corresponds to a Carbon Efficiency of 79.25% and the maximum corresponds to a Carbon Efficiency of 100%

From the error analysis of the integration using the regularized incomplete beta function (Table 2.39) it is possible to see that the highest absolute percentage error (1.395%) corresponds to the median value, closely followed by the lower quartile's error (1.381%). Comparatively the error for the higher quartile isn't as relevant (0.479%) while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value.

With an integration profile for the Carbon Efficiency built using the regularized incomplete beta function the same reasoning is applied to Kumaraswamy distribution's cumulative distribution function (Equation 2.74).

Equation 2.74. Kumaraswamy distribution's cumulative distribution function

$$F(x; \alpha, \beta) = 1 - (1 - x^\alpha)^\beta$$

As with the regularized incomplete beta function, the Carbon Efficiency first needs to be normalized by using Equation 2.73 with the lower bound being considered 32% and the upper bound being considered 100%. Afterwards the α and β are determined through a genetic algorithm using MATLAB. The optimization was carried out by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 32.00%), the median (set as a 0.50 integration for 74.00%) and the upper quartile (set as a 0.75 integration for 79.25%). The results of the optimization were as follows (Figure 2.32):

```
                                   Best          Mean        Stall
Generation        Func-count       f(x)          f(x)      Generations
   271              81600        7.963e-08     8.065e-08       40
   272              81900        7.963e-08     8.057e-08       41
   273              82200        7.963e-08     8.064e-08       42
   274              82500        7.963e-08     8.053e-08       43
   275              82800        7.963e-08     8.064e-08       44
   276              83100        7.963e-08     8.058e-08       45
   277              83400        7.963e-08     8.045e-08       46
   278              83700        7.963e-08     8.056e-08       47
   279              84000        7.963e-08     8.058e-08       48
   280              84300        7.963e-08     8.052e-08       49
   281              84600        7.963e-08     8.051e-08       50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 5.57
 Beta parameter estimation = 9.87
```

Figure 2.32. Genetic algorithm optimization results for Kumaraswamy distribution's cumulative distribution function from MATLAB

Figure 2.32 shows the obtained results for the optimization of Kumaraswamy distribution's cumulative distribution function via MATLAB. The optimized parameters are $\alpha = 5.57$ and $\beta = 9.87$, with the minimized square error being approximately $7.963 * 10^{-8}$. With the form parameters determined, the error analysis can be conducted for the integration (Table 2.40):

Table 2.40. Error analysis for the Kumaraswamy distribution's cumulative distribution function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.000	0.000	0.000	0.000	0.000
Q1	0.250	0.251	0.001	0.276	0.276
Median	0.500	0.502	0.002	0.414	0.414
Q3	0.750	0.751	0.001	0.082	0.082
Maximum	1.000	1.000	0.000	0.000	0.000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Carbon Efficiency of 32%, the lower quartile (Q1) corresponds to a Carbon Efficiency of 68%, the median corresponds to a Carbon Efficiency of 74%, the upper quartile (Q3) corresponds to Carbon Efficiency of 79.25% and the maximum corresponds to a Carbon Efficiency of 100%

From the error analysis of the integration using Kumaraswamy distribution's cumulative distribution function (Table 2.40), it is possible to realize that the highest absolute percentage error (0.414%) corresponds to the median value, followed by the lower quartile's error (0.276%). Comparatively, the error for the higher quartile isn't as relevant (0.082%) while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value.

Having carried out both error analyses, the profiles were built in order to have a graphic comparison (Figure 2.33):
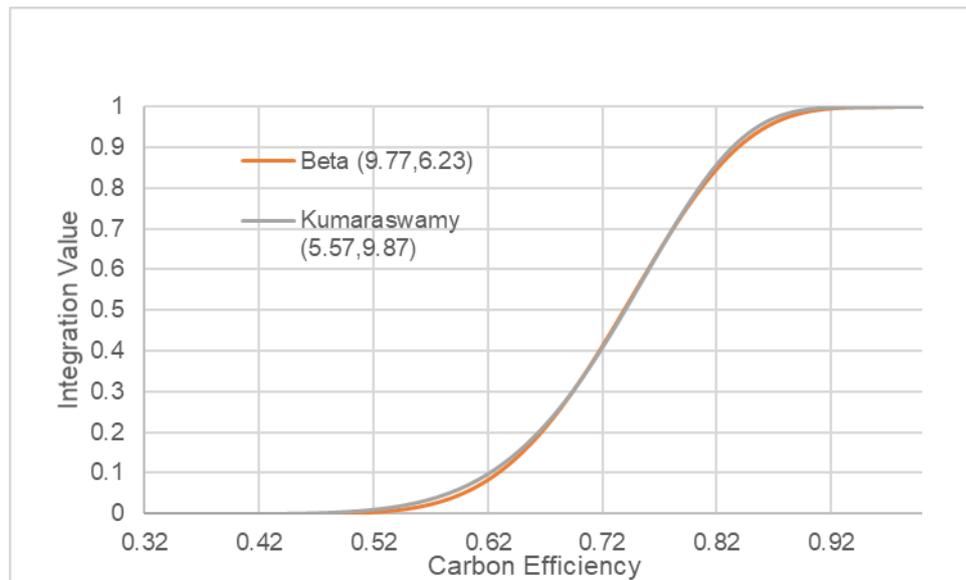
Figure 2.33. Carbon Efficiency integration profiles for both the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, values for the Carbon Efficiency below 0.32 are considered to have an integrated value of 0

From Figure 2.33 the Kumaraswamy distribution's cumulative distribution function has higher integration values closer to the limits while having slightly lower values near the median integration (corresponding to a Carbon Efficiency of 0.74). This data is in accordance with the error analyses that were made (Table 2.39 and Table 2.40), as they showed a higher obtained value for both quartiles and lower obtained value for the median using the Kumaraswamy distribution's cumulative distribution function when compared with the regularized incomplete beta function. Additionally, by comparing the absolute percentage error of both functions (Table 2.39 for the regularized incomplete beta function and Table 2.40 for Kumaraswamy distribution's cumulative distribution function) it can be seen that Kumaraswamy distribution's cumulative distribution function has a lower error for all analysed points.

After carrying out the comparison between the error analyses (Table 2.39 and Table 2.40) and the integration profiles (Figure 2.33) for the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, the chosen function for the integration of the Carbon Efficiency to a non-linear scale from 0 to 1 is Kumaraswamy distribution's cumulative distribution function (Figure 2.34).

Figure 2.34. Carbon Efficiency integration profile, values for the Carbon Efficiency below 0.32 are considered to have an integrated value of 0

Considering the profile presented in Figure 2.34 an example on the application of this principle for the synthesis of benzoic hydrazide through a conventional method and a "greener" method using microwave irradiation follows (Table 2.41):

Table 2.41. Example using the synthesis of benzoic hydrazide for the integration of Carbon Efficiency for the Green Chemistry grid

Process	Carbon Efficiency (%)	Integrated Carbon Efficiency (Figure 2.34)
Conventional	77.8 [27]	0.69
Greener	100.0 [27]	1.00

From the example (Table 2.41), the integrated value for the method considered "greener" is higher than the integrated value of the conventional process. These results are as intended and allow to be concluded that, according to this suggested principle, the method considered "greener" is in fact the better option.

2.2.12. Principle 14

For the Green Chemistry Grid, a 14th principle was added, Reaction efficiency. This proposed principle can be stated as "Design of cleaner reactions with higher yields and incorporation of reactants into final product.". The suggested metric to be used alongside it is Curzons Reaction Mass Efficiency (Equation 2.75). This principle is similar to Atom Economy but taking into consideration the reaction's yield and stoichiometry.

Equation 2.75. Curzons Reaction Mass Efficiency [25]

$$Curzons\ Reaction\ Mass\ Efficiency\ (\%) = \frac{Mass\ of\ product\ (kg)}{\sum Mass\ of\ reagents\ (kg)} * 100$$

As can be seen from Equation 2.75, the Curzons Reaction Mass Efficiency varies between 0% and 100%. This allows for an integration between 0 and 1 (as proposed in section 2.2 in order to facilitate data treatment) to be done linearly (Equation 2.76).

Equation 2.76. Linear integration of the Curzons Reaction Mass Efficiency

$$Integrated\ Curzons\ Reaction\ Mass\ Efficiency = Curzons\ Reaction\ Mass\ Efficiency$$

Following the same line of reasoning as was made for the other principles with percentage-based metrics between 0% and 100% (Atom Economy, see section 2.2.2, and Carbon Efficiency, see section 2.2.11), a linear integration can be disadvantageous due to a lack of differentiation in the integration profile between lower values and higher values (for example, changing from 1% to 2%, 49% to 50% or 99% to 100% all have the same impact in the integrated value). The proposed alternative is, as such, usage of a function with the following characteristics:

- Must represent a double-bounded interval;
- Strictly increasing since, according to the principle, higher values of the Curzons Reaction Mass Efficiency are better;
- Adaptable to different medians of the Mass Efficiency with a large variation near the considered Mass Efficiency's median value.

Considering these characteristics, two functions fit the criteria: (i) the regularized incomplete beta function and (ii) Kumaraswamy distribution's cumulative distribution function.

As was performed for the Atom Economy (section 2.2.2) and Carbon Efficiency (section 2.2.11), the choice of function will be made by building an integration profile for both and considering the average Curzons reaction mass efficiency in different types of chemical processes (Table 2.42).

Table 2.42. Curzons RME average values [125]

Chemistry type	Curzons RME (%)	Chemistry type	Curzons RME (%)
Acid salt	83	Epoxidation	58
Base salt	80	Borohydride	58
Hydrogenation	75	Iodination	56
Sulfonation	69	Cyclisation	56
Decarboxylation	68	Amination	54
Esterification	67	Lithal	52
Knoevenagel	66	Base hydrolysis	52
Cyanation	65	C-Acylation	51
Bromination	63	Acid hydrolysis	50
N-Acylation	62	Chlorination	46
S-Alkylation	61	Elimination	45
C-Alkylation	61	Grignard	42
N-Alkylation	60	Resolution	31
O-Arylation	58	N-Dealkylation	27

Using the data from Table 2.42, the minimum value was determined to be 27%, the lower quartile was determined to be 51.75%, the median was determined to be 58% and the higher quartile was determined to be 65.25%. Using this, the bounds for the integration were considered to be the minimum (27%) and 100% (the principle's objective is maximization of Curzons reaction mass efficiency). Values below the minimum bound ($[0\%; 27\%[$) were considered to have an automatic integrated value of 0, as they are lower than the "worst case scenario" under study.

With these considerations in mind, the profile for the integration using the regularized incomplete beta function (Equation 2.77) can be built.

Equation 2.77. Regularized incomplete beta function. B (x, α, β) is the beta function calculated for the value of x with form parameters α and β

$$I(x, \alpha, \beta) = \frac{B(x, \alpha, \beta)}{B(1, \alpha, \beta)}$$

In order to use Equation 2.10, the Curzons reaction mass efficiency first needs to be normalized from the considered range ($[27\%; 100\%]$) to a value range between 0 and 1. Afterwards the α and β parameters (numerical values between 0 and $+\infty$ responsible for the shape that the integration function takes, see section 2.2.2) need to be determined.

To normalize the Curzons reaction mass efficiency to the proposed range ($[0; 1]$), Equation 2.78 can be used. In this context, y is the Curzons reaction mass efficiency, the lower bound is considered to be 27% (Table 2.42) and the upper bound is considered to be 100%.

Equation 2.78. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Having a method to normalize the Curzons reaction mass efficiency (Equation 2.78), the α and β parameters need to be determined. This can be done through a genetic algorithm approach in MATLAB by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 51.75%), the median (set as a 0.50 integration for 58.00%) and the upper quartile (set as a 0.75 integration for 65.25%). The results of the optimization were as follows (Figure 2.35):

```
                              Best        Mean      Stall
Generation     Func-count     f(x)        f(x)    Generations
   181           54600      0.0001324   0.0001324      35
   182           54900      0.0001324   0.0001324      36
   183           55200      0.0001324   0.0001324      37
   184           55500      0.0001324   0.0001324      38
   185           55800      0.0001324   0.0001324      39
   186           56100      0.0001324   0.0001324      40
   187           56400      0.0001324   0.0001324      41
   188           56700      0.0001324   0.0001324      42
   189           57000      0.0001324   0.0001324      43
   190           57300      0.0001324   0.0001324      44
   191           57600      0.0001324   0.0001324      45
   192           57900      0.0001324   0.0001324      46
   193           58200      0.0001324   0.0001324      47
   194           58500      0.0001324   0.0001324      48
   195           58800      0.0001324   0.0001324      49
   196           59100      0.0001324   0.0001324      50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

Alfa parameter estimation = 5.71
Beta parameter estimation = 7.55
```

Figure 2.35. Genetic algorithm results for the regularized incomplete beta function optimization from MATLAB

As can be seen from Figure 2.35, the optimization of the regularized incomplete beta function obtained results for $\alpha = 5.71$ and $\beta = 7.55$ with the minimized total square error of approximately 0.0001. Having carried out the optimization, the error analysis is conducted (Table 2.43).

Table 2.43. Error analysis for the regularized incomplete beta function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.000	0.000	0.000	0.000	0.000
Q1	0.250	0.257	0.007	2.723	2.723
Median	0.500	0.493	0.007	-1.459	1.459
Q3	0.750	0.755	0.005	0.668	0.668
Maximum	1.000	1.000	0.000	0.000	0.000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Mass Efficiency of 27%, the lower quartile (Q1) corresponds to a Mass Efficiency of 51.75%, the median corresponds to a Mass Efficiency of 58%, the upper quartile (Q3) corresponds to Mass Efficiency of 65.25% and the maximum corresponds to a Mass Efficiency of 100%

From the error analysis of the integration using the regularized incomplete beta function (Table 2.43), it is possible to see that the highest absolute percentage error (2.723%) corresponds to the lower quartile followed by the median value's error (1.459%). The error for the higher quartile is comparatively lower (0.668%) while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value. This distribution of errors shows a better fit for the regularized incomplete beta function at higher values than at lower values for the data.

Having built an integration profile for the Curzons reaction mass efficiency using the regularized incomplete beta function, the same reasoning is applied to Kumaraswamy distribution's cumulative distribution function (Equation 2.79).

Equation 2.79. Kumaraswamy distribution's cumulative distribution function with α and β form parameters. x is the normalized Curzons reaction mass efficiency obtained using Equation 2.12.

$$F(x; \alpha, \beta) = 1 - (1 - x^\alpha)^\beta$$

As with the regularized incomplete beta function, the Curzons reaction mass efficiency first needs to be normalized by using Equation 2.78 with the lower bound being considered 27% and the upper bound being considered 100%. Afterwards, the α and β form parameters (similarly to the regularized incomplete beta function (Equation 2.77), values between 0 and $+\infty$ responsible for the shape that the function takes) must be determined.

