Background to green chemistry

The emergence of green chemistry has been one of the most significant developments in the chemical sciences in recent years. The term is accepted worldwide as being synonymous with the development of more environmentally friendly and sustainable chemical products and processes. Green chemistry has both very wide application and relevance, and this module provides the background information on the subject as well as introducing some key concepts.

Learning Objectives

By the end of this module you should be able to:

- Define the terms “green chemistry”, “green engineering” and “sustainable design”, and understand how they interrelate;
- Understand the definitions and applications of the twelve principles of green chemistry;
- Understand the economic, environmental and societal drivers for the implementation of greener methods;

and be aware of:

- The benefits of using catalytic and biocatalytic methods;
- The need for metrics to measure the greenness of a process.

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Green chemistry, green engineering and sustainable design

This material is reproduced from J. H. Clark, Green and Sustainable Chemistry: An Introduction, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 1, pp. 1-11..

Green chemistry is quite well defined by the twelve principles of Anastas and Warner. [1] These principles focus on how to make a greener synthetic process, chemical product or chemical reaction, resulting in minimising its environmental impact. The twelve principles gained prominence in 1998 but as the scope of green chemistry has broadened, so have the potential applications. This is explored further in the lesson Twelve principles for the twenty-first century.

Green engineering can be defined as the design, commercialisation and use of processes and products that are feasible and economical, while minimising generation of pollution at source and risk to human health and the environment [2]. Green engineering uses the tools of recycling, process intensification and design optimisation to maximise the efficiency of a process, and reduce its negative impact on the environment. This approach evaluates the manufacturing process as a system and seeks to optimise its design, and in the truest sense, incorporates the concepts of life-cycle analysis and environmental economics into an appropriate evaluation of the overall environmental impact. The development of a set of metrics is required that appropriately evaluates the environmental parameters that we seek to control.

Sustainable design looks even more broadly to try to understand the relationships between the manufacturing system and the ecosystem. Sustainability focuses on the triple bottom line: the integration of ecological integrity, societal responsibility and economic viability. This applies the broadest level systems approach, looking at the

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planet as the system of interest. In order to optimise design at this scale, new ways of measuring human impacts on the environment are required.

Recommended reading and resources:

- J. H. Clark, Green and Sustainable Chemistry: An Introduction, in *Green and Sustainable Medicinal Chemistry : Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 1, pp. 1-11.
- Green Chemistry Initiative, University of Toronto: video series on the 12 principles, written by students for students
- ACS GCI PR statement of the principles with accompanying commentary from experts in each area

1. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
2. P. T. Anastas, Green engineering and sustainability, *Environ. Sci. Technol.*, 2003, **37**, 423A-423A.

Multiple choice question

1. Which of the following are cross-cutting themes among Green Chemistry, Green Engineering and Sustainable Design?
    1. Making efficient use of resources
    2. Use of renewable resources
    3. Reducing pollution
    4. Safety
    5. Equipment design
    6. Use of benign materials

Answers on last page

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Drivers for change

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The chemical and allied industries now face as tough a challenge as they have ever faced. The 20th century saw enormous growth in chemicals manufacturing but this growth has come at a cost. Inefficient processes leading to unacceptable levels of pollution, hazardous operations resulting in a number of disasters, and a lack of knowledge of the human and environmental toxicity of most chemicals in widespread use, all leading to an exponential growth in chemicals legislation. The industry now needs to achieve environmental and social acceptability as well as economically viable manufacturing in the toughest ever legislative framework.

Legislation

Legislation such as REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) are trying to minimise hazardous chemicals use within Europe, with more and more substances being put forward for authorisation, meaning that they can only be used under strictly controlled conditions. Other unofficial initiatives such as ChemSec's SIN list and rising numbers of environmental laws are also impacting on the way chemical industries do business. In this video James Clark at the Green Chemistry Centre of Excellence, University of York discusses these points in more detail.

To study this area in more depth, see Environmental legislation

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Transcript

Hazardous chemical should be replaced, so there's one of the big mantras in the principles of green chemistry, something which, you know, we've been driving.

A lot of research in green chemistry has been based on that principle.

So where are we today? Well the big issue today, of course, is REACH and, you know, I'm always disappointed when I talk to students of chemistry and they don't know what REACH is or they have some vague idea.

I mean, to me it's THE most important of all the chemical legislative drivers.

It's incredibly powerful and it's going to have - its impact is only just beginning to reach.

People are just beginning to realize it, because it's just beginning to happen.

So the first substances so-called for authorization; which basically means: if something's going forward for authorization, it means that there's gonna be a massive red flag waving over it.

You are only going be able to use it under very strictly controlled conditions and there's going to be a huge amount of pressure on you find a replacement.

So really you don't want to go into that space.

And more and more substances are now being put forward for authorisation.

Some of it's very predictable.