The chosen method to determine the optimal value for the α and β form parameters is through a genetic algorithm using MATLAB. The optimization was carried out by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 51.75%), the median (set as a 0.50 integration for 58.00%) and the upper quartile (set as a 0.75 integration for 65.25%). The results of the optimization were as follows (Figure 2.36):

```
                               Best          Mean       Stall
Generation      Func-count     f(x)          f(x)     Generations
   301            90600       0.0003672     0.0003672      43
   302            90900       0.0003672     0.0003672      44
   303            91200       0.0003672     0.0003672      45
   304            91500       0.0003672     0.0003672      46
   305            91800       0.0003672     0.0003672      47
   306            92100       0.0003672     0.0003672      48
   307            92400       0.0003672     0.0003672      49
   308            92700       0.0003672     0.0003672      50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 3.45
 Beta parameter estimation = 12.45
```

Figure 2.36. Genetic algorithm optimization results for Kumaraswamy distribution's cumulative distribution function from MATLAB

Figure 2.36 shows the obtained results for the optimization of Kumaraswamy distribution's cumulative distribution function via MATLAB. The optimized parameters are $\alpha = 3.45$ and $\beta = 12.45$, with the minimized square error being approximately 0.0004. With the form parameters determined, the error analysis can be conducted for the integration (Table 2.44):

Table 2.44. Error analysis for the Kumaraswamy distribution's cumulative distribution function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.000	0.000	0.000	0.000	0.000
Q1	0.250	0.260	0.010	4.183	4.183
Median	0.500	0.486	0.014	-2.843	2.843
Q3	0.750	0.756	0.006	0.845	0.845
Maximum	1.000	1.000	0.000	0.000	0.000

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to a Mass Efficiency of 27%, the lower quartile (Q1) corresponds to a Mass Efficiency of 51.75%, the median corresponds to a Mass Efficiency of 58%, the upper quartile (Q3) corresponds to Mass Efficiency of 65.25% and the maximum corresponds to a Mass Efficiency of 100%

From the error analysis of the integration using Kumaraswamy distribution's cumulative distribution function (Table 2.44) it is possible to realize that the highest absolute percentage error (4.183%) corresponds to the higher quartile, followed by the median value's error (2.843%). Comparatively the error for the lower quartile is lower (0.845%) while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value.

Having carried out both error analyses, the profiles were built to have a graphic comparison (Figure 2.37):
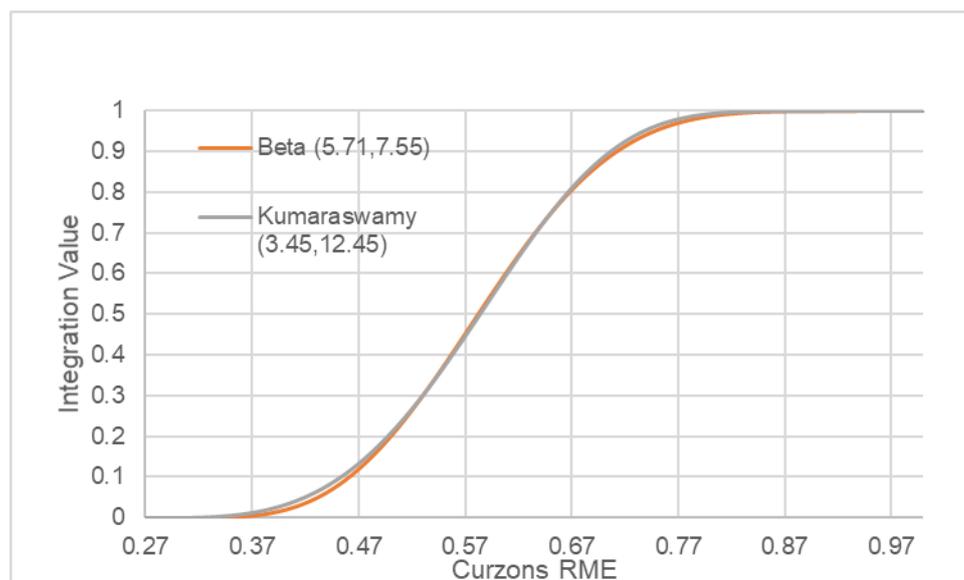
Figure 2.37. Curzons Reaction Mass Efficiency integration profiles for both the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, values for the Curzons Reaction Mass Efficiency below 0.27 are considered to have an integrated value of 0

From Figure 2.37 the Kumaraswamy distribution's cumulative distribution function has higher integration values closer to the limits while having slightly lower values near the median integration (corresponding to a Mass Efficiency of 0.58). This data is in accordance with the error analyses that were made (Table 2.43 and Table 2.44), as they showed a higher obtained value for both quartiles and lower obtained value for the median using the Kumaraswamy distribution's cumulative distribution function when compared with the regularized incomplete beta function. Additionally, by comparing the absolute percentage error of both functions Table 2.43 for the regularized incomplete beta function and Table 2.44 for Kumaraswamy distribution's cumulative distribution function) it can be seen that the regularized incomplete beta function has a lower error for all analysed points.

After carrying out the comparison between the error analyses (Table 2.43 and Table 2.44) and the integration profiles (Figure 2.37) for the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, the chosen function for the integration of the Curzons reaction mass efficiency to a non-linear scale from 0 to 1 is the regularized incomplete beta function (Figure 2.38).
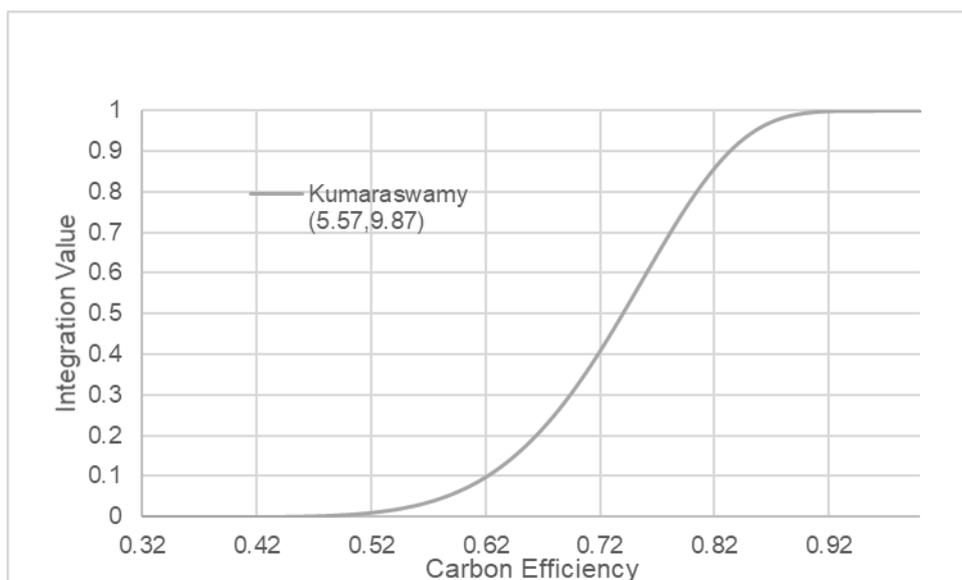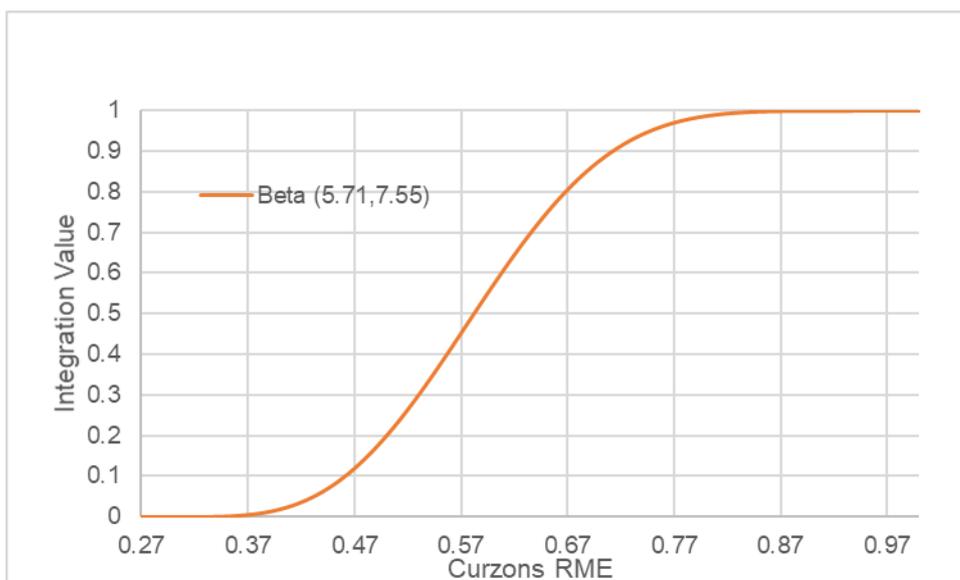
Figure 2.38. Curzons reaction mass efficiency integration profile, values for the Curzons reaction mass efficiency below 0.32 are considered to have an integrated value of 0

Considering the profile presented in Figure 2.38 an example on the application of this principle for the synthesis of benzoic hydrazide through a conventional method and a "greener" method.

The conventional method was carried out through a two-step process: The first step was the synthesis of an ester from benzoic acid and the second step was the synthesis of the benzoic hydrazide from the ester [27]. The "greener" method was carried out in a one-step reaction between benzoic acid and hydrazine hydrate under microwave irradiation [27]. Comparison of both processes according to the proposed methodology for this principle follows (Table 2.45):

Table 2.45. Example using the synthesis of benzoic hydrazide for the integration of Curzons Reaction Mass Efficiency for the Green Chemistry grid

Process	Curzons Reaction Mass Efficiency (%)	Integrated Curzons RME (Figure 2.38)
Conventional	16.0 [27]	0.00
Greener	69.2 [27]	0.86

From the example (Table 2.45), the integrated value for the method considered "greener" is much higher (0.86) than the integrated value of the conventional process (0.00, as the Curzons Reaction Mass Efficiency is below 27%). These results are as intended and allow to be concluded that, according to this suggested principle, the method considered "greener" the better option by a large margin.

2.2.13.   Principle 15

The final principle proposed for the Green Chemistry Grid is Mass Productivity. This principle can be stated as "Design of processes with lower resources waste. To that matter it's important to understand how many resources are used in every step and where it is possible to reduce waste.".

This proposed principle has a metric associated to it, the same named Mass Productivity (Equation 2.80) (also called Generalized Reaction Mass Efficiency).

Equation 2.80. Mass Productivity [25]

$$Mass\ Productivity\ (\%) = \frac{Mass\ of\ product\ (kg)}{Total\ mass\ into\ process\ (kg)} * 100$$

From Equation 2.80, it can be seen that the Mass Productivity varies between 0% and 100%. This allows for an integration between 0 and 1 (as proposed in section 2.2 in order to facilitate data treatment) to be done linearly (Equation 2.81).

Equation 2.81. Linear integration of the Mass Productivity

$$Integrated\ Mass\ Productivity = Mass\ Productivity$$

As with the other principles with mass-based metrics that vary between 0% and 100% (Atom Economy, see section 2.2.2, Carbon Efficiency, see section 2.2.11, and Curzons Reaction Mass Efficiency, see section 2.2.12), a linear integration can be a disadvantage as it makes a change in Mass Productivity from 1% to 2% to have the same impact in the integrated value as a change from 49% to 50% or 99% to 100%. The proposed alternative for the integration is the usage of a function with the following characteristics:

- Must represent a double-bounded interval;
- Strictly increasing since, according to the principle, higher values of the Mass Productivity are better;
- Adaptable to different medians of the Mass Productivity with a large variation near the considered Mass Productivity's median value.

Considering these characteristics, two functions fit the criteria: (i) the regularized incomplete beta function and (ii) Kumaraswamy distribution's cumulative distribution function.

As was performed for Atom Economy (section 2.2.2), Carbon Efficiency (section 2.2.11) and Curzons Reaction Mass Efficiency (see section 2.2.12), the choice of function will be made by building an integration profile for both and taking into account the average Mass Productivity in different types of chemical processes (Table 2.46).

Table 2.46. Mass Productivity average values [125]

Chemistry type (1)	Mass Productivity (%)	Chemistry type (2)	Mass Productivity
Acid salt	6.3	Epoxidation	5.9
Base salt	4.9	Borohydride	5.6
Hydrogenation	5.4	Iodination	15.4
Sulfonation	6.1	Cyclisation	4.8
Decarboxylation	5.0	Amination	8.9
Esterification	8.8	Lithal	4.7
Knoevenagel	16.4	Base hydrolysis	3.8
Cyanation	7.6	C-Acylation	6.6
Bromination	7.2	Acid hydrolysis	9.3
N-Acylation	5.3	Chlorination	9.5
S-Alkylation	10	Elimination	3.0
C-Alkylation	7.1	Grignard	3.3

N-Alkylation	5.1	Resolution	2.5
O-Arylation	8.7	N-Dealkylation	9.9

Using the data from Table 2.46, the minimum value was determined to be 2.5%, the lower quartile was determined to be 4.975%, the median was determined to be 6.2% and the higher quartile was determined to be 8.825%. Using this, the bounds for the integration were considered to be the minimum (2.5%) and 100% (the principle's objective is maximization of the Mass Productivity). Values below the minimum bound ($[0\%; 2.5\%[$) were considered to have an automatic integrated value of 0, as they are lower than the "worst case scenario" under study.

With these considerations in mind, the profile for the integration using the regularized incomplete beta function (Equation 2.82) can be built.

Equation 2.82. Regularized incomplete beta function, B (x, α, β) is the beta function calculated for the value of x with form parameters α and β

$$I(x, \alpha, \beta) = \frac{B(x, \alpha, \beta)}{B(1, \alpha, \beta)}$$

In order to use the above equation (Equation 2.82) the Mass Productivity first needs to be normalized from the considered range ($[2.5\%; 100\%]$) to a value ranging between 0 and 1. Afterwards, the α and β parameters (numerical values between 0 and $+\infty$ responsible for the shape that the integration function has, see section 2.2.2) need to be determined.

To carry out the normalization of the Mass Productivity to the required range ($[0; 1]$), Equation 2.83 can be used. In this context, y is the Mass Productivity, the lower bound is considered to be 2.5% (Table 2.46) and the upper bound is considered to be 100%.

Equation 2.83. Normalization of a double bounded variable

$$x = \frac{y - lower\ bound}{upper\ bound - lower\ bound}$$

Having a method to normalize the Mass Productivity (Equation 2.83), the α and β parameters must be determined. This can be performed through a genetic algorithm approach in MATLAB by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 4.975%), the median (set as a 0.50 integration for 6.200%) and the upper quartile (set as a 0.75 integration for 8.825%). The results of the optimization were as follows (Figure 2.39):

```
                              Best          Mean        Stall
Generation      Func-count    f(x)          f(x)     Generations
  181           54600       0.002019      0.002019      38
  182           54900       0.002019      0.002019      39
  183           55200       0.002019      0.002019      40
  184           55500       0.002019      0.002019      41
  185           55800       0.002019      0.002019      42
  186           56100       0.002019      0.002019      43
  187           56400       0.002019      0.002019      44
  188           56700       0.002019      0.002019      45
  189           57000       0.002019      0.002019      46
  190           57300       0.002019      0.002019      47
  191           57600       0.002019      0.002019      48
  192           57900       0.002019      0.002019      49
  193           58200       0.002019      0.002019      50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 2.11
 Beta parameter estimation = 43.30
```

Figure 2.39. Genetic algorithm results for the regularized incomplete beta function optimization from MATLAB

As can be seen from Figure 2.39, the optimization of the regularized incomplete beta function obtained results for $\alpha = 2.11$ and $\beta = 43.30$ with the minimized total square error of approximately 0.002. Having carried out the optimization, the error analysis is conducted (Table 2.47).

Table 2.47. Error analysis for the regularized incomplete beta function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.00	0.00	0.00	0.00	0.00
Q1	0.25	0.27	0.02	9.52	9.52
Median	0.50	0.47	0.03	-6.91	6.91
Q3	0.75	0.77	0.02	2.15	2.15
Maximum	1.00	1.00	0.00	0.00	0.00

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to Mass Productivity of 2.5%, the lower quartile (Q1) corresponds to a Mass Productivity of 4.975%, the median corresponds to a Mass Productivity of 6.2%, the upper quartile (Q3) corresponds to a Mass Productivity of 8.825% and the maximum corresponds to a Mass Productivity of 100%

From the error analysis of the integration using the regularized incomplete beta function (Table 2.39), it is possible to see that the highest absolute percentage error (9.52%) corresponds to the lower quartile followed by the median value's error (6.91%). The error for the higher quartile is comparatively lower (2.15%), although still considerable, while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value.

Having built an integration profile for Mass Productivity using the regularized incomplete beta function, the same reasoning is applied to Kumaraswamy distribution's cumulative distribution function (Equation 2.84).

Equation 2.84. Kumaraswamy distribution's cumulative distribution function with α and β form parameters. x is the normalized Mass Productivity obtained using Equation 2.12

$$F(x; \alpha, \beta) = 1 - (1 - x^\alpha)^\beta$$

As with the regularized incomplete beta function, the Mass Productivity first needs to be normalized by using Equation 2.84 with the lower bound being considered 2.5% and the upper bound being considered 100%. Afterwards the α and β form parameters (similarly to the regularized incomplete beta function (Equation 2.82), values between 0 and +∞ responsible for the shape that the function takes) must be determined.

The chosen method to determine the optimal value for the α and β form parameters is through a genetic algorithm using MATLAB. The optimization was carried out by minimizing the total quadratic error for the lower quartile (set as a 0.25 integration for 4.975%), the median (set as a 0.50 integration for 6.200%) and the upper quartile (set as a 0.75 integration for 8.825%). The results of the optimization were as follows (Figure 2.40):

```
                            Best        Mean       Stall
Generation     Func-count    f(x)       f(x)     Generations
  1621          486600      0.0026     0.0026        47
  1622          486900      0.0026     0.0026        48
  1623          487200      0.0026     0.0026        49
  1624          487500      0.0026     0.0026        50
Optimization terminated: average change in the fitness value less than options.FunctionTolerance.

 Alfa parameter estimation = 1.56
 Beta parameter estimation = 104.02
```

Figure 2.40. Genetic algorithm optimization results for Kumaraswamy distribution's cumulative distribution function from MATLAB

Figure 2.40 shows the obtained results for the optimization of Kumaraswamy distribution's cumulative distribution function via MATLAB. The optimized parameters are $\alpha = 1.52$ and $\beta = 104.02$, with the minimized square error being approximately 0.0026. With the form parameters determined, the error analysis can be conducted for the integration (Table 2.48):

Table 2.48. Error analysis for the Kumaraswamy distribution's cumulative distribution function integration

Parameter	Predicted value	Obtained value	Absolute error	Percentage error (%)	Absolute percentage error (%)
Minimum	0.00	0.00	0.00	0.00	0.00
Q1	0.25	0.28	0.03	12.45	12.45
Median	0.50	0.46	0.04	-7.36	7.36
Q3	0.75	0.77	0.02	2.23	2.23
Maximum	1.00	1.00	0.00	0.00	0.00

*Number of decimal places chosen as minimum for the error to be perceivable. At the time of study, the minimum corresponds to Mass Productivity of 2.5%, the lower quartile (Q1) corresponds to a Mass Productivity of 4.975%, the median corresponds to a Mass Productivity of 6.2%, the upper quartile (Q3) corresponds to a Mass Productivity of 8.825% and the maximum corresponds to a Mass Productivity of 100%

From the error analysis of the integration using Kumaraswamy distribution's cumulative distribution function (Table 2.48) it is possible to realize that the highest absolute percentage error (12.45%) corresponds to the higher quartile, followed by the median value's error (7.36%). Comparatively the error for the lower quartile is lower (2.23%), although still considerable, while the minimum and maximum are working as intended with a 0.000% deviation from the predicted value.

Having carried out both error analyses, the profiles were built to have a graphic comparison (Figure 2.41):
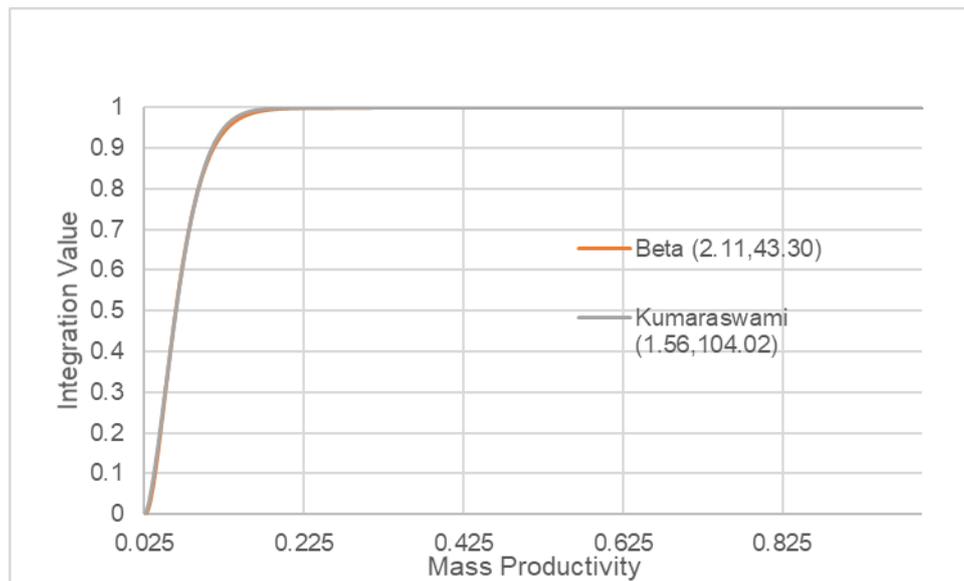
Figure 2.41. Mass Productivity integration profiles for both the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, values for the Mass Productivity below 0.025 are considered to have an integrated value of 0

From Figure 2.41 the Kumaraswamy distribution's cumulative distribution function has higher integration values closer to the limits while having slightly lower values near the median integration (corresponding to a Mass Productivity of 0.062). This data is in accordance with the error analyses that were made (Table 2.47 and Table 2.48), as they showed a higher obtained value for both quartiles and lower obtained value for the median using the Kumaraswamy distribution's cumulative distribution function when compared with the regularized incomplete beta function. Additionally, by comparing the absolute percentage error of both functions (Table 2.47 for the regularized incomplete beta function and Table 2.48 for Kumaraswamy distribution's cumulative distribution function) it can be seen that the regularized incomplete beta function has a lower error for all analysed points.

After carrying out the comparison between the error analyses (Table 2.47 and Table 2.48) and the integration profiles (Figure 2.41) for the regularized incomplete beta function and Kumaraswamy distribution's cumulative distribution function, the chosen function for the integration of the Mass Productivity to a non-linear scale from 0 to 1 is the regularized incomplete beta function (Figure 2.42).
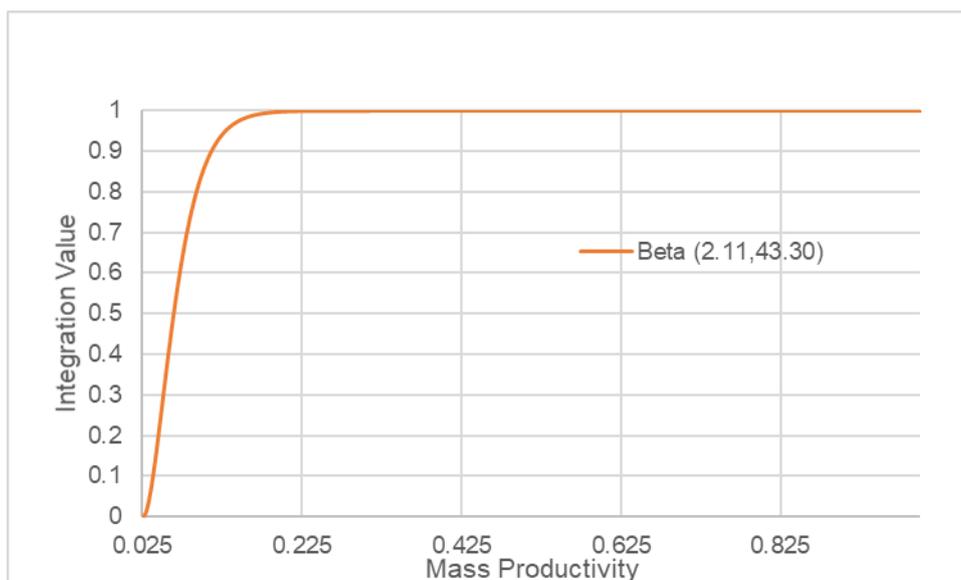
Figure 2.42. Mass Productivity integration profile, values for the Mass Productivity below 0.025 are considered to have an integrated value of 0

Considering the profile presented in Figure 2.42, an example on the application of this principle for the synthesis of benzoic hydrazide through a conventional method and a "greener" method.

The conventional method was carried out through a two-step process: The first step was the synthesis of an ester from benzoic acid and the second step was the synthesis of the benzoic hydrazide from the ester [27]. The "greener" method was carried out in a one-step reaction between benzoic acid and hydrazine hydrate under microwave irradiation [27]. Comparison of both processes according to the proposed methodology for this principle follows (Table 2.49):

Table 2.49. Example using the synthesis of benzoic hydrazide for the integration of Mass Productivity for the Green Chemistry grid

Process	Mass Productivity (%)	Mass Productivity (Figure 2.38)
Conventional	18.18 [27]	0.995
Greener	76.92 [27]	1.000

From the example (Table 2.49) it can be seen that the integrated value for the method considered "greener" is only slightly higher than the integrated value for the conventional process. These results are due to the high Mass Productivity of the conventional process when compared to the industry averages (Table 2.46). As a result, both methods can be considered "green" according to the principle, despite the difference in Mass Productivity (with the method considered "greener" being only slightly superior).

2.2.14.   Green Index

After proposing the methods to calculate a value between 0 and 1 for each of the principles of green chemistry and the three adittional principles proposed by the Geo Ground Engineering Operations, Lda Grid (Section 2.2.1 to Section 2.2.13), the overall "greeness" of the assessed process can be calculated. The proposed method for determining the overall "greeness" of the process is through the sum total of all the principles, as no principle is considered to be more important than another (the Green Index (Equation 2.85)).

Equation 2.85. Green Index

$$Green\ Index = \sum Integrated\ principles$$

The obtained value for the Green Index (Equation 2.85) can then be used to classify the process as being green or not. The final classification for each assessement is proposed to be done with the following divisions (Table 2.50):

Table 2.50. Greenness classification

Value Range	Classification
0.00-3.00 (inclusive)	Unsustainable Process
3.00-6.00 (inclusive)	Poor Process
6.00-9.00 (inclusive)	Average Process
9.00-12.00 (inclusive)	Satisfactory Process
12.00-15.00 (inclusive)	Green Process

3. Results and Discussion

3.1. Case study: Synthesis of benzoic hydrazide

In the previous section (Section 2.2), the Green Chemistry grid was proposed. In order to test if it is working as intended the assessment of two different methods for the synthesis of benzoic hydrazide will be made. These two methods are the "Conventional" method, through which benzoic hydrazide is produced from ethyl benzoate which, in turn, is produced from benzoic acid; and the "Greener" method, through which benzoic hydrazide is produced directly from benzoic acid through microwave irradiation, proposed by A. Saha, R. Kumar, R. Kumar and C. Devakumar [27].

Aditionaly, as the "greeness" assessment carried out in the reference ([27]) is only related to a few principles, the case study will analyse three scenarios for each method as described in Table 3.1:

Table 3.1. Assessed methods for the synthesis of benzoic hydrazide

Method	Description
Conventional	Conventional method using the results present in reference [27]
Greener	Greener method using the results present in reference [27]
Full Conventional	Conventional method simulating the process as described in reference [27] and using the obtained results for all principles
Full Greener	Greener method simulating the process as described in reference [27] and using the obtained results for all principles
Full Conventional (with recirculation)	Conventional method simulating the process as described in reference [27] asssuming that some currents can be recirculated and using the obtained results for all principles
Full Greener (with recirculation)	Greener method simulating the process as described in reference [27] assuming that some currents can be recirculated and using the obtained results for all principles

All of the assessed methods are described in further detail in the reference ([27]).

3.1.1. Variable definition

To carry out the assessment, the lists of process inputs, reagents, auxiliary susbtances, desired products and generated waste are summarised in Table 3.2, Table 3.3, Table 3.4 and Table 3.5 for the "Greener" process and in Table 3.6, Table 3.7, Table 3.8, Table 3.9, Table 3.10 and Table 3.11 for the "Conventional" process.

For the "Greener" process, the only mass inputs into the process in the given example are benzoic acid (0.0100 mol) and benzoic hydrazide (0.0120 mol) [27] (Table 3.2). This represents a total mass input of approximately 0.00182 kg.

Table 3.2. Greener process mass inputs

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic Acid	0.0100	0.1221	0.00122
Benzoic Hydrazide	0.0120	0.0501	0.00060
Total			0.00182

Of the mass inputs in Table 3.2, all of them are used as reagents in the process (Table 3.3):

Table 3.3. Greener process reagents

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic acid	0.0100	0.1221	0.00122
Hydrazine hydrate	0.0120	0.0501	0.00060
Total		0.1722	0.00182

The desired product of the "Greener" process is benzoic hydrazide of which 0.00120 kg are obtained when carrying out the operation. [27] (Table 3.4):

Table 3.4. Greener process desired products

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic hydrazide	0.0090	0.1362	0.00120

Lastly, after carrying out the process the only generated waste is 0.0010 mol of benzoic acid and 0.0030 mol of hydrazine hydrate due to the reaction not having a 100% yield (Table 3.5). Considering the molar masses of benzoic acid (0.1221 kg/mol) and of hydrazine hydrate (0.0501 kg/mol), these values correspond to a total mass of 0.00027 kg of generated waste.

Table 3.5. Greener process generated waste (no recirculation)

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic Acid	0.0010	0.1221	0.00012
Hydrazine Hydrate	0.0030	0.0501	0.00015
Total			0.00027

All of the generated waste can be recirculated as reagents for the reaction, leading to no waste in the "Greener" process when recirculation is applied.

For the "Conventional" process the mass inputs are benzoic acid (0.0246 mol), ethanol (0.2500 mol), sulphuric acid (0.00050 kg), carbon tetrachloride (10 mL), sodium hydrogen carbonate (enough to neutralize benzoic acid in solution) and hydrazine hydrate (10% more mol than the intermediate product, ethyl benzoate) (Table 3.6). This translates into an approximate total mass input of 0.03238 kg, where the main substances are ethanol (0.01152 kg) and carbon tetrachloride (0.01590 kg).

Table 3.6. Conventional process mass inputs

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic acid	0.0246	0.1221	0.00300
Ethanol	0.2500	0.0461	0.01152
Sulphuric acid	0.0051	0.0981	0.00050
Carbon tetrachloride	0.1034	0.1538	0.01590
Sodium hydrogen carbonate	0.0034	0.0840	0.00029
Hydrazine hydrate	0.0233	0.0501	0.00116
Total			0.03238

Of the inputs in Table 3.6, benzoic acid, ethanol and hydrazine hydrate are used as reagents in the process (Table 3.7). This represents a total of 0.01569 kg of reagents in the process, approximately 48% of the mass inputs.

Table 3.7. Conventional process reagents

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic Acid	0.2460	0.1221	0.00300
Ethanol	0.2500	0.0461	0.01152
Hydrazine hydrate	0.2327	0.0501	0.00116
Total		0.2183	0.01569

The auxiliary substances used in the process are ethyl benzoate (the intermediate product, 0.00318 kg), carbon tetrachloride (used as a separation agent, 0.01590 kg), sodium hydrogen carbonate (used as a separation agent, 0.00029 kg) and sulphuric acid (in order to initialize the first chemical reaction, 0.00050 kg) (Table 3.8).