Some of the substances going forward now like chromates, you might understand why.

Others it's less obvious.

I saw toluene on a recent list which is going to have a huge impact on the process chemical industry.

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So REACH is gonna happen.

It's big time.

It's getting more and more important, the number of substances that are going to be considered is growing all the time.

So that has to be taken into consideration.

Now because REACH is taking a long time, it will take at least 10 years to test all the significant volumes substances in use.

In Europe it's probably about a hundred thousand different chemicals that's going to have to be tested under REACH.

Then actually that means, of course; you know nature abhors a vacuum and all that and NGOs have moved into the space.

Most famously: ChemSec, which is probably Europe's best-known NGO, and ChemSec have published something called the SIN list, the 'Substitute It Now' list.

And ChemSec are taken very, very seriously; some of those sectors I implied in my previous slide like, for example, retail, they take it terribly seriously.

So Marks and Spencers, for example, would instruct their suppliers: they don't want anything on the SIN list in their articles.

So you have to go and have a look at the SIN list.

If you haven't done it already, go on, it's free, just go on to ChemSec and look at 'Sin List'.

There's about 500 chemicals listed there which they consider should be replaced.

Some again, you probably, most of you will go 'Yeah, I can understand why', but there may be some surprises for you as well.

That's probably, I would say, that's one of the better unofficial lists.

There are some other ones; I mean I saw one from the European Trade Unions Congress which was extraordinary and had some chemicals on that you really would think: "Why on earth are they there?" So, you know, bear in mind that there's all sorts of things going

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on out there making people think about chemicals more than they did before.

Don't move the problem! Just because you got rid of something you'd rather not use: "OK, good news I'm not using Chromate and I'm using something else!" Just think about, as I said before, think about where you're shifting the problem to.

You may be shifting it upstream, you may be shifting it downstream.

Be aware, as I said across the life cycle.

Be aware of life cycle issues.

They are fundamentally important whenever you do anything.

And the legislation, as I said, is getting very powerful: this just gives you an idea of how much legislation's impacting on chemicals.

I'm not talking about pharmaceuticals here, I'm talking about chemicals.

There's been an exponential growth in the legislation, the amount of legislation, directly impacting on chemicals.

Some people say it coincides with Rachel Carson's famous book, if you don't know where that is look it up.

We celebrated the 50th anniversary last year, the publication.

Rachel Carson was the first person to publish a book that really addressed the issue of chemical pollution, really brought it into the public eye.

And it has become, of course, a very important issue ever since.

All sorts of legislation en route, there's been some really interesting ones.

So way back before Green Chemistry was even a term, we had 'Best Available Technique'.

So the UK which, of course is really good at inventing things, not so good at following up on them.

So the UK invented the concept of Best Available Technique, BAT, and you've probably come across that before, it's still now being used in some legislation.

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> This is 1991, and I remember going to the first meeting in Manchester, funnily enough, talking about what was then called 'BATNEEC', it was Best Available Technology Not Entailing Excessive Costs.
>
> And one guy from a certain company not too far from here stood up and said "Well we prefer 'CATNIP' which is Cheapest Available Technology Not Involving Prosecution" which sort of focuses the mind with regards to what really they're trying to do.
>
> Anyway, the point is legislation is getting more and more of an issue..

Supply risk

This material taken from J. H. Clark, Green and Sustainable Chemistry: An Introduction, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 1, pp. 1-11. .

In addition to substances becoming restricted or unavailable due to changes in legislation, they may also be at risk due to **issues with supply**. While renewable carbon has been a hot topic since the 2000s, more recently that attention has been broadened to include other critical elements including phosphorus and many metals.

To study this area in more depth, see Critical elements

Economic cost

In order to improve sustainability, chemistry needs to be more efficient – most chemical reactions create more waste than product. Waste is expensive – the issues surrounding lost production, waste disposal, environmental aspects and public relations all incur a

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cost to a business, and most of these costs are rising over time. In this video James Clark at the Green Chemistry Centre of Excellence, University of York discusses these points in more detail.

R. A. Sheldon, The E Factor: fifteen years on, *Green Chem.*, 2007, 9, 1273-1283.

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Transcript

It's still driven by the fact that chemistry does need to be more efficient and something I'm sure many of you have seen, which is a table that was generated by a good friend of mine, a man called Roger Sheldon, some of you may know and 22 years ago, 23 years ago, Roger was just in his transition from Shell to University of Delft, where he's still based.

And he came up with this interesting analysis of efficiency of different sectors.

And what he showed was that as basically as the complexity of the synthesis and the value of the molecules went up, the efficiency of the processing went down.

But the real reason for doing this was to make people appreciate the fact, as I said at the bottom, actually most chemical reactions make more waste than product; they're not very efficient.

And that has become, I don't think those numbers have been particularly challenged by people, I think it's helped people to understand why we're doing what we're doing.

We are not very efficient so fundamentally, whatever you understand about, you know what the issues are in terms of how expensive waste is, it's almost intuitive if you think that we should be doing better than that.

But in fact when you do start looking at it a bit more, you begin to see, just waste of course, that means we're therefore making a lot of waste and waste is very expensive.

And this is something I did fifteen years ago, and it hasn't really changed because, you

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know the issues are still there, they're even worse than they were and they get worse all the time.

Because if you got waste it's going to cost you, obviously, in terms of lost production, obviously, in terms of waste disposal, obviously, in terms of environmental issues and in terms of PR and so on.

And wherever there's a box there, a green box, it's got worse, so you know, the cost of waste disposal goes up and up all the time.

The costs, all sorts of issues become critical and this was the original driver, the motivation, for the chemical industry to take the whole movement seriously in the 1990's and still today, because wastes are so expensive.

So that kind of helps from an economic point of view to justify why we're moving in that direction..

Public attitudes

This material taken from J. H. Clark, Green and Sustainable Chemistry: An Introduction, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 1, pp. 1-11. .

Shifts in public attitude mean that there is increasing pressure, especially from consumers, on manufacturers to produce bio-derived chemicals as replacements for fossil resources and substances now considered to be hazardous to us or to the environment. Vijayendran [1] recently estimated that by 2025, over 15 % of the $3 trillion global chemical market will be derived from bio-derived sources. As we begin to move away from petrochemicals, the use of biomass as a chemical feedstock will become increasingly important.

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To study this area in more depth, see Renewable resources

1. B. Vijayendran-Batelle, Biobased Chemicals: Technology, Economics and Markets (Last accessed: October 2, 2015).

Multiple choice question

1. Which of these factors can impact the profitability of a company in a negative way?
    1. Generation of waste
    2. Poor public image
    3. Use of hazardous materials
    4. Scarcity of raw materials
    5. Breach of legislation

Answers on last page

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Twelve principles for the 21st century

The twelve principles came to prominence in 1998 [1] and since then the field of green chemistry has grown significantly. In this video James Clark at the Green Chemistry Centre of Excellence, University of York traces the development of the twelve principles, and discusses how there is now a greater awareness of green issues across the full lifecycle including raw materials and end products, rather than focussing mainly on the processing stage.

1. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.

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Transcript

But wherever you go I mean, there are green issues being talked about; everybody wants to be seen to be green.

And everybody wants to know what's green and what isn't green, but I'm afraid there isn't a simple answer, it's very difficult to say, all we can try to do is move in a greener direction.

And in doing that I always say, whatever sector you're in, do be aware of the life cycle issues.

Because the reality is there's so many pressures on chemicals these days and, you know, we are ultimately talking about making chemical entities, so we are talking about chemicals and unfortunately a lot of people have got very negative views about chemicals which influence legislation.

There's all sorts of real issues now at stake with regards to chemicals that weren't there

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when Green Chemistry started; I mean it's interesting to go back in time and think back, you know, in terms of where this all came from, and certainly my first awareness of the area goes way back to the late nineteen eighties and we were publishing papers and what we called environmentally friendly catalysis and there were people already doing some very interesting efforts to try and find greener ways of doing very important reactions like Friedel-Crafts oxidations and so on.

And then in the early nineties the US EPA, which was a very proactive organization at the time, decided they wanted to encourage the chemical industry in particular to move in a greener direction, especially to reduce waste.

The big focus was on waste.

I'll come back to waste in a moment.

And what happened was EPA started up something called the Green Chemistry Presidential Awards, which still run today, very successful program, which awarded industry and inventors, on you know, things that were considered to be green.

It encouraged Green Chemistry through awards programs and there was a guy called Joe Green at the time, I got to know very well, who encouraged the movement, he had a protégé called Paul Anastas.

Paul, staying in the EPA, then got to working with John Warner, who was working in industry at the time and they got together to create the 12 Principles of Green Chemistry, which of course you've already seen listed, in which has become very much the kind of , you know, the philosophy underpinning the area of Green Chemistry.

But in those days it was very process focused.

Really, people were interested in the manufacture of chemicals.

They were looking at the middle of the life cycle.

They weren't really thinking terribly much about raw materials, they weren't thinking terribly much about products; although you see the principles do make references to those, you'll also notice that the vast majority are focused on chemical processing.

If you wrote them again today, you would undoubtedly have a different balance between them because nowadays, of course, we're very concerned about resources and we're

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very concerned about products.

And we have legislation to support that and we have reality, in terms of availability and so on which I'll come on to a bit later, with regards to resources.

So there's all sorts of factors and I always say whatever you're doing try to think like, don't try to do an LCA every time you move otherwise you won't make any progress at all, but try to be life cycle aware when you're introducing a new catalyst into a process for good reason.