Table 3.8. Conventional process auxiliary substances

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Ethyl benzoate	0.0212	0.1502	0.00318
Carbon tetrachloride	0.1034	0.1538	0.01590
Sodium hydrogen carbonate	0.0034	0.0840	0.00029
Sulphuric acid	0.0051	0.0981	0.00050
Total			0.01987

The desired product of this process is benzoic hydrazide, which is obtained in the amount of 0.00259 kg [27] (Table 3.9):

Table 3.9. Conventional process desired products

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Benzoic hydrazide	0.0190	0.1362	0.00259

Laslty, after carrying out the process, the obtained waste is shown in Table 3.10 when no recirculation is done. Due to solvents being required, and a yield inferior to 100%, several substances are wasted, with the most prominent ones being ethanol (0.2288 mol; 0.0105 kg) and carbon tetrachloride (0.1034; 0.0159 kg). In total, the generated waste is of 0.02940 kg.

Table 3.10. Conventional process generated waste (no recirculation)

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Ethanol	0.2288	0.0461	0.01054
Sulphuric acid	0.0051	0.0981	0.00050
Sodium benzoate	0.0034	0.1441	0.00050
Carbon dioxide	0.0034	0.0440	0.00015
Carbon tetrachloride	0.1034	0.1538	0.01590
Ethyl benzoate	0.0021	0.1502	0.00032
Hydrazine hydrate	0.0042	0.0501	0.00021
Ethanol	0.0190	0.0461	0.00088
Water	0.0225	0.0180	0.00040
Total			0.02940

On the other hand, the ethanol can be recirculated as it is completely separated from any impurities in the ideal scenario (Table 3.11). In this case, the total waste is reduced from 0.02940 kg to 0.01798 kg.

Table 3.11. Conventional process generated waste (recirculation)

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Sulphuric acid	0.0051	0.0981	0.00050
Sodium benzoate	0.0034	0.1441	0.00050
Carbon dioxide	0.0034	0.0440	0.00015
Carbon tetrachloride	0.1034	0.1538	0.01590
Ethyl benzoate	0.0021	0.1502	0.00032
Hydrazine hydrate	0.0042	0.0501	0.00021
Water	0.0225	0.0180	0.00040
Total			0.01798

3.1.2. Greeness assessment

Principle 1

Following the methodology proposed in section 2.2.1, the results for the first principle, which analyzes generated waste, are as follows in Table 3.12:

Table 3.12. Principle 1 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	E-factor (Kg of waste/Kg of product) (Equation 2.2)	Product type	Integrated 1st principle (Equation 2.5, Figure 2.6)
Conventional	4.5000	Fine chemical	0.54
Greener	0.3000	Fine chemical	0.96
Full Conventional	11.1854	Fine chemical	0.21
Full Greener	0.2222	Fine chemical	0.97
Full Conventional (with recirculation)	6.7803	Fine chemical	0.38
Full Greener (with recirculation)	0.0000	Fine chemical	1.00

These results (Table 3.12) show that the full analysis of the processes (with and without recirculation) present different results for the 1ˢᵗ principle. This can be due to differences in the definition of "waste" (the proposed definition for use in the Green Chemistry grid is similar to the one proposed by Roger A. Sheldon [24] of "everything but the desired product and water", but with water being considered waste when mixed with any impurity), the lack of information on what could or not be recirculated during the test in the reference ([27]) or deviations from reality caused by approximations during the simulated full process.

Overall, the results show that, in terms of mass of generated waste, the "greener" processes have a superior integration (0.96, 0.97 and 1.00) when compared with the conventional processes (0.64, 0.21 and 0.38).

Principle 2

Following the methodology proposed in section 2.2.2, the results for the assessment of the 2ⁿᵈ principle, which analyzes the Atom Economy of the chemical reactions, are presented in Table 3.13:

Table 3.13. Principle 2 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Atom Economy (%) (Equation 2.8)	Normalized Atom Economy (Equation 2.12, Table 2.5)	Integrated 2nd principle (Equation 2.14, Figure 2.16)
Conventional	62.30	0.0000	0.00
Greener	79.10	0.4194	0.35
Full Conventional	62.38	0.0000	0.00
Full Greener	79.08	0.4188	0.35
Full Conventional (with recirculation)	62.38	0.0000	0.00
Full Greener (with recirculation)	79.08	0.4188	0.35

From Table 3.13 it can be seen that the Atom Economy for the simulated process is aproximately the same as the values in the reference ([27]). This is as expected since the Atom Economy depends only on the molar weight of the reagents used in the chemical reaction. The small difference of 0.08% for the Atom Economy of the conventional process (simulated vs reference [27]) and 0.02% for the Atom Economy of the greener process (simulated vs reference [27]) can be explained by approximations on the molar weight of the assessed substances, for example, due to number of considered significant digits.

Overall, the results allow the conclusion that when comparing the "Greener" and the conventional processes the "Greener" process is superior (0.35 integration vs 0.00 integration for the conventional process).

Principle 3

Following the methodology proposed in section 2.2.3, the results for the assessment of the 3ʳᵈ principle, which analyzes the toxicity of used auxiliary substances, are as follows (Table 3.14):

Table 3.14. Principle 3 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Human Tolerability Index (Equation 2.20, Figure 2.18)	Environmental Toxicity Index (Equation 2.25)	Hazard Index (Equation 2.15)
Full Conventional	0.0000	0.5504	0.28
Full Greener	0.9764	0.4714	0.72
Full Conventional (with recirculation)	0.0000	0.5504	0.28
Full Greener (with recirculation)	0.9764	0.4714	0.72

*Data used for the determination of the Human Tolerability Index and Environmetal Toxicity Index present in Annexes 2, 3, 4, 5, 6 and 7

The results in Table 3.14 show that the Hazard Index is much lower for the conventional process when compared with the "greener" process (0.28 vs 0.72, respectively). When looking at the Toxicity Indexes individually, however, it can be seen that while the conventional process has an extremely lower score for the Human Tolerability Index when compared with the "greener" process (0.000 vs 0.9764, respectively) it has a slightly higher score for the Environmental Toxicity Index (0.5504 vs 0.4714, respectively). This allows the conclusion that, purely in terms of the toxicity of used and generated substances, the conventional process is more environmentally friendly at the cost of being more dangerous for the human beings involved in the it when compared with the "greener" process.

Principle 4

Following the methodology proposed in section 2.2.3, the results for the assessment of the 4th principle, which analyzes the toxicity of the desired product, are shown in Table 3.15:

Table 3.15. Principle 4 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Human Tolerability Index (Equation 2.20, Figure 2.18)	Environmental Toxicity Index (Equation 2.25)	Hazard Index (Equation 2.15)
Full Conventional	0.0000	0.5387	0.27
Full Greener	0.9842	0.5387	0.76
Full Conventional (with recirculation)	0.0000	0.5387	0.27
Full Greener (with recirculation)	0.9842	0.5387	0.76

*Data used for the determination of the Human Tolerability Index and Environmental Toxicity Index present in Annexes 8, 9, 10, 11, 12 and 13

From Table 3.15 it can be seen that the "greener" process has a higher Hazard Index than the conventional process (0.76 vs 0.27, respectively). As the desired product is the same in both cases, this is most likely the result of the higher times of exposure to it in the conventional process when compared with the "greener" process.

Principle 5

Following the methodology proposed in section 2.2.4, the results for the assessment of the 5th principle, which assesses the hazard of used auxiliary substances, are as follows (Table 3.16):

Process (Table 3.1)	Process Hazard Index (Equation 2.31)	Normalized Hazard Index (Equation 2.33)	Integrated Process Hazard (Equation 2.32, Figure 2.22)
Full Conventional	5.8534	0.3658	0.74
Full Greener	0.0000	0.0000	1.00
Full Conventional (with recirculation)	5.8534	0.3658	0.74
Full Greener (with recirculation)	0.0000	0.0000	1.00

*Data used for the determination of the Process Hazard Index present in Annex 14

From Table 3.16, it can be seen that the Integrated Process Hazard for the simulated conventional process is lower (0.74) when compared with the simulated "greener" process which has an Integrated Process Hazard of 1 due to no auxiliary substances being required in it. These results were obtained by using the GHS hazard warnings [163] due to these warnings being more common in the European Union when compared with the NFPA hazard warnings (Section 1.8, Figure 1.4 [145] [146]).

Principle 6

Following the methodology proposed in section 2.2.5, the results for the assessment of the 6th principle, which assesses the energetic costs of the process, are presented in Table 3.17:

Table 3.17. Principle 6 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Economic Cost Index (Equation 2.38, Figure 2.23)	Environmental Cost Index (Equation 2.41, Figure 2.24)	Energy Index (Equation 2.43)
Conventional	0.2176	0.2131	0.22
Greener	0.9962	0.9961	1.00
Full Conventional	0.2176	0.2131	0.22
Full Greener	0.9962	0.9961	1.00
Full Conventional (with recirculation)	0.2176	0.2131	0.22
Full Greener (with recirculation)	0.9962	0.9961	1.00

*Data used for the determination of the Economic Cost Index and Environmental Cost Index present in Annexes 15 and 16

From Table 3.17 it is possible to conclude that the conventional process is, according to the 6th principle, inferior to the "greener" process (1.00 integration for the "greener" process when compared with a 0.22 integration for the conventional process).. These results are due to the exceedingly lower energetic requirements of the "greener" process (about 400 times inferior), as demosntrated in the reference ([27]).

Principle 7

Following the methodology proposed in section 2.2.6, the results for the assessment of the 7th principle, which analyzes the renewability of used feedstocks, follow (Table 3.18):

Table 3.18. Principle 7 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Total Feedstock	Integrated Feedstock

	(Equation 2.51)	(Equation 2.52,Figure 2.25)
Full Conventional	0.0173	0.99
Full Greener	0.0000	1.00
Full Conventional (with recirculation)	0.0173	0.99
Full Greener (with recirculation)	0.0000	1.00

*Data used for the determination of the Total Feedstock present in Annexes 17 and 18

From Table 3.18 it can be seen that both processes have similar values for the Integrated Feedstock (0.99 for the conventional process and 1.00 for the "greener" process). This due to the only "critical" substance being sulphuric acid, which is only used in small amounts and only for the conventional process.

Principle 8

Following the methodology proposed in section 2.2.7, the results for the assessment of the 8th principle, which analyzes the usage of derivatives, follow (Table 3.19):

Table 3.19. Principle 8 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Derivatives (kg/kg of product) (Equation 2.54)	Integrated Derivatives (Equation 2.56, Figure 2.27)
Full Conventional	0.0000	1.00
Full Greener	0.0000	1.00
Full Conventional (with recirculation)	0.0000	1.00
Full Greener (with recirculation)	0.0000	1.00

As can be seen from Table 3.19, none of the simulated processes require derivatives and, as a result, the integrated value for this principle is 1 (the best case scenario).

Principle 9

Following the methodology proposed in section 2.2.8, the results for the assessment of the 9th principle, which analyses the use of catalysts, are presented in Table 3.20:

Table 3.20. Principle 9 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Catalyst Usage	Reaction yield (%)	Integrated Catalyst Usage (Table 2.29)
Full Conventional	Not Used	77.00	0.00
Full Greener	Not Used	77.00	0.00
Full Conventional (with recirculation)	Not Used	90.00	0.00
Full Greener (with recirculation)	Not Used	90.00	0.00

From Table 3.20 it can be seen that the integrated value for the 9th principle is 0.00 in all of the scenarios due to no catalyst being used while not having a yield of 100%.

Principle 10

Following the methodology proposed in section 2.2.9, the results for the assessment of the 10th principle, which analyzes the biodegradability of the product, are presented in Table 3.21:

Table 3.21. Principle 10 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Half-life (days)	Normalized Half-life (Equation 2.62)	Half-life Index (Equation 2.61, Figure 2.29)
Full Conventional	0.1642 [184]	0.0027	0.99
Full Greener	0.1642 [184]	0.0027	0.99
Full Conventional (with recirculation)	0.1642 [184]	0.0027	0.99
Full Greener (with recirculation)	0.1642 [184]	0.0027	0.99

As can be seen from Table 3.21, the obtained results for the Half-life index of any of the simulated processes is of 0.99. This is due to regardless of the chosen process the obtained product being the same (benzoic hydrazide, which has a half-life of 0.1642 days [184]).

Principle 11

Following the methodology proposed in section 2.2.4, the results for the assessment of the 11th principle, which analyses the safety of the process, are as follows (Table 3.22):

Table 3.22. Principle 11 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Process Hazard Index (Equation 2.31)	Normalized Process Hazard (Equation 2.33)	Integrated Process Hazard (Equation 2.32, Figure 2.22
Full Conventional	3.0000	0.1875	0.95
Full Greener	3.0000	0.1875	0.95
Full Conventional (with recirculation)	3.0000	0.1875	0.95
Full Greener (with recirculation)	3.0000	0.1875	0.95

*Data used for the determination of the Process Hazard Index present in Annex 19

From Table 3.22, it can be seen that the Integrated Process Hazard for the any of the processes is the same (0.95). This is due to the 11th principle dealing only with the product, which in this case study is the same (benzoic hydrazide) regardless of the chosen process. The chosen method to determine the Process Hazard Index was using the GHS hazard warnings [163] as they are more commonly found in the European Union than the NFPA fire diamond (Section 1.8, Figure 1.4 [145] [146]).

Principle 12

Following the methodology proposed in section 2.2.10, the results for the assessment of the 12th principle, which analyses the risk of chemical accidents, are presented in Table 3.23:

Table 3.23. Principle 12 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Accident	Normalized	Integrated

	Prevention Index (Equation 2.65)	Accident Prevention (Equation 2.69)	Accident Prevention (Equation 2.68, Figure 2.30)
Full Conventional	3.4444	0.5741	0.36
Full Greener	4.0000	0.6667	0.21
Full Conventional (with recirculation)	3.4444	0.5741	0.36
Full Greener (with recirculation)	4.0000	0.6667	0.21

*Data used for the determination of the Accident Prevention Index present in Annexes 20, 21, 22 and 23

As can be seen in Table 3.23, the Integrated Accident Prevention is lower for the "greener" processes when compared with the conventional process (0.21 vs 0.36, respectively). This means that the coventional process has a lower risk of chemical accidents than the "greener" process, despite its other shortcomings (for example, more generated waste and toxicity).

Principle 13

Following the methodology proposed in section 2.2.11, the results for the assessment of the proposed 13th principle, which analyzes the Carbon Efficiency of the process, are presented in Table 3.24:

Table 3.24. Principle 13 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Carbon Efficiency (%) (Equation 2.70)	Normalized Carbon Efficiency (Equation 2.73)	Integrated Carbon Efficiency (Equation 2.74, Figure 2.34)
Conventional	77.80	0.6735	0.73
Greener	100.00	1.0000	1.00
Full Conventional	77.78	0.6732	0.73
Full Greener	100.00	1.0000	1.00
Full Conventional (with recirculation)	77.78	0.6732	0.73
Full Greener (with recirculation)	100.00	1.0000	1.00

From Table 3.24 it can be seen that the Carbon Efficiency for the simulated process is aproximately the same as the values in the reference ([27]). This allows the conclusion that the assumed chemical reactions during the simulated processes are, in terms of carbon chemistry, close to what happened according to the reference ([27]). The small difference of 0.02% for the Carbon Efficiency of the conventional process (simulated vs reference [27]) can be explained due to the number of significant decimal places considered (if only one decimal place is considered significant no diference exists in obtained values).

Overall, the "greener" process can be concluded to be superior in terms of carbon chemistry as it has an integrated value of 1.000 when compared with the conventional process, which has an integrated value of 0.73

Principle 14

Following the methodology proposed in section 2.2.12, the results for the assessment of the proposed 14th principle, which analyses the reaction mass efficiency of the process, follow (Table 3.25):

Table 3.25. Principle 14 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Curzons Reaction Mass Efficiency (%) (Equation 2.75)	Normalized Reaction Mass Efficiency (Equation 2.78)	Integrated Reaction Mass Efficiency (Equation 2.77, Figure 2.38)
Conventional	16.00	0.0000	0.00
Greener	69.20	0.5781	0.86
Full Conventional	16.53	0.0000	0.00
Full Greener	67.26	0.5515	0.81
Full Conventional (with recirculation)	16.53	0.0000	0.00
Full Greener (with recirculation)	67.26	0.5515	0.81

From Table 3.25 it can be seen that the Curzons Reaction Mass Efficiency for the simulated process is aproximately the same as the values in the reference ([27]). This allows the conclusion that the assumed chemical reactions during the simulated processes are, in terms of mass, close to what happened according to the reference ([27]). As the Curzons Reaction Mass Efficiency depends only on the desired product and used reagents (both well described in the reference ([27])), the difference of 0.53% for the Curzons Reaction Mass Efficiency of the conventional process (simulated vs reference [27]) and of 1.94% for the Reaction Mass Efficiency of the "greener" process is most likely due to approximations on the molar weight of the used reagents and product .

Overall, the "greener" process can be concluded to be superior in terms of reaction mass efficiency as it has an integrated value of 0.86 (when using the reference data [27]) or 0.81 (when using simulated data) when compared with the conventional process, which has an integrated value of 0.00.

Principle 15

Following the methodology proposed in section 2.2.13, the results for the assessment of the proposed 15th principle, which analyses the mass productivity of the process, are presented in Table 3.26:

Table 3.26. Principle 15 results for the synthesis of benzoic hydrazide

Process (Table 3.1)	Mass Productivity (%) (Equation 2.80)	Normalized Mass Productivity (Equation 2.83)	Integrated Mass Productivity (Equation 2.82, Figure 2.42)
Full Conventional	8.01	0.0565	0.70
Full Greener	67.26	0.6642	1.00
Full Conventional (with recirculation)	8.01	0.0565	0.70
Full Greener (with recirculation)	67.26	0.6642	1.00

From Table 3.26, it is possible to conclude that the Mass Productivity of the "greener" process is much higher than the Mass Productivity of the conventional proces (67.26% vs 8.01%, respectively). This large difference, however, only translates into a difference of 0.30 in the integrated value (1.00 vs 0.70, respectively). This result is to be expected as the conventional process, despite its much lower Mass Productivity, is already above the average Mass Productivity of the studied process types (see section 2.2.13, Table 2.46) resulting in it being considered "greener than most".

Green Index

Following the methodology proposed in section 2.2.14, the summary results for the integrated value of each principle follow (Table 3.27, Figure 3.1 and Figure 3.2):

Table 3.27. Summary results for the assessment of each principle for the synthesis of benzoic hydrazide

Process (Table 3.1)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
Conventional	0.54	0.00	-	-	-	0.22	-	-	-	-	-	-	0.73	0.00	-
Greener	0.96	0.35	-	-	-	1.00	-	-	-	-	-	-	1.00	0.86	-
Full Conventional	0.21	0.00	0.28	0.27	0.74	0.22	0.99	1.00	0.00	0.99	0.95	0.36	0.73	0.00	0.70
Full Greener	0.97	0.35	0.72	0.76	1.00	1.00	1.00	1.00	0.00	0.99	0.95	0.21	1.00	0.81	1.00
Full Conventional (with recirculation)	0.38	0.00	0.28	0.27	0.74	0.22	0.99	1.00	0.00	0.99	0.95	0.36	0.73	0.00	0.70
Full Greener (with recirculation)	1.00	0.35	0.72	0.76	1.00	1.00	1.00	1.00	0.00	0.99	0.95	0.21	1.00	0.81	1.00

*P1 to P15 represent principles 1 to 15
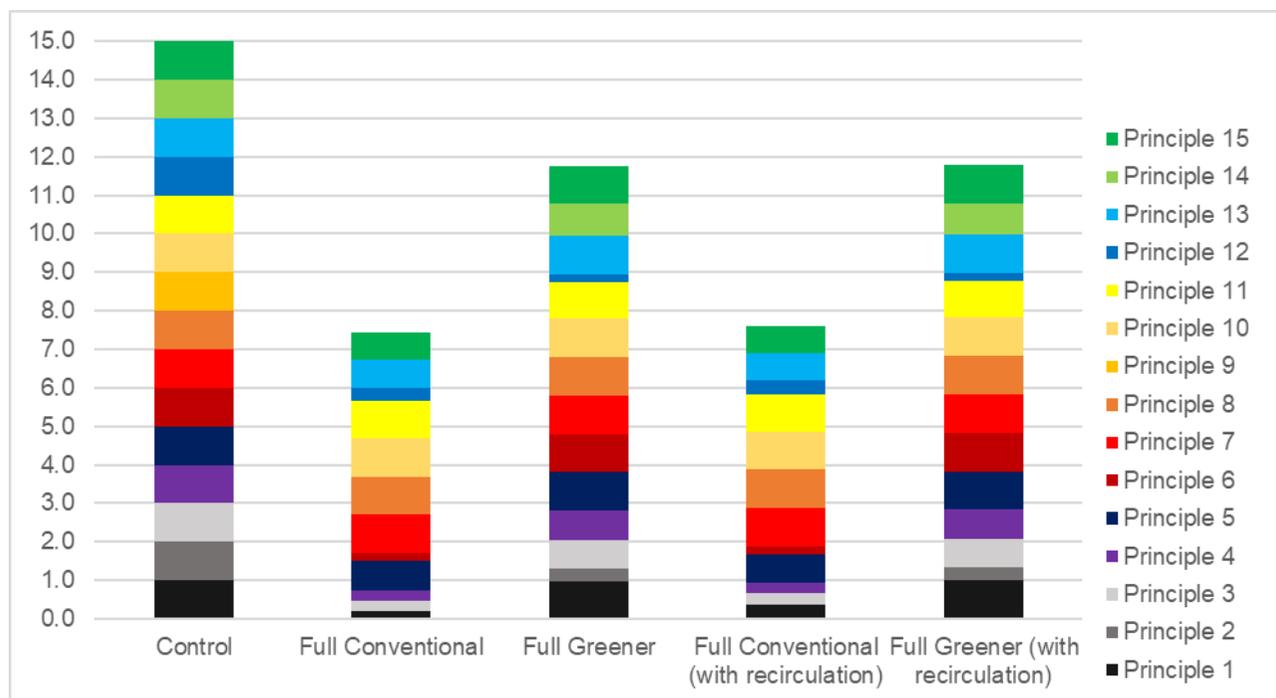
Figure 3.1. Summary results for the assessment of each principle for the synthesis of benzoic hydrazide
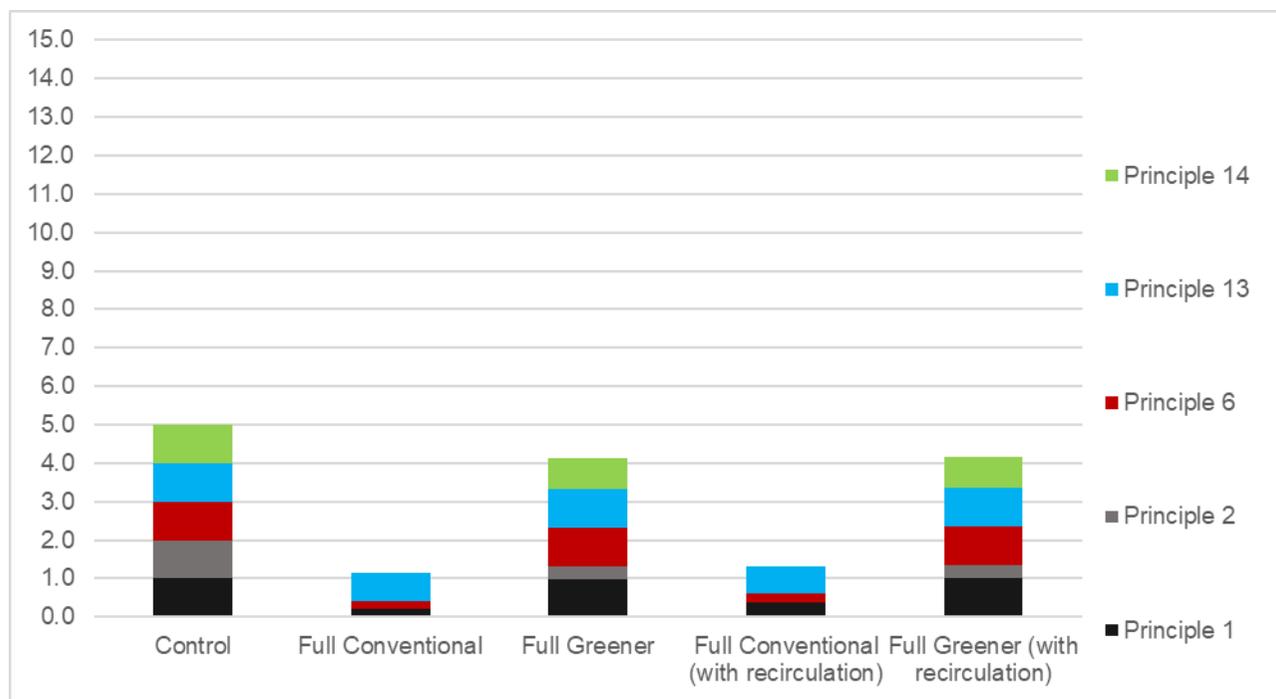
Figure 3.2. Summary results for the assessment of principles 1, 2, 6, 13 and 14 for the synthesis of benzoic hydrazide

With the data from Table 3.27, the Green Index (Equation 2.85) for each of the processes can be determined. First, in order to allow a direct comparison between the results described in the reference ([27]) and the simulated results the Green Index will be calculated using only principles 1, 2, 6, 13 and 14 (Table 3.28).

Table 3.28. Green Index comparison using only principles 1, 2, 6, 13 and 14

Process (Table 3.1)	Green Index (Equation 2.85)
Conventional	1.48
Greener	4.17
Full Conventional	1.16
Full Greener	4.13
Full Conventional (with recirculation)	1.32
Full Greener (with recirculation)	4.16

From Table 3.28, it can be seen that the Green Index of the "greener" process using the results on the reference ([27]), or simulating the whole process using its data is aproximately the same (4.17 vs 4.16, respectively). This means that the assumptions made in terms of reactions are closer to reality, as described in the reference ([27]). On the other hand, the results for the conventional process vary between the reference value (1.48), the simulated value without recirculation (1.16, a difference of 0.32 in a scale from 0 to 5, as only 5 principles are being assessed) and the simulated value with recirculation (1.32, a difference of 0.16 in a scale from 0 to 5, as only 5 principles are being assessed). As the simulated values assuming the possibility of recirculating some currents are closer to the reference values, they will be considered closer to the reality of the study [27] and used in further comparisons.

Next, a comparison between the conventional process results as described in the reference ([27]) and the results obtained by simulating the process with recirculation will be carried out (Table 3.29):

Table 3.29. Green Index comparison between the Conventional process using only principles 1, 2, 6, 13 and 14 and using all principles

Process (Table 3.1)	Green Index (Equation 2.85)
Conventional*	4.44*
Full Conventional (with recirculation)	7.61

*The Green Index for the Conventional process is calculated using only principles 1, 2, 6, 13 and 14 using the results in the reference (varying between 0 and 5) and normalized to a value between 0 and 15 to allow for comparison with the Full Conventional process ([27]).

From Table 3.29 it can be seen that by using all principles for the assessment, the Conventional process' Green Index increases from 4.44 to 7.61, which also results in an increase for the proposed scale from a Poor process to an Average process. This result shows that the Conventional process is, according to the proposed Green Chemistry Grid, better (7.61, an Average process) than it would first seem using only a few of the principles (4.44, a Poor process) for the assessment. These results can be explained by it being a relatively safe process (although special

cares to avoid hazards are required) which, although wasteful, generates and uses small amounts of dangerous pollutants (Table 3.27).

Following this same line of thought for the "greener" processes (Table 3.30):

Table 3.30. Green Index comparison between the Greener process using only principles 1, 2, 6, 13 and 14 and using all principles

Process (Table 3.1)	Green Index (Equation 2.85)
Greener*	12.51*
Full Greener (with recirculation)	11.80

*The Green Index for the Greener process is calculated using only principles 1, 2, 6, 13 and 14 using the results in the reference (varying between 0 and 5) and normalized to a value between 0 and 15 to allow for comparison with the Full Greener process ([27]).

From Table 3.30 it can be seen that by using all principles for the assessment, the "greener" process' Green Index decreases from 12.51 (a Green process according to the proposed Green Index classifications in section 2.2.14) to 11.80 (a Satisfactory process). This result shows that the "greener" process is, according to the proposed Green Chemistry Grid, approximately as good when assessed using only principles 1, 2, 6, 13 and 14 or all of them, but reducing it's category in the proposed Green Index from Green process to a Satisfactory process. These results can be explained by it being a quick process with no generated waste, with the downside of having a low atom economy and needing special cares to avoid hazards (Table 3.27).

Lastly, the comparison between the conventional method and the greener method can be carried out:

Table 3.31. Green Index comparison between the Conventional and Greener processes using only principles 1, 2, 6, 13 and 14 and using all principles

Process (Table 3.1)	Green Index (Equation 2.85)
Conventional*	4.44*
Full Conventional (with recirculation)	7.61
Greener*	12.51*
Full Greener (with recirculation)	11.80

*The Green Index for the Conventional and Greener processs is calculated using only principles 1, 2, 6, 13 and 14 using the results in the reference (varying between 0 and 5) and normalized to a value between 0 and 15 to allow for comparison with the Full processes ([27]).

From the results presented in Table 3.31, the "greener" process can be seen to be vastly superior to the conventional process when using the results provided in the reference ([27]) (12.51, a Green process vs 4.44, a Poor process). These results are as expected, as the reference described the "greener" process as being vastly superior.

The difference between the obtained results however, isn't as large when considering all principles instead of only a few (11.80, a Satisfactory process vs 7.61, an Average process; respectively). This difference can be explained due to the conventional process being relatively safe, which is something not assessed in the reference ([27]).

These results also allow the conclusion that, according to the proposed Green Chemistry Grid, all of the assessed processes had a different classification according to the proposed Green Index classification (Section 2.2.14, Table 2.50):

- the Conventional process using only the data described in the reference is a Poor process (Green Index between 3.00 and 6.00);
- the Full Conventional process with recirculation is considered an Average process (Green Index between 6.00 and 9.00);
- the Full Greener process with recirculation is considered a Satisfactory process (Green Index between 9.00 and 12.00);
- the Greener process using only the data described in the reference is a Green process (Green Index between 12.00 and 15.00)

3.2. Case study: Synthesis of an anionic polyacrylamide copolymer

In the previous section (Section 3.1), the Green Chemistry grid was tested using two different synthesis methods for a fine chemical (benzoic hydrazide). In order to further test the grid, another case study will be conducted, this time for the synthesis of polyacrylamide copolymers from two different methods. These two methods are the "Copolymerization" method, through which the anionic polyacrylamide is produced from a copolymerization of sodium acrylate (which in turn is synthesised from acrylica acid) with acrylamide [185]; in the other method, "Hydrolysis", the anionic polyacrylamide copolymer is produced from the hydrolysis of polyacrylamide (synthesised from polymerization of acrylamide) [186]:

Table 3.32. Assessed methods for the synthesis of anionic polyacrylamide copolymer

Method	Description
Copolymerization	Simulated method using the data present in reference [185]
Hydrolysis	Simulated method using the data present in reference [186]

All of the assessed methods are described in further detail in the references ([185] and [186]).