Try and think about it from the point of view of: What are the resource implications of switching to this catalyst? What are the possible and life implications when it comes to, say the waste that will come out the process? Because everything eventually, remember, would end up in the environment..

Misunderstandings of green chemistry

It is helpful when learning about the foundations of modern green chemistry to look at some common misconceptions and how chemists in the area are working to counteract them. In a 2012 article, James Clark at the Green Chemistry Centre of Excellence, University of York highlighted some of the ways in which the traditional principles have been misunderstood.[1]

In this video, he focuses on biodegradability (principle 10: design for degradation), in particular its tension with newer recycling techniques (born out of principles 1 and 2), illustrating that a naïve understanding of the twelve principles is not sufficient in modern green chemistry thinking.

1. J. Clark, The 12 Misunderstandings of Green Chemistry (Last accessed: October 2, 2015).

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Transcript

'Chemical should be biodegradable.' This is a lovely one, I love this because it's so interesting and so controversial.

So it's like the plastic bag.

Should the plastic bag be biodegradeable? And it's like ok, so we've got options here.

So what happens to a plastic bag when you finish using it? It can either go into a landfill site or you can use it again.

You can maybe use it again for a different purpose.

So if it goes in a landfill site you want to be biodegradable.

But if you want to use it again you don't want to be biodegradeable.

You want to have something you can use and use and use again.

So, this is a really interesting issue and it's not as simple as - there's no simple answer, like most things in green chemistry, there's no simple answer - because it can conflict with recyclability.

We can't afford, as I said before, to follow the linear route where we would basically extract, we modify we consume, we dispose.

Logically we live in a single planet, you know, we're not going to be able to do that for much longer.

So we need to find ways to get that resource back again after we finish its primary use and use it again; maybe for different applications.

You know, anaerobic digestion destroys all that wonderful chemical functionality that nature gave us.

I think that's - OK, I suppose, if nothing else is available, maybe - but it really is a classic sort of first generation technology for dealing with these problems..

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Introduction to green metrics

The field of Green Chemistry has evolved over the decades. In the 1980s, the focus was on pollution control, with the publication of the 12 principles of green chemistry [1] in the late 1990s encouraging a more holistic approach, through to the 2010s, which has seen an explosion in the number of publications claiming to include green reaction processes [2]. Answering the question as to whether a reaction is genuinely 'green' is not straightforward and requires an objective method of measuring its environmental impact.

In order to assess the greenness of a reaction, a number of 'green metrics' have been developed, which allow chemists to quantify and qualify the environmental impact of their reactions and assist with the comparison of different routes/methods. Early green metrics focused largely on efficiencies in terms of mass inputs and outputs, but this has since expanded to incorporate a much more comprehensive and holistic approach.

To study this area in more depth, see Metrics

Recommended reading:

The following references provide an excellent overview of available green chemistry metrics:

D. J. C. Constable, A. D. Curzons and V. L. Cunningham, Metrics to 'green' chemistry-which are the best?, *Green Chem.*, 2002, **4**, 521-527.

C. Jimenez-Gonzalez, D. J. C. Constable and C. S. Ponder, Evaluating the "Greenness" of chemical processes and products in the pharmaceutical industry-a green metrics primer, *Chem. Soc. Rev.*, 2012, **41**, 1485-1498.

R. C. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, Towards a holistic approach to metrics for the 21st century pharmaceutical industry, *Green Chem.*, 2015, **17**, 3111-3121.

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1. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
2. J. A. Linthorst, An overview: origins and development of green chemistry, *Found. Chem.*, 2010, **12**, 55-68.

The CHEM21 toolkit

The CHEM21 project has developed a unified metrics toolkit to comprehensively evaluate the sustainability of chemical and bio-chemical reactions based on a series of key parameters (see **Figure 1**). Moving beyond the use of 'mass based metrics' alone, the toolkit uses a blend of both qualitative and quantitative criteria to assess how green a reaction is, as well as considering factors both upstream and downstream of the reaction itself. This ensures a truly holistic approach.

The rationale behind the toolkit and the methodology employed is now available in an open access publication [1]. As part of the background to this work CHEM21 performed a survey of available Green Chemistry metrics, which is accessible within the supplementary information of this paper.