3.2.1. Variable definition

To carry out the assessment the lists of process inputs, reagents, auxiliary susbtances, desired products and generated waste are presented summarised in this section.

For the "Copolymerization" process, the mass inputs are composed of acrylic acid (0.00231 kg), sodium carbonate (0.00753 kg), acrylamide (0.00200 kg), ammonium persulfate (0.00020 kg) sodium sulfite (0.00020 kg), nitrogen (0.00011), ethanol (0.24218 kg) and water (0.09433) (Table 3.33). This represents a total mass input of 0.34885 kg, where ethanol and water are aproximately 96% of those inputs.

Table 3.33. Copolymerization process mass inputs

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Acrylic Acid	0.0320	0.0721	0.00231
Sodium Carbonate	0.0711	0.1060	0.00753
Acrylamide	0.0281	0.0711	0.00200
Ammonium Persulfate	0.0009	0.2282	0.00020
Sodium Sulfite	0.0016	0.1260	0.00020
Nitrogen	0.0038	0.0280	0.00011
Ethanol	5.2727	0.0461	0.24218
Water	5.2407	0.018	0.09433
Total			0.34885

Of the mass inputs in Table 3.33, acrylic acid, sodium carbonate and acrylamide are used as reagents in the process, for a total of 0.01184 kg (Table 3.34). This is approximately 3% of the mass inputs in Table 3.33.

Table 3.34. Copolymerization process reagents

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Acrylic Acid	0.0320	0.0721	0.00231
Sodium Carbonate	0.0711	0.1060	0.00753
Acrylamide	0.0281	0.0711	0.00200
Total			0.01184

The auxiliary substances used in the "Copolymerization" process are ammonium persulfate, sodium sulphite, nitrogen, ethanol and sodium acrylate (an intermediate product) (Table 3.35), for a total of 0.24672 kg. For the most part, this value is due to the used ethanol (0.24218 kg).

Table 3.35. Copolymerization process auxiliary substances

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Ammonium Persulfate	0.0009	0.2282	0.00020
Sodium Sulfite	0.0016	0.1260	0.00020
Nitrogen	0.0038	0.0280	0.00011
Ethanol	5.2567	0.0461	0.24218
Sodium Acrylate	0.0320	0.1260	0.00403
Total			0.24672

The desired product of the "Copolymerization" process is Poly (acrylamide-co-acrylic acid) of which 0.00279 kg are obtained when carrying out the operation as described in the reference [185] (Table 3.36):

Table 3.36. Copolymerization process desired product

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)

| Poly (acrylamide-co-acrylic acid) | N.A.* | N.A.* | 0.00279 |

*Both the number of mole and the molar weight of the Poly (acrylamide-co-acrylic acid) depend on the percentage of acrylamide/acrylic acid the chain length of the polymer.

Lastly, after carrying out the process the generated waste assuming that none of the output currents could be reused (as it would required further steps) is represented in Table 3.37.

Table 3.37. Copolymerization process generated waste

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Carbon Dioxide	0.0160	0.0440	0.00070
Nitrogen	0.0038	0.0280	0.00011
Ethanol	5.2567	0.0461	0.24218
Water	5.2567	0.0180	0.09462
Sodium Acrylate	0.0236	0.0940	0.00222
Ammonium Persulfate	0.0009	0.2282	0.00020
Sodium Sulfite	0.0016	0.1260	0.00020
Total			0.34022

For the "Hydrolysis" process the mass inputs are composed by acrylamide (0.07108 kg), sodium hydroxide (0.02132 kg), ammonium persulfate (0.00711 kg), sodium metabisulfite (0.00711 kg), 2-propanol (0.00359), nitrogen (0.00184 kg) and water (1.42081 kg), representing a total of 1.53285 kg of mass inputs (Table 3.38). This value is mostly due to the used water (approximately 93% of the mass inputs).

Table 3.38. Hydrolysis process mass inputs

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Acrylamide	1.0000	0.0711	0.07108
Sodium Hydroxide	0.5332	0.0400	0.02132
Ammonium persulfate	0.0312	0.2282	0.00711
Sodium metabisulfite	0.0374	0.1901	0.00711
2-propanol	0.0597	0.0601	0.00359
Nitrogen	0.0655	0.0280	0.00184
Water	78.9339	0.0180	1.42081
Total			1.53285

Of the inputs in Table 3.38, acrylamide and sodium hydroxide are used as reagents in the "Hydrolysis" process (Table 3.39) for a total of 0.09240 kg. This is approximately 6% of the mass inputs into the process (Table 3.38).

Table 3.39. Hydrolysis process reagents

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Acrylamide	1.0000	0.0711	0.07108
Sodium Hydroxide	0.5332	0.0400	0.02132
Total		0.1111	0.09240

The auxiliary substances used in the "Hydrolysis" process are ammonium persulfate, sodium metabisulfite, 2-propanol, nitrogen and polyacrylamide (an intermediate product) (Table 3.40).

Table 3.40. Hydrolysis process auxiliary substances

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Ammonium persulfate	0.0312	0.2282	0.00711
Sodium metabisulfite	0.0374	0.1901	0.00711
2-propanol	0.0597	0.0601	0.00359
Nitrogen	0.0655	0.0280	0.00184
Polyacrylamide	N.A.*	N.A.*	0.07108
			0.09072

*Both the number of mol and the molar weight of the Polyacrylamide depend on the chain length of the polymer.

The desired product of this process is Poly(acrylamide-co-acrylic acid), which is obtained in the amount of 0.0833 kg when following the process described in the reference [186] (Table 3.41):

Table 3.41. Hydrolysis process desired products

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Poly (acrylamide-co-acrylic acid)	N.A.*	N.A.*	0.08332

*Both the number of mole and the molar weight of the Poly (acrylamide-co-acrylic acid) depend on the percentage of acrylamide/acrylic acid the chain length of the polymer.

Lastly, after carrying out the process the generated waste assuming that none of the output currents could be reused (as it would required further steps) is represented in Table 3.42:

Table 3.42. Hydrolysis process generated waste

Substance	Mole (mol)	Molar weight (kg/mol)	Mass (kg)
Ammonium persulfate	0.2282	0.2282	0.05207
Sodium metabisulfite	0.1901	0.1901	0.03614
2-propanol	0.0601	0.0601	0.00361
Ammonia	0.0091	0.0170	0.00015
Nitrogen	0.0655	0.0280	0.00184
Water	89.5900	0.0180	1.61262
Total			1.70643

3.2.2. Greeness assessment

Principle 1

Following the methodology proposed in section 2.2.1, the results for the first principle, which analyzes generated waste, are as follows in Table 3.43:

Table 3.43. Principle 1 results for the synthesis of an anionic polyacrylamide copolymer

Process (Table 3.32)	E-factor (Kg of waste/Kg of product) (Equation 2.2)	Product type	Integrated 1st principle (Equation 2.5, Figure 2.6)
Copolymerization	121.78	Bulk chemical	0.00
Hydrolysis	20.48	Bulk chemical	0.00

The obtained results (Table 3.43) show that both processes generate large amounts of waste (121.78 kg of waste/kg of product for the "Copolymerization" process and 20.48 kg of waste/kg of product for the "Hydrolysis" process). This leads to an integrated value for the 1st principle of 0.00 for both process as, although the "Copolymerization" process generates much more waste when compared with the "Hydrolysis" process (121.78 vs 20.48, respectively), they both generate unaceptable amounts of waste when compared with the industrial average values (see section 2.2.1).

Principle 2

Following the methodology proposed in section 2.2.2, the results for the assessment of the 2nd principle, which analyzes the Atom Economy of the chemical reactions, are presented in Table 3.44:

Table 3.44. Principle 2 results for the synthesis of an anionic polyacrylamide copolymer

Process (Table 3.32)	Atom Economy (%) (Equation 2.8)	Normalized Atom Economy (Equation 2.12, Table 2.5)	Integrated 2nd principle (Equation 2.14, Figure 2.16)
Copolymerization	75.21	0.3113	0.21
Hydrolysis	84.70	0.5750	0.58

From Table 3.44 it can be seen that the integrated value for the 2nd principle is higher for the "Hydrolysis" process when compared with the "Copolymerization" process (0.58 vs 0.21, respectively) due to its higher Atom Economy (84.70 % vs 75.21 %, respectively).

Principle 3

Following the methodology proposed in section 2.2.3, the results for the assessment of the 3rd principle, which analyzes the toxicity of used auxiliary substances, are as follows (Table 3.45):

Table 3.45. Principle 3 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Human Tolerability Index (Equation 2.20, Figure 2.18)	Environmental Toxicity Index (Equation 2.25)	Hazard Index (Equation 2.15)
Copolymerization	0.5386	0.8836	0.71
Hydrolysis	0.5562	0.7248	0.64

*Data used for the determination of the Human Tolerability Index and Environmetal Toxicity Index present in Annexes 24, 25, 26, 27, 28 and 29

The results in Table 3.45 show that the Hazard Index is higher for the "Copolymerization" process (0.71 vs 0.64). When analyzing the Human Toxicty Index and the Environmental Toxicity Index of both processes, it can be seen that the Human Tolerability Index is similar for both (0.5386 for the "Copolymerization" process vs 0.5562 for the "Hydrolysis" process) while the Environmental Toxicity Index is higher for the "Hydrolysis" process (0.8836 vs 0.7248 for the "Copolymerization" process). This is the result of a large part of the "Copolymerizaztion process" outputs being Ethanol (Table 3.37) which has a low environmental impact when compared with other substances.

Principle 4

Following the methodology proposed in section 2.2.3, the results for the assessment of the 4th principle, which analyzes the toxicity of the desired product, are shown in Table 3.46:

Table 3.46. Principle 4 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Human Tolerability Index (Equation 2.20, Figure 2.18)	Environmental Toxicity Index (Equation 2.25)	Hazard Index (Equation 2.15)
Copolymerization	0.8867	0.5656	0.73
Hydrolysis	0.8867	0.5656	0.73

*Data used for the determination of the Human Tolerability Index and Environmental Toxicity Index present in Annexes 30, 31, 32, 33, 34 and 35

From Table 3.46 it can be seen that the both processes have the same Hazard Index (0.73). This is as expected, due to the desired product and the exposure time to it being the same for both processes.

Principle 5

Following the methodology proposed in section 2.2.4, the results for the assessment of the 5th principle, which assesses the hazard of used auxiliary substances, are as follows (Table 3.47):

Table 3.47. Principle 5 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Process Hazard Index (Equation 2.31)	Normalized Process Hazard (Equation 2.33)	Integrated Process Hazard (Equation 2.32, Figure 2.22)
Copolymerization	4.9946	0.3122	0.82
Hydrolysis	3.5996	0.2250	0.92

*Data used for the determination of the Process Hazard Index present in Annexes 36 and 37

From Table 3.47, it can be seen that the Integrated Process Hazard for the "Copolymerization" process is lower than that of the "Hydrolysis" process. This result is due to the use of large amounts of ethanol in the "Copolymerization" process (Table 3.35) which has a high risk of fire and effects on human health [187]. These results were obtained by using the GHS hazard warnings [163] due to these warnings being more common in the European Union when compared with the NFPA hazard warnings (Section 1.8, Figure 1.4 [145] [146]).

Principle 6

Following the methodology proposed in section 2.2.5, the results for the assessment of the 6th principle, which assesses the energetic costs of the process, are presented in Table 3.48:

Table 3.48. Principle 6 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Economic Cost Index (Equation 2.38, Figure 2.23)	Environmental Cost Index (Equation 2.41, Figure 2.24)	Energy Index (Equation 2.43)
Copolymerization	0.2548	0.2500	0.25
Hydrolysis	0.5048	0.5000	0.50

*Data used for the determination of the Economic Cost Index and Environmental Cost Index present in Annexes 38 and 39

From Table 3.48 it is possible to conclude that the "Copolymerization" process is, according to the 6th principle, inferior to the "Hydrolysis" process (0.25 vs 0.50 Energy Index, respectively). These results are as expected because, due to lack of information, the only difference between both processes was the required energy, which was assumed to be the median value for the least energy intensive process (Hydrolysis) and then doubled for the "Copolymerization" process due to it requiring the same temperature for double the time in the most time-consuming step.

Principle 7

Following the methodology proposed in section 2.2.6, the results for the assessment of the 7th principle, which analyzes the renewability of used feedstocks, follow (Table 3.49):

Table 3.49. Principle 7 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Total Feedstock (Equation 2.51)	Integrated Feedstock (Equation 2.52, Figure 2.25)
Copolymerization	0.0018	1.00
Hydrolysis	0.1445	0.90

*Data used for the determination of the Total Feedstock present in Annexes 40 and 41

From Table 3.49 it can be seen that the "Copolymerization" process is, according to the 7th principle, superior to the "Hydrolysis" process (1.00 vs 0.90, respectively). These results are due to the use of sulphur (a critical raw material) based substances in substancial quantities used in the Hydrolysis process.

Principle 8

Following the methodology proposed in section 2.2.7, the results for the assessment of the 8th principle, which analyzes the usage of derivatives, follow (Table 3.50):

Table 3.50. Principle 8 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Derivatives (kg/kg of product) (Equation 2.54)	Integrated Derivatives (Equation 2.56, Figure 2.27)
Copolymerization	0.0000	1.00
Hydrolysis	0.0000	1.00

As neither process requires the use of derivatives, the results shown in Table 3.50 are as expected, with an Integrated value of 1.00 for this principle (best case scenario).

Principle 9

Following the methodology proposed in section 2.2.8, the results for the assessment of the 9th principle, which analyses the use of catalysts, are presented in Table 3.51:

Table 3.51. Principle 9 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Catalyst	Reaction yield (%)	Integrated Catalyst

	Usage		Usage (Table 2.29)
Copolymerization	Used	100.00	1.00
Hydrolysis	Used	100.00	1.00

From Table 3.51 it can been that the integrated value for the 9th principle is 1.00 for both processes. This is due not only the use of catalysts but also to the reaction yield of 100% in both cases.

Principle 10

Following the methodology proposed in section 2.2.9, the results for the assessment of the 10th principle, which analyzes the biodegradability of the product, are presented in Table 3.52:

Table 3.52. Principle 10 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Half-life (days)	Normalized Half-life (Equation 2.62)	Half-life Index (Equation 2.61, Figure 2.29)
Copolymerization	2400 [188]	40.00	0.00
Hydrolysis	2400 [188]	40.00	0.00

As can be seen from Table 3.52, the obtained Half-life Index for both processes is of 0.00. This is a result of both processes having the same desired product and of the Half-life of anionic polyacrylamide being estimated at about 2400 days [188], far above the proposed limits in section 2.2.9.

Principle 11

Following the methodology proposed in section 2.2.4, the results for the assessment of the 11th principle, which analyses the safety of the process, are as follows (Table 3.53):

Table 3.53. Principle 11 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Process Hazard Index (Equation 2.31)	Normalized Process Hazard(Equation 2.33)	Integrated Process Hazard (Equation 2.32, Figure 2.22)
Copolymerization	0.0000	0.0000	1.00
Hydrolysis	0.0000	0.0000	1.00

*Data used for the determination of the Process Hazard Index present in Annex 42

From Table 3.53, it can be seen that the Integrated Process Hazard for the both processes is the same (1.00). This is due to the 11th principle dealing only with the product, which in this case study is the same for both assessed processes. The chosen method to determine the Process Hazard Index was using the GHS hazard warnings [163] as they are more commonly found in the European Union than the NFPA fire diamond (Section 1.8, Figure 1.4 [145] [146]).