To study this area in more depth, see CHEM21 metrics toolkit

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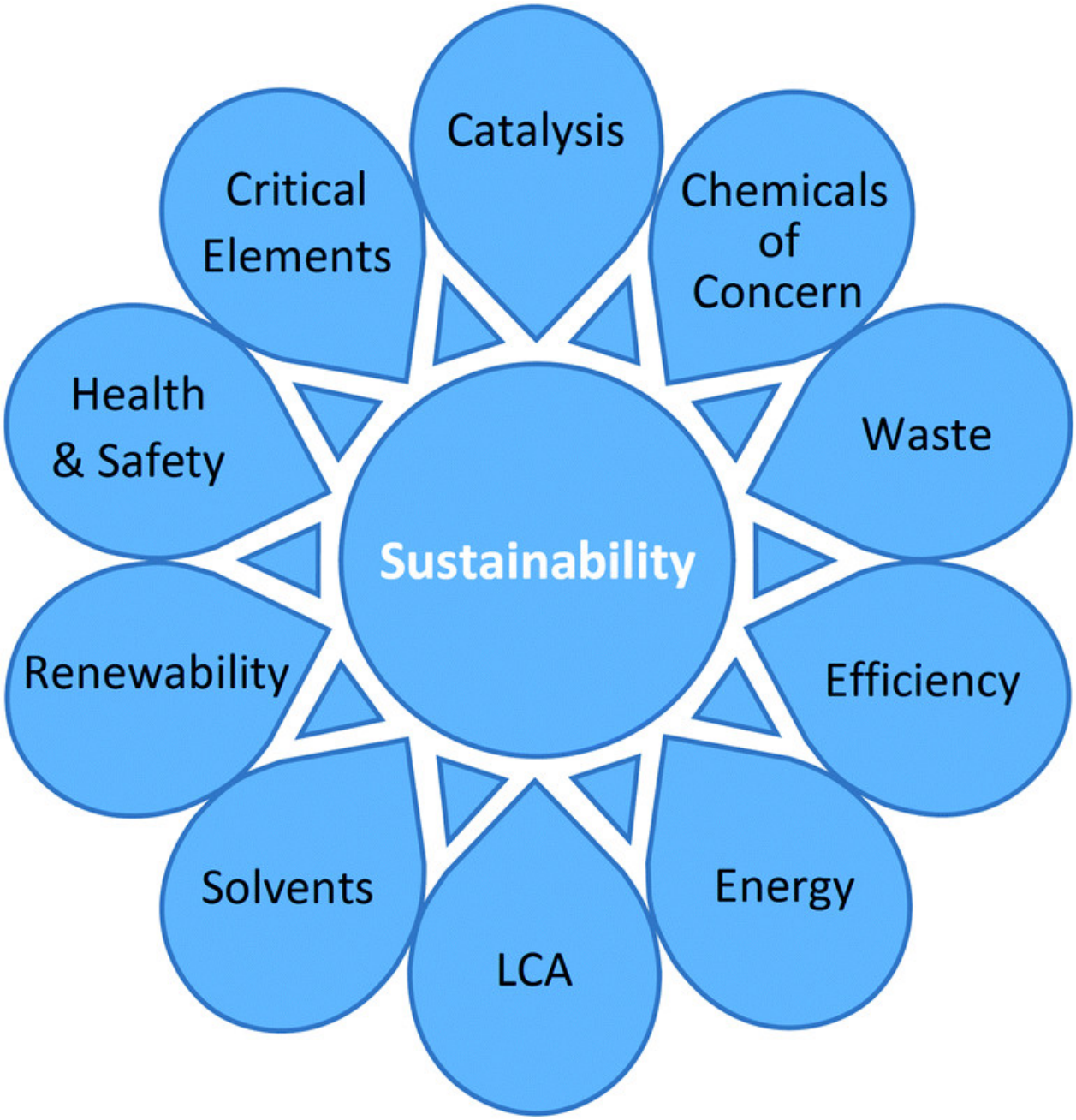

Figure 1: ***Summary of the key parameters covered by the metrics toolkit [1], reproduced with the permission of the Royal Society of Chemistry.***

1. R. C. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, Towards a holistic approach to metrics for the 21st century pharmaceutical

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industry, *Green Chem.*, 2015, **17**, 3111-3121.

Multiple choice questions

1. What factors should be objectively measured to assess the ‘greenness’ of a reaction?
    1. Amount of material used
    2. Cost of material used
    3. Amount of waste generated
    4. Public perception of materials and processes used
    5. Inherent hazards of materials used
2. What are the drawbacks of mass-based metrics?
    1. They cannot provide information on the financial costs from an industrial perspective
    2. They don’t provide information on the inherent hazards of materials used and produced
    3. They don’t provide information on life cycle of materials used
    4. Energy intensity of a process isn’t accounted for

Answers on last page

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Introduction to catalysis

Catalysis, one of the overarching principles of green chemistry, is capable of producing substantial material and energy savings as well as economic benefits. When comparing catalytic methods to traditional stoichiometric syntheses, catalysis offers undisputable economy in reagent use. Stoichiometric reactions would require at least one mole of reagent per mole of starting material, whereas a catalyst, subject to turnover number (TON), can carry out a transformation multiple times per mole of catalyst. Catalytic reagents can be used to improve product selectivity, by enabling diastereomeric control and site specific transformations in multi-functionalised molecules. Moreover catalysts allow reactions to proceed under milder reaction conditions. Moreover, catalytic methods can circumvent the need for pre-functionalisation of the starting materials with activating or directing groups, which would later need to be removed from the final molecule. Thus the use of catalytic rather than stoichiometric methods can dramatically enhance the atom economy of a synthesis, save time and energy, as well as decreasing the amount of raw materials consumed and waste generated. The development and application of catalytic methods can significantly improve both the economic and environmental profile when designing synthetic routes within process research and development (R&D). [1].