Principle 12

Following the methodology proposed in section 2.2.10, the results for the assessment of the 12th principle, which analyses the risk of chemical accidents, are presented in Table 3.54:

Table 3.54. Principle 12 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Accident Prevention Index (Equation 2.65)	Normalized Accident Prevention (Equation 2.69)	Integrated Accident Prevention (Equation 2.68, Figure 2.30)
Copolymerization	2.5000	0.4167	0.65
Hydrolysis	2.5000	0.4167	0.65

*Data used for the determination of the Accident Prevention Index present in Annexes 43, 44, 45 and 46

As can be seen in Table 3.54, the Integrated Accident Prevention is the same for both processes. This is due to both processes using substances that, although different, have similar characteristics in terms of safety in a chemical process.

Principle 13

Following the methodology proposed in section 2.2.11, the results for the assessment of the proposed 13th principle, which analyzes the Carbon Efficiency of the process, are presented in Table 3.55:

Table 3.55. Principle 13 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Carbon Efficiency (%) (Equation 2.70)	Normalized Carbon Efficiency (Equation 2.73)	Integrated Carbon Efficiency (Equation 2.74, Figure 2.34)
Copolymerization	75.00	0.6324	0.6697
Hydrolysis	100.00	1.0000	1.0000

From Table 3.55 it can be seen that the Carbon Efficiency for the "Copolymerization" process is lower than that of the "Hydrolysis" process (75% vs 100%, respectively) This difference is explained by the formation of carbon dioxide during the "Copolymerization" reactions. As a result, the "Hydrolysis" process is considered, acording to the proposed 13th principle, greener than the "Copolymerization" process.

Principle 14

Following the methodology proposed in section 2.2.12, the results for the assessment of the proposed 14th principle, which analyses the reaction mass efficiency of the process, follow (Table 3.56):

Table 3.56. Principle 14 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Curzons Reaction Mass Efficiency (%) (Equation 2.75)	Normalized Reaction Mass Efficiency (Equation 2.78)	Integrated Reaction Mass Efficiency (Equation 2.77, Figure 2.38)
Copolymerization	23.60	0.0000	0.00

| Hydrolysis | 90.17 | 0.8654 | 1.00 |

From Table 3.56 it can be seen that the Curzons Reaction Mass Efficiency of the "Copolymerization" process is much lower than that of the "Hydrolysis" process (23.60% vs 90.17%, respectively). This difference results in the integrated value varying between the lowest possible value (0.00, for the "Copolymerization" process) and the highest possible value (1.00, for "Hydrolysis" process). These results are as expected due to the "Copolymerization" process being carried out with excess amounts of acrylic acid and sodium carbonate, which, unlike the Atom Economy, is assessed in the Curzons Reaction Mass Efficiency.

Overall, the "Hydrolysis" process is considered to be, according to the proposed 14th principle, greener than the "Copolymerization" process.

Principle 15

Following the methodology proposed in section 2.2.13, the results for the assessment of the proposed 15th principle, which analyses the mass productivity of the process, are presented in Table 3.57:

Table 3.57. Principle 15 results for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	Mass Productivity (%) (Equation 2.80)	Normalized Mass Productivity (Equation 2.83)	Integrated Mass Productivity (Equation 2.82, Figure 2.42)
Copolymerization	0.80%	0.0000	0.00
Hydrolysis	5.44%	0.0302	0.36

From Table 3.57, it is possible to conclude that the Mass Productivity of the "Copolymerization" process is lower than the Mass Productivity of the "Hydrolysis" process (0.80% vs 5.44%, respectively). This difference result in an integrated value for the principle of 0.00 for the "Copolymerization" process and of 0.36 for the "Hydrolysis" process.

These low values are as expected due to the large amounts of solvents used for both processes (over 90% of the inputs are solvents), with the "Hydrolysis" process, which uses less solvents, being considered, according to the proposed 15th principle, greener.

Green Index

Following the methodology proposed in section 2.2.14, the summary results for the integrated value of each principle follow (Table 3.58 and Figure 3.3)

Table 3.58. Summary results for the assessment of each principle for the synthesis of anionic polyacrylamide copolymer

Process (Table 3.32)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
Copolymerization	0.00	0.21	0.71	0.73	0.82	0.25	1.00	1.00	1.00	0.00	1.00	0.65	0.67	0.00	0.00
Hydrolysis	0.00	0.58	0.64	0.73	0.92	0.50	0.90	1.00	1.00	0.00	1.00	0.65	1.00	1.00	0.36

*P1 to P15 represent principles 1 to 15
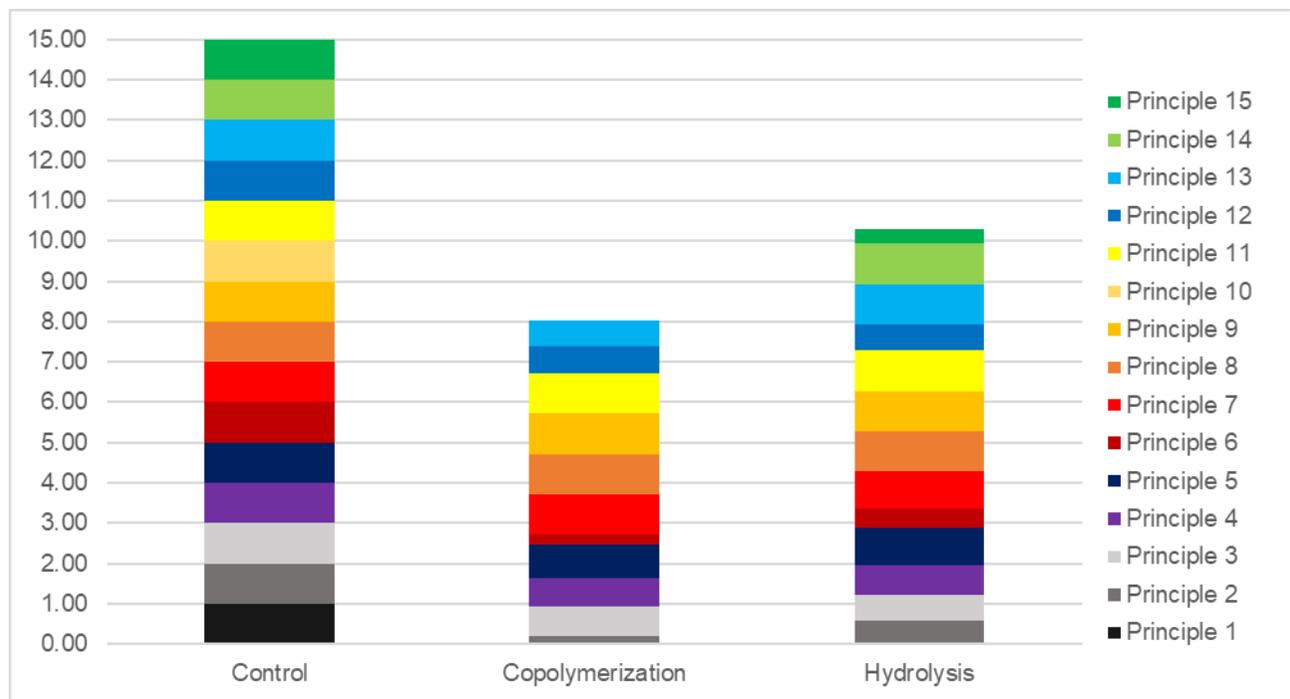
Figure 3.3. Summary results for the assessment of each principle for the synthesis of anionic polyacrylamide copolymer

With the data from Table 3.58, the Green Index (Equation 2.85) for each of the processes can be determined (Table 3.59).

Table 3.59. Green Index comparison

Process (Table 3.32)	Green Index (Equation 2.85)
Copolymerization	8.04
Hydrolysis	10.29

From Table 3.59 it can be seen that the Green Index of the "Copolymerization" process is inferior to the Green Index of the "Hydrolysis" process (8.04 vs 10.29, respectively). This means that, according to the proposed Green Chemistry grid's Green Index (Section 2.2.14, Table 2.50), the "Hydrolysis" process is considered a Satisfactory process (Green Index between 9.00 and 12.00) while the "Copolymerization" process is considered an Average process.

The results also show that, despite the large amounts of waste that both processes generate and causes them to have low scores on most waste based principles (for example, principle 1), they are relatively safe to both humans and the environment, "compensating" for that flaw.

4. Conclusion

A general method to assess the greenness of a process according to all the 12 principles of green chemistry at the same time has been sought after since they were initially proposed, as described in section 1. Most methods and metrics however, failed to account for all principles or used subjective words or expressions, resulting in "incomplete" assessments or giving a higher priority to certain principles.

It was in that optic that the Green Chemistry grid (section 0) was proposed, as a method capable of assessing the greenness of a process according to all principles without sacrificing objectivity. For this grid, and in order to give more detailed results, 3 additional principles were proposed and tested based on currently existing and commonly used green metrics (Carbon Efficiency, Curzons Reaction Mass Efficiency and Mass Productivity).

Based on the results obtained from the case studies in section 3, it is possible to conclude that the proposed Green Chemistry grid is working as intended, allowing a comparison between different processes in terms of greenness and also allowing comparisons inside the same process on how well it is doing according to each principle. As such, the proposed Green Chemistry grid shows itself as a potential alternative to the currently used methodologies.

It should be noted, however, that the proposed Green Chemistry grid is based on what is considered "green" or average in the chemical industry, at the time of writing. This is subject to change over time as, for example, the technologies evolve or the laws change, and as a consequence, a process that is considered "Green" today will become "Unsustainable" tomorrow. This means that the proposed Green Chemistry grid must take into account its dynamic nature, with its expressions updated over time, in order to always give the most detailed and relevant results.

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6. Annexes

Annex 1: MATLAB code example for the optimization of the 2nd principle

```matlab
function [Q1,Q2,Q3] = readP2

        cd '../'

        file = "Principle 2 Analysis Excel";

        sheetdata = "Atom Economy statistic analysis";

        rangedata = "F6:H6";

        [rawdata,~,~] = xlsread(file,sheetdata,rangedata); %reads the data in the excel related to the
data analysis sheet

        Q1=rawdata(1,1); %obtains lower quartile information

        Q2=rawdata(1,2); %obtains median information

        Q3=rawdata(1,3); %obtains upper quartile information

        cd 'Solver code'

end

function optimum = solveP2

        global Q1 Q2 Q3

        [Q1,Q2,Q3]=readP2; %read the quartiles values from the associated excel

        options=optimoptions('ga','FunctionTolerance',0,'MaxGenerations',3000,'PopulationSize',300,
'CrossoverFraction',0.3,'MaxStallGenerations',50,'EliteCount',5,'Display','iter');

        lb = [0,0]; %lower bounds for alfa and beta

        ub = [100,100]; %upper bounds for alfa and beta

        result = ga(@errbetafunc,2,[],[],[],[],lb,ub,[],options); %run genetic algorithm

        optimum = round(result,2); %round optimization to 2 decimal places

        fprintf('\n Alfa parameter estimation = %.2f',optimum(1)); %prints alfa

        fprintf('\n Beta parameter estimation = %.2f \n',optimum(2)); %prints beta

        function err = errbetafunc (param);
```

```
step = 1/2000; %step for each consecutive test value

x = [0:step:1]; %test values

err = 0; %initialize error

p = betacdf(x,param(1),param(2)); %test beta function

% Positions of the set values

Q1pos = round(Q1/step,0);

Q2pos = round(Q2/step,0);

Q3pos = round(Q3/step,0);

% Quadratic error of the test values

errQ1 = (p(Q1pos) - 0.25)^2; %0.25 predicted value for Q1

errQ2 = (p(Q2pos) - 0.50)^2; %0.5 predicted value for median

errQ3 = (p(Q3pos) - 0.75)^2; %0.75 predicted value for Q2

err = errQ1 + errQ2 + errQ3; %total quadratic error

    end

end
```

Annex 2: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Exposure level of substances in the Conventional process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Benzoic acid	1158819	1[a]	60[a]	10[b]	1931.36
Ethanol	4442749	1[a]	60[a]	10[b]	7404.58
Hydrazine hydrate	449377	1[a]	60[a]	10[b]	748.96
Ethyl benzoate	1225491	1[a]	60[a]	10[b]	2042.49
Carbon tetrachloride	6133250	1[a]	60[a]	10[b]	10222.08
Sulphuric acid	192869	1[a]	60[a]	10[b]	321.45
Sodium benzoate	191435	1[a]	60[a]	10[b]	319.06
Carbon dioxide	58467	1[a]	60[a]	10[b]	97.44
Sodium hydrogen carbonate	111602	1[a]	60[a]	10[b]	186.00

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 3: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Human Tolerability of substances in the Conventional process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Benzoic acid	1931.36	0.13	500	0.48
Ethanol	7404.58	0.13	1400	0.66
Hydrazine hydrate	748.96	0.13	40	2.34
Ethyl benzoate	2042.49	0.25	2100	0.24
Carbon tetrachloride	10222.08	0.13	429	2.98
Sulphuric acid	321.45	0.13	135	0.30
Sodium benzoate	319.06	0.13	1600	0.02
Carbon dioxide	97.44	0.13	830000	0.00
Sodium hydrogen carbonate	186.00	0.13	3360	0.01

Annex 4: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Pondered Environmental Toxicity of substances in the Conventional process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Benzoic acid	1881	0.65	0.05
Ethanol	587	0.89	0.28
Hydrazine hydrate	4864	0.10	0.00
Ethyl benzoate	5000	0.08	0.01
Carbon tetrachloride	3293	0.39	0.17
Sulphuric acid	1873	0.65	0.01
Sodium benzoate	1357	0.75	0.01
Carbon dioxide	1	1.00	0.00
Sodium hydrogen carbonate	967	0.82	0.01

Annex 5: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Exposure level of substances in the Greener process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Benzoic acid	996584	1[a]	60[a]	10[b]	1660.97
Hydrazine hydrate	49022	1[a]	60[a]	10[b]	817.05

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 6: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Human Tolerability of substances in the Greener process

Substance	Exposure	Exposure time (days/kg	LDLo/LD50	Human

	level	of product)	(mg/kg)	Tolerability
Benzoic acid	1660.97	0.0007	500	0.0023
Hydrazine hydrate	817.05	0.0007	40	0.0142

Annex 7: Synthesis of benzoic hydrazide. Principle 3 data for determination of the Pondered Environmental Toxicity of substances in the Greener process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Benzoic acid	1881	0.65	0.44
Hydrazine hydrate	4864	0.10	0.03

Annex 8: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Exposure level of the product in the Conventional process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Benzoic hydrazide	1000000	1[a]	60[a]	10[b]	1666.67

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 9: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Human Tolerability of the product in the Conventional process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Benzoic hydrazide	1666.67	0.1250	122.0000	1.7077

Annex 10: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Pondered Environmental Toxicity of the product in the Conventional process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Benzoic hydrazide	2500	0.5387	0.5387

Annex 11: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Exposure level of the product in the Greener process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Benzoic	1000000	1[a]	60[a]	10[b]	1666.67

hydrazide

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 12: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Human Tolerability of the product in the Greener process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Benzoic hydrazide	1666.67	0.0007	122.0000	0.0095

Annex 13: Synthesis of benzoic hydrazide. Principle 4 data for determination of the Pondered Environmental Toxicity of the product in the Greener process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Benzoic hydrazide	2500	0.5387	0.5387

Annex 14: Synthesis of benzoic hydrazide. Principle 5 data for determination of the Total Index of the Conventional process