There are several factors to consider when selecting a catalyst in terms of its green credentials, including:

- Catalyst efficacy eg. product yield, Turnover number (TON), space-time yield etc.
- Homogeneous or heterogeneous catalysts: while homogeneous catalysis tends to afford high activity and selectivity, heterogeneous systems benefit from ease of operational use and catalyst recovery and recycling, which has obvious advantages in terms of economy and sustainability. Catalysts can be heterogenised by the entrapping or grafting of the active molecules onto the surfaces or pores of solid supports such silica, alumina and ceria among others (Also known as immobilised catalysts).
- Chemical catalysts vs biological catalysts (enzymes). Chemical catalysts can often rely on the usage of rare and precious heavy metals (see Critical Elements module) to achieve the desired chemistry whilst biological catalysts can require dilute conditions and operate under a smaller range of solvents.

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As catalysts play a crucial role in synthetic chemistry, they are covered in more detail in the Synthetic Toolbox topic, whilst methods for objectively measuring greenness are covered in the Metrics module.

Recommended further reading

A. Hunt, *Sustainable Catalysis : With Non-endangered Metals, Parts 1 and 2* , Royal Society of Chemistry, 2015.
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Multiple choice question

1. Which of the following are true of all catalysts, whether chemo- or bio-catalysts?
    1. They increase rate of reactions
    2. They lower the activation energy of a reaction to allow otherwise energetically unfavourable reactions to proceed
    3. They favourably alter the free energy loss of a reaction
    4. They shift the equilibrium of a reaction in favour of the product
    5. They are not consumed in the reaction themselves
    6. Only small amounts are required

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Answers on last page

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Introduction to biocatalysis

Biocatalysis have many advantages over chemocatalysis in the context of green chemistry, which include mild reaction conditions (physiological pH and temperature), the use of environmentally compatible catalysts (enzymes) and solvents (usually water), high catalytic activity and good regio- and chemo-selectivities for multifunctional molecules. As a result, the use of enzymes can avoid the need for functional group activation, or unnecessary protection/deprotection steps.

This simple overview demonstrates that biocatalytic transformations can potentially satisfy eight out of the twelve principles of green chemistry. They often result in a shorter, less wasteful, environmentally and economically appealing processes when compared to conventional chemical syntheses. Biocatalysis has already become widespread in industrial organic synthesis with over 130 commercialised processes. Some of the major themes in biocatalysis are as follows:

- Biocatalysts (enzymes/whole cells) can **replace** chemo-catalysts in synthetic routes.
- Biocatalysts can enable **new synthetic pathways** which may be shorter, more efficient and more sustainable.
- Combining **chemo- and bio-catalysis** generates opportunities for the design of synthetic routes.
- Biocatalysts with a **broad substrate scope** that are **active and stable** under the conditions of a chemical process are needed.
- There are a range of **emerging technologies for biocatalyst development** (directed evolution/pathway engineering).

Biocatalysis is covered in more detail in the Biocatalysis module of the Synthetic Toolbox topic.

Recommended reading

- S. M. Roberts, N. J. Turner, A. J. Willetts and M. K. Turner, *Introduction to Biocatalysis Using Enzymes and Microorganisms*, Cambridge University Press, Cambridge, UK,

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Transcript

So bio-catalysts can replace chemo-catalysts in synthetic routes.

Ok, this is the easy thing to do, I think.

What chemists increasingly do in academia, industry, the generic companies are very keen on this, we look at synthetic routes; so this is the API for the generic drug Singulair, and it's a relatively complex molecule: it's got this chiral asymmetric centre here.

One of the key precursors is an alcohol.

Classically that alcohol was generated by asymmetric reduction of ketones using stoichiometric chiral reducing agents.

For the past few years, I would say, there's been a lot of interest in asking the question: Can replace a sort of rather unpleasant chemical reagent with a bio-catalytic step?

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That's easy in the sense you just replace one reagent with another bio-catalyst.

And so the way this is done now is, it's possible to find enzymes that do this, it's possible to do co-factor recycling; so the whole technology has moved on massively to the point where a lot of people in the pharmaceutical industry tell me now if they want to do a ketone reduction, we start off with an enzyme and then they perhaps move to a non bio-catalytic approach.

So that the whole approach has completely changed from chemo- to bio- catalysis.

That's very interesting and that would be nice if in the next few years that became true for a broader range of technologies.

And then you can read very nice papers, particularly by Codexis, who publish data where they go through all of the parameters for the bio-catalytic and the stoichiometric processes and they argue why the bio-catalytic process is better.