Substance	Mass used (kg/kg of product)	Hazard Warnings	Max. Health Hazard	Max. Fire Hazard	Max. Stability Hazard	Max. Environmental Hazard	Total Index
Sulphuric Acid	0.1929	H290, H314	4	0	0	0	4
Carbon tetrachloride	6.1332	H301+ H311+ H331, H317, H351, H372, H412, H420	3	0	0	3	6
Sodium hydrogen carbonate	0.1116	H320	1	0	0	0	1

Annex 15: Synthesis of benzoic hydrazide. Principle 6 data for determination of the Economic Cost Index

Process	Energy requirements (kWh/kg of product)	Energy price (euro/kWh)	Economic Cost (euro/kg of product)	Economic Cost Index
Conventional	6.0000	0.1100*	0.6600	0.2176
Greener	0.0150	0.1100*	0.0017	0.9962
Full Conventional	6.0000	0.1100*	0.6600	0.2176
Full Greener	0.0150	0.1100*	0.0017	0.9962

Process				
Full Conventional (with recirculation)	6.0000	0.1100*	0.6600	0.2176
Full Greener (with recirculation)	0.0150	0.1100*	0.0017	0.9962

*Energy price is considered to be the average price of energy in the European Union

Annex 16: Synthesis of benzoic hydrazide. Principle 6 data for determination of the Environmental Cost Index

Process	Energy requirements (kWh/kg of product)	CO_2 emissions of energy (g.CO_2 /kWh)	Environmental Cost (g.CO_2 /kg of product)	Environmental Cost Index
Conventional	6.0000	216.2000*	1297.2000	0.2131
Greener	0.0150	216.2000*	3.2430	0.9961
Full Conventional	6.0000	216.2000*	1297.2000	0.2131
Full Greener	0.0150	216.2000*	3.2430	0.9961
Full Conventional (with recirculation)	6.0000	216.2000*	1297.2000	0.2131
Full Greener (with recirculation)	0.0150	216.2000*	3.2430	0.9961

*CO_2 emissions of energy considered to be the average CO_2 emissions of energy in Europe

Annex 17: Synthesis of benzoic hydrazide. Principle 7 data for determination of the Total Feedstock in the Conventional process

Substance	Mass requirements (kg/kg of product)	Sustainability factor	Feedstock (%)
Benzoic acid	1.1588	0.0000	9.28
Ethanol	4.4427	0.0000	35.57
Sulphuric acid	0.1929	1.1200*	1.54
Carbon tetrachloride	6.1332	0.0000	49.11
Sodium hydrogen carbonate	0.1116	0.0000	0.89
Hydrazine hydrate	0.4494	0.0000	3.60

*Sulphuric acid was considered to be similar, in terms of sustainability, to sulphur.

Annex 18: Synthesis of benzoic hydrazide. Principle 7 data for determination of the Total Feedstock in the Greener process

Substance	Mass requirements (kg/kg of product)	Sustainability factor	Feedstock (%)
Benzoic acid	0.9966	0.0000	67.00
Hydrazine hydrate	0.4902	0.0000	32.97

Annex 19: Synthesis of benzoic hydrazide. Principle 11 data for determination of the Total Index of the product

Substance	Hazard Warnings	Health Hazard	Fire Hazard	Stability Hazard	Environmental Hazard	Total Index
Benzoic hydrazide	H301,H315,H319,H335	3	0	0	0	3

Annex 20: Synthesis of benzoic hydrazide. Principle 12 data for determination of the Accident Prevention of substances in the Conventional Process

Substance	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Benzoic acid	0	1	0	1	1	0	2
Ethanol	0	1	1	1	1	0	2
Hydrazine hydrate	0	0	0	1	1	0	2
Ethyl benzoate	0	1	0	1	1	0	2
Carbon tetrachloride	0	0	0	1	0	0	1
Sulphuric acid	0	1	0	1	0	0	1
Sodium benzoate	0	1	0	0	1	0	1
Carbon dioxide	0	1	0	1	0	0	1
Sodium hydrogen carbonate	0	1	0	1	0	0	1

Annex 21: Synthesis of benzoic hydrazide. Principle 12 data for determination of the Accident Prevention of the Conventional Process

Process	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Conventional	0	1	1	1	1	0	2

Annex 22: Synthesis of benzoic hydrazide. Principle 12 data for determination of the Accident Prevention of substances in the Greener Process

Substance	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Benzoic acid	0	1	0	1	1	0	2
Hydrazine hydrate	0	0	0	1	1	0	2

Annex 23: Synthesis of benzoic hydrazide. Principle 12 data for determination of the Accident Prevention of the Greener Process

Process	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Greener	0	1	0	1	1	0	2

Annex 24: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Exposure level of substances in the Copolymerization process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Acrylic Acid	825355	1[a]	60	10[b]	1375.59
Sodium Carbonate	2696298	1[a]	60	10[b]	4493.83
Acrylamide	715858	1[a]	60	10[b]	1193.10
Ammonium Persulfate	71586	1[a]	60	10[b]	119.31
Sodium Sulfite	71586	1[a]	60	10[b]	119.31
Nitrogen	38403	1[a]	60	10[b]	64.00
Ethanol	86681491	1[a]	60	10[b]	144469.15

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 25: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Human Tolerability of substances in the Copolymerization process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Acrylic Acid	1375.59	0.021	150	0.1911
Sodium Carbonate	4493.83	0.021	714	0.1311
Acrylamide	1193.10	0.021	100	0.2486
Ammonium Persulfate	119.31	0.021	689	0.0036
Sodium Sulfite	119.31	0.021	175	0.0142
Nitrogen	64.00	0.000	830000	0.0000
Ethanol	144469.15	0.042	19440	0.3096

Annex 26: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Pondered Environmental Toxicity of substances in the Copolymerization process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Acrylic Acid	2955	0.45	0.0041
Sodium Carbonate	1047	0.81	0.0239
Acrylamide	1753	0.68	0.0053
Ammonium Persulfate	1225	0.77	0.0006
Sodium Sulfite	954	0.82	0.0006
Nitrogen	1	1.00	0.0004
Ethanol	587	0.89	0.8486

Annex 27: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Exposure level of substances in the Hydrolysis process

Substance	Mass of chemicals	Number of	Average	Exposure	Exposure

	(mg/kg of product)	people	weight (kg)	area (%)	level
Acrylamide	853071	1[a]	60	10[b]	1421.78
Sodium Hydroxide	255921	1[a]	60	10[b]	426.54
Ammonium persulfate	85307	1[a]	60	10[b]	142.18
Sodium metabisulfite	85307	1[a]	60	10[b]	142.18
2-propanol	43066	1[a]	60	10[b]	71.78
Polyacrylamide	853071	1[a]	60	10[b]	1421.78
Ammonia	1856	1[a]	60	10[b]	3.09
Nitrogen	22029	1[a]	60	10[b]	36.71

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 28: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Human Tolerability of substances in the Hydrolysis process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Acrylamide	1421.78	0.021	100	0.2962
Sodium Hydroxide	426.54	0.021	40	0.2222
Ammonium persulfate	142.18	0.021	689	0.0043
Sodium metabisulfite	142.18	0.021	192	0.0154
2-propanol	71.78	0.042	2770	0.0011
Polyacrylamide	1421.78	0.042	1000	0.0592
Ammonia	3.09	0.000	132	0.0000
Nitrogen	36.71	0.000	830000	0.0000

Annex 29: Synthesis of anionic polyacrylamide copolymer. Principle 3 data for determination of the Pondered Environmental Toxicity of substances in the Hydrolysis process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Acrylamide	1753	0.68	0.26
Sodium Hydroxide	2747	0.49	0.06
Ammonium persulfate	1225	0.77	0.03
Sodium metabisulfite	1358	0.75	0.03
2-propanol	52	0.99	0.02
Polyacrylamide	1000	0.82	0.32
Ammonia	3931	0.27	0.00
Nitrogen	1	1.00	0.01

Annex 30: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Exposure level of the product in the Copolymerization process

Substance	Mass of chemicals	Number of people	Average weight (kg)	Exposure area (%)	Exposure level

	(mg/kg of product)				
Poly(acrylamide-co-acrylic acid)	1000000	1[a]	60	10[b]	1666.67

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 31: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Human Tolerability of the product in the Copolymerization process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Poly(acrylamide-co-acrylic acid)	1666.67	0.0417	1000	0.0694

Annex 32: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Pondered Environmental Toxicity of the product in the Copolymerization process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Poly(acrylamide-co-acrylic acid)	2354	0.5656	0.5656

Annex 33: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Exposure level of the product in the Hydrolysis process

Substance	Mass of chemicals (mg/kg of product)	Number of people	Average weight (kg)	Exposure area (%)	Exposure level
Poly(acrylamide-co-acrylic acid)	1000000	1a	60	10b	1666.67

[a] For the assessment it was assumed that a single person was working in the process with a weight of 60 kg. [b] The exposure area was determined considering a person with a complete lab coat, gloves and a mouth mask. This means that only the neck and part of the head are exposed, resulting in approximately 10% exposure of the body.

Annex 34: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Human Tolerability of the product in the Hydrolysis process

Substance	Exposure level	Exposure time (days/kg of product)	LDLo/LD50 (mg/kg)	Human Tolerability
Poly(acrylamide-co-acrylic acid)	1666.67	0.0417	1000	0.0694

Annex 35: Synthesis of anionic polyacrylamide copolymer. Principle 4 data for determination of the Pondered Environmental Toxicity of the product in the Hydrolysis process

Substance	Environmental Toxicity Rank	Normalized environment toxicity rank	Pondered Environmental Toxicity
Poly(acrylamide-co-acrylic acid)	2354	0.5656	0.5656

Annex 36: Synthesis of anionic polyacrylamide copolymer. Principle 5 data for determination of the Total Index of the Copolymerization process

Substance	Mass used (kg/kg of product)	Hazard Warnings	Max. Health Hazard	Max. Fire Hazard	Max. Stability Hazard	Max. Environmental Hazard	Total Index
Ammonium Persulfate	0.0716	H272, H302, H315, H317, H319, H334, H335	3	1	1	0	5
Sodium Sulfite	0.0716	-	0	0	0	0	0
Nitrogen	0.0384	H280	0	0	2	0	2
Ethanol	86.6815	H225, H319	2	3	0	0	5

Annex 37 Synthesis of anionic polyacrylamide copolymer. Principle 5 data for determination of the Total Index of the Hydrolysis process

Substance	Mass used (kg/kg of product)	Hazard Warnings	Max. Health Hazard	Max. Fire Hazard	Max. Stability Hazard	Max. Environmental Hazard	Total Index
Ammonium persulfate	0.3739	H272, H302, H315, H317, H319, H334, H335	3	1	1	0	5
Sodium metabisulfite	0.4487	H302, H318	3	0	0	0	3
2-propanol	0.7166	H225, H319, H336	2	3	0	0	5
Nitrogen	0.7865	H280	0	0	2	0	2

Annex 38: Synthesis of anionic polyacrylamide copolymer. Principle 6 data for determination of the Economic Cost Index

Process	Energy requirements (kWh/kg of product)	Energy price (euro/kWh)	Economic Cost (euro/kg of product)	Economic Cost Index
Copolymerization	5.3800[a]	0.1100[b]	0.5918	0.2548

Hydrolysis	2.6900[a]	0.1100[b]	0.2959	0.5048

[a]As no information exists on the energy requirements of the process, the energy requirements for the Hydrolysis were considered to be the average energy requirements of a chemical process and the energy requirements for the Copolymerization were considered to be the double since it requires the same temperature for double the time [b]Energy price is considered to be the average price of energy in the European Union

Annex 39: Synthesis of anionic polyacrylamide copolymer. Principle 6 data for determination of the Environmental Cost Index

Process	Energy requirements (kWh/kg of product)	CO_2 emissions of energy (g.CO_2 /kWh)	Environmental Cost (g.CO_2 /kg of product)	Environmental Cost Index
Copolymerization	5.3800[a]	216.2000[b]	1163.1560	0.2500
Hydrolysis	2.6900[a]	216.2000[b]	581.5780	0.5000

[a]As no information exists on the energy requirements of the process, the energy requirements for the Hydrolysis were considered to be the average energy requirements of a chemical process and the energy requirements for the Copolymerization were considered to be the double since it requires the same temperature for double the time [b]CO_2 emissions of energy considered to be the average CO_2 emissions of energy in Europe

Annex 40: Synthesis of anionic polyacrylamide copolymer. Principle 7 data for determination of the Total Feedstock in the Copolymerization process

Substance	Mass requirements (kg/kg of product)	Sustainability factor	Feedstock (%)
Acrylic Acid	0.8254	0.0000	0.91
Sodium Carbonate	2.6963	0.0000	2.96
Actylamide	0.7159	0.0000	0.79
Ammonium Persulfate*	0.0716	1.1200	0.08
Sodium Sulfite*	0.0716	1.1200	0.08
Nitrogen	0.0384	0.0000	0.04
Ethanol	86.6815	0.0000	95.15

*Sulphur based substances was considered to be similar, in terms of sustainability, to sulphur.

Annex 41: Synthesis of anionic polyacrylamide copolymer. Principle 7 data for determination of the Total Feedstock in the Hydrolysis process

Substance	Mass requirements (kg/kg of product)	Sustainability factor	Feedstock (%)
Acrylamide	0.8531	0.0000	64.50
Sodium Hydroxide	0.2559	0.0000	19.35
Ammonium persulfate*	0.0853	1.1200	6.45
Sodium metabisulfite*	0.0853	1.1200	6.45
2-propanol	0.0431	0.0000	3.26

*Sulphur based substances was considered to be similar, in terms of sustainability, to sulphur.

Annex 42: Synthesis of anionic polyacrylamide copolymer. Principle 11 data for determination of the Total Index of the product

Substance	Hazard Warnings	Health Hazard	Fire Hazard	Stability Hazard	Environmental Hazard	Total Index
Poly(Acrylamide-co-acrylic acid)	-	0	0	0	0	0

Annex 43: Synthesis of anionic polyacrylamide copolymer. Principle 12 data for determination of the Accident Prevention of substances in the Copolymerization process

Substance	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Acrylic Acid	0	1	0	1	0	0	1
Sodium Carbonate	0	1	0	0	0	0	0
Sodium Hydroxide	0	1	0	0	0	0	0
Sodium Acrylate	0	1	0	0	0	0	0
Acrylamide	0	0	0	0	0	0	0
Ammonium Persulfate	0	0	0	0	0	0	0
Sodium Sulfite	0	0	0	0	0	0	0
Nitrogen	0	0	0	1	0	0	1
Ethanol	0	0	0	1	1	0	2
Carbon Dioxide	0	0	0	1	0	0	1

Annex 44: Synthesis of anionic polyacrylamide copolymer. Principle 12 data for determination of the Accident Prevention of the Copolymerization process

Process	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Copolymer.	0	1	0	1	1	0	2

Annex 45: Synthesis of anionic polyacrylamide copolymer. Principle 12 data for determination of the Accident Prevention of substances in the Hydrolysis process

Substance	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Acrylamide	0	1	0	0	0	0	0
Ammonium persulfate	0	1	0	0	0	0	0
Sodium metabissulfite	0	1	0	0	0	0	0
2-propanol	0	1	0	1	1	0	2
Polyacrylamide	0	0	0	0	0	0	0
Nitrogen	0	0	0	1	0	0	1
Sodium Hydroxide	0	0	0	0	0	0	0
Ammonia	0	0	0	1	0	0	1

Annex 46: Synthesis of anionic polyacrylamide copolymer. Principle 12 data for determination of the Accident Prevention of the Greener Process

Process	Ignition	Oxygen	Combustible	Evaporation	Fire	Explosion	Accident P.
Hydrolysis	0	1	0	1	1	0	2