In terms of, not just catalysis but the temperature, use of solvents, which we've heard a lot about before lunch.

So this is my impression, that bio-catalysis often ticks several boxes.

So it might be chief starting material for environmentally acceptable, better uses of solvents.

But what I would argue is more exciting, from my perspective, is that you use bio-catalysis to make and design new synthetic pathways, you don't just do replacement chemistry, you think about making a product in a completely different way because of the availability of bio-catalysts.

And if that is shorter, more efficient, more sustainable, that could offer even more benefits.

So here's a nice example from DSM.

So this is an API called Perindopril, anti-hypertensive.

The key building block is this molecule here with three asymmetric centres.

The classical approach to that is Fischerindole synthesis, so you essentially used the Fischer-indole synthesis to build up a precursor which then making racemic for when you

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do a sort of classical resolution.

And obviously you lose half of the material en route.

So the DSM route re-designs that approach.

It takes advantage of an asymmetric amination, using ammonia lyase, to put in this amino group at the alpha-position, which is interesting, because that's not what...

It's sort of counter- intuitive in terms of the reactivity of the cinnamic acid.

And then you do a copper catalyzed intramolecular amination reduction so you've got a completely new way of making that molecule, that's sort of so much more efficient than the classical Fishcer-Indole synthesis.

So for me, particularly as an Academic, this is the future; is making molecules more efficiently, but it relies on having more enzymes to do more synthetic steps than we currently have.

So Theme 3 which DSM touched on, is actually we're not just going to use bio- or chemo-catalysis, probably, we're going to use combinations of bio- and chemo- catalysis.

Maybe one step after another, maybe even together in the same reaction.

And people are obviously developing ways of doing this and that's very exciting, to use the benefits of bio- and chemo-catalysis, so I think that's going to be a major thing that will increase.

I will give you an example of this, this is from our work.

These are very important drugs that launched about 18 months ago by Johnson-Johnson and also Merck.

They are new treatments for hepatitis C.

Telaprevir, I understand is the fastest selling drug ever.

Sales of Telaprevir, I think, were a billion dollars in the first...

a billion euros, in the first 12 months.

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Because essentially, these drugs cure large numbers of people of hepatitis C.

So we were interested in making the central bit, particularly with this idea of combining chemo- and bio- catalysis.

So worked on the bio-catalysis, we engineered an enzyme called monoamine oxidase to do a desymmeritisation of this fairly cheap symmetrical starting material, to make this chiral imine, which interestingly trimerises and you can recrystallized it to optical purity.

So that was the bio-catalysis bit And in fact, you can take that imine and you can make it, that building block, via a fairly classical synthesis, by just elaboration of the chiral imine.

But we wanted to do something a little bit more interesting, to sort of build on the chemo synthesis part.

And so this was a very interesting collaboration with the Free University of Amsterdam, who are part of Chem21, where we took the bio-catalytic building block and developed a highly convergent synthesis using their expertise in multicomponent chemistry, so one of the reasons we were keen to get Free University of Amsterdam into Chem21 is they've got a lot of very powerful ways of building molecular complexity in this sort of highly convergent way.

So we took our bio-catalytic building block, the two other...

this is all colour-coded to make it easy to follow...

the two other building blocks and in one step you make a molecule that is two steps away from the API.

So that instead of a linear synthetic route, you've got a convergence synthetic route, ok, so this offers the prospects of making this drug in a much more cost effective manner.

And in fact we we published, but we also patented this chemistry, we've licensed this chemistry now to third party who are scaling this as a route to manufacture of that API.

But the message is that we combined bio- and chemo- catalysis.

And then the final two themes, which I've lumped together, if you're gong to do this, we need to develop bio- catalysts with broad substrate scope and importantly, that are active and stable under the conditions of the chemical process.

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So the phrase that people use now is in the old days, because the bio-catalysts weren't so effective you fitted the chemical process to your, rather inefficient, biocatalyst.

Now we can make our bio-catalyst fit the chemical process.

And that's a very, very powerful technology.

And I've got a slide which addresses that.

So enzyme evolution, which interestingly, if you trace the history of directed evolution of enzymes ,the first papers started to appear in the early to mid 1980's and then there was an explosion of interest.

And I would say, this field has almost become a sort of standard method that is used now in development of bio-catalysts for practical application.

So in 25 years it goes from a paper in Science to something that is almost routinely used and the reason it's routine used is it's it's extremely general and it's extremely powerful; you can take an enzyme you can make a library of, you can convert it to a library of proteins you can screen that library of enzymes for pretty much any activity you're interested in.

And then you can find the best hits, go back and do it again and again and again until out pops your optimized bio-catalyst.

And the main issue, I think, with this approach at the moment is how quickly you can do it.

And at the moment it's ok, but it's not quick enough.

So you need to...

if you can do this in weeks, then the uptake of bio-catalysis would be enormous.

Because everything's a competition and chemists can probably improve their catalysis faster than we can improve our bio-catalysis, but we will we will solve that problem, it just takes a little bit of time.

So it's almost the final slide, synthetic biology is gonna be a major theme in everybody's life if you work in this area, because synthetic biology, I think, brings together a lot what I've talked about.

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And different people think of it in different ways but it's gonna be used, I think, almost as an umbrella term to bring all of these technologies that are around, essentially, developing systems to make chemical products, including pharmaceuticals, in a much more efficient way.

So definitely includes bio-catalysis, includes directed evolution, rational redesign of proteins.

It includes making sure those enzymes work on synthetically useful substrates.

It really does include combining bio-catalysis and chemo- catalysis to do multi-step transformations, which is very much what WP4 addresses, and it also as I said, includes combining bio- and chemo-catalysis and includes other things as well, particularly in the context of doing a lot of this in a whole cell system to make to make the approach even more sustainable and efficient.

So challenges, and this is my final slide.

Something we think about a lot in Manchester: Can we design new engines and general synthetic routes to broad classes of products? So the things that feature in API's, ok, so this goes back to the point of looking at the whole synthesis and coming out with a new route.

When you learn chemistry at University you, in the second year of your course, will be taught retro synthesis, ok.

So you'll be told how to make molecules, based on disconnections, breaking into fragments which you can then assemble using synthetic methods.

When you get to the end of your chemistry course, somebody will say this thing called bio-catalysis and, even in Manchester, because I give this course, it's the last course students take before they go away and do their exams.

So I think a lot of people think this has got to be brought in much, much earlier, when we teach retrosynthesis, like Aldol condensations, Wittig reactions, we need to teach: 'oh by the way, you can do a keto- reduction, or you can do an aldolase reaction', otherwise the students get completely confused because they think bio-catalysis is something that's what we put at the end of the course because it's not really that important, but you know, just in case you need it when you go out there.

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So where are the gaps in bio-catalysis? When you do this whole analysis and you find out what enzymes we're lacking.

So this is happening; the bio-catalysis toolbox is expanding but I think you need a much more strategic approach to this role than hope enzymes will become available.

We need to do more of a sort of gap analysis and say, well frankly, "We're missing some pretty important enzymes and they need to be developed sooner rather than later.W.

Multiple choice question

1. What are the advantages of bio-catalysts compared to chemo-catalysts?
    1. They generally run in mild conditions
    2. They are more environmentally friendly
    3. They can access molecules/functional groups that may be difficult to achieve via chemo-catalysis
    4. They can be used alongside chemo-catalysts to broaden the synthetic toolbox
    5. They are highly regio- and stereo-selective
    6. They can be used as direct drop-in replacements for reagents and chemo-catalysts
    7. Development of new bio-catalysts is more rapid

Answers on last page

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Summary and further reading

The products of the chemical industry are everywhere and have led to a significant improvement to our quality of life, although it is essential that these products are manufactured in an environmentally compatible and economically viable way using green and sustainable methodologies. Increased pressure on the chemical and related industries due to increasing demand for chemicals worldwide, depleting resources, stricter legislation and the rising cost of waste disposal is also driving the need for green chemistry solutions. To realise a step-change in the way we manufacture chemical products requires a both change in mindset and an awareness of the principles and practices of green chemistry and sustainability from the beginning of a process.

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- Green Chemistry Initiative, University of Toronto: video series on the 12 principles, written by students for students
- ACS GCI PR statement of the principles with accompanying commentary from experts in each area
- ChemSec's SIN list

Metrics

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Quiz answers

Green chemistry, green engineering and sustainable design - Multiple choice question

1. Which of the following are cross-cutting themes among Green Chemistry, Green Engineering and Sustainable Design?
   ***Correct answers**:*
   - *(u'Making efficient use of resources',)*
   - *(u'Reducing pollution',)*
   - *(u'Safety',)*

Drivers for change - Multiple choice question

1. Which of these factors can impact the profitability of a company in a negative way?
   ***Correct answers**:*
   - *(u'Generation of waste',)*
   - *(u'Poor public image',)*
   - *(u'Use of hazardous materials',)*
   - *(u'Scarcity of raw materials',)*
   - *(u'Breach of legislation',)*

Introduction to green metrics - Multiple choice questions

1. What factors should be objectively measured to assess the ‘greenness’ of a

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reaction?

***Correct answers**:*

- *(u'Amount of material used',)*
- *(u'Amount of waste generated',)*
- *(u'Inherent hazards of materials used',)*

2. What are the drawbacks of mass-based metrics?

***Correct answers**:*

- *(u'They don\u2019t provide information on the inherent hazards of materials used and produced',)*
- *(u'They don\u2019t provide information on life cycle of mater*

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