Metrics

Metrics can be used to guide reaction discovery to design an effective and inherently green methodology. Highlighting potential issues as early as possible in discovery stage, will allow problems to be addressed earlier in the development process. In order to assess the greenness of a reaction or process, quantitative and qualitative metrics should be employed. There are a multitude of metrics available in the literature that can be used to measure, compare and assess methodologies and often difficulty arises when deciding which metrics to use. Rather than viewing one step or substance in isolation, or focussing solely on mass based metrics, it is essential that a holistic viewpoint is taken, considering a full range of issues. This is to ensure that a balance is struck and the best possible outcome for the methodology as a whole is found.

Learning Objectives

By the end of this module you should:

- Understand the importance of adopting a holistic approach to assessing the greenness of a reaction and the limitations of focussing solely on mass based metrics;
- Understand how metrics can be used to work towards greener and more sustainable solutions by:
  - Identifying hot spots/areas of concern;
  - Identifying where reactions are performing well in terms of their greenness;
  - Facilitating benchmarking – obtaining a baseline against which to compare new methods;
- Be able to think critically about sustainability and environmental acceptability, by analysing advantages and disadvantages of synthetic routes.

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Why are metrics important?

In this video Louise Summerton at the Green Chemistry Centre of Excellence, University of York explains why we need metrics to provide a mechanism to assess the greenness of a reaction.[1]

1. L. Summerton and A. Constandinou, Beyond Mass-based Metrics: Evaluating the Greenness of Your Reaction, 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. 4, pp. 41-53.

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Choosing a method exercise

Looking at the PDF below, here are a couple of questions to consider:

- Which one would you choose as the greenest method?
- How much can we tell from yield alone?

We will revisit this example at the end of the module.

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Efficiency-based metrics

The video on this page reproduces content from L. Summerton and A. Constandinou, Beyond Mass-based Metrics: Evaluating the Greenness of Your Reaction, 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. 4, pp. 41-53..

In this video Louise Summerton at the Green Chemistry Centre of Excellence, University of York describes commonly used efficiency based metrics, typically based on mass inputs/outputs, that can be readily calculated and interpreted to give an indication of the greenness of a reaction.

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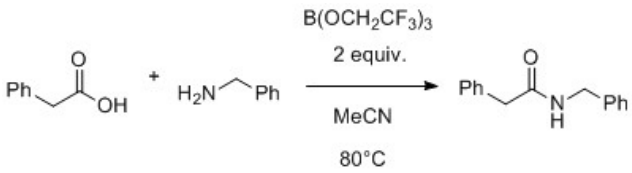
Direct amidation exercise (part 1)

Here is an an example reaction (Scheme 1) and a series of questions (see below) to provide you with some practice of calculating efficiency based metrics. You will find the information you need to make these calculations in the accompanying data sheet.



Scheme 1: ***Reproduced from Starkov and Shepherd [1] with permission from the Royal Society of Chemistry***

After completing the exercise you can check your answers against the answer sheet.

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1. P. Starkov and T. D. Sheppard, Borate esters as convenient reagents for direct amidation of carboxylic acids and transamidation of primary amides, *Organic & Biomolecular Chemistry*, 2011, 9, 1320-1323.

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Further metrics and key considerations

The video on this page reproduces content from L. Summerton and A. Constandinou, Beyond Mass-based Metrics: Evaluating the Greenness of Your Reaction, 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. 4, pp. 41-53..

In this video Louise Summerton at the Green Chemistry Centre of Excellence, University of York describes a variety of other parameters, aside from efficiency based metrics, that should be taken into consideration when assessing the greenness of a reaction.

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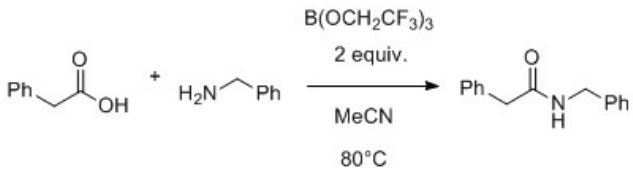
Direct amidation exercise (part 2)

In this exercise (see below) we revisit the direct amidation example looked at earlier, and examine some of the wider considerations to assess the greenness of the reaction (Scheme 1). You will need to use the data sheet to complete the exercise.



Scheme 1: ***Direction amidation example reaction[1]***

After completing the exercise you can check your answers against the answer sheet.

1. P. Starkov and T. D. Sheppard, Borate esters as convenient reagents for direct amidation of carboxylic acids and transamidation of primary amides, *Organic & Biomolecular Chemistry*, 2011, 9, 1320-1323.

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CHEM21 metrics toolkit

Following on from the introduction to the metrics toolkit that was developed by the CHEM21 consortium that was provided in Introduction to green metrics, in this video Louise Summerton provides a more detailed overview of the metrics toolkit and how it can be used to assess the greenness of a reaction via a comprehensive and holistic range of criteria.

The rationale behind the creation of the toolkit and description of the methodologies adopted is available as an open access publication [1] and the Toolkit itself is available in the form of a user friendly excel spreadsheet in the supplementary information of the publication.

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

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Zero pass in more detail

The CHEM21 Metrics Toolkit is specifically structured with a series of 'passes' to cover everything from bench top research right through to industrial scale with increasing level of complexity. In this video Sarah Abou-Shehada at the Green Chemistry Centre of Excellence, University of York examines '*Zero Pass*' in more detail. Zero pass is aimed at the assessment of reactions at the discovery scale and provides an initial light tough appraisal for screening reactions (few mg scale).

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Zero pass interactive tool

You can use this interactive tool at the reaction discovery level. Click the elements of

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the chart below to proceed through the metric stages. The most promising reactions as indicated by your green metrics can then be taken to first pass and beyond.

Yield, Conversion and Selectivity
Considers limiting reactant and product

- High yield is desirable
- If yield is low but conversion is high- reaction requires optimisation
- If yield is low and conversion is low- reaction requires redesign

Yield is high	Yield low but selectivity high (low conversion)	Yield low and selectivity low (high conversion)
✔	Reaction can be optimised	You need to return to your reaction and redesign it

Atom economy
Considers all reactants
Assumes 100% yield

- Atom Economy (AE) measures the efficiency of the reaction by the number of the atoms from the reactants that appear in the final product.
- AE assumes 100% yield and stoichiometric loading
- AE is an excellent metric to access the inherent efficiency of a reaction with respect to use of reactants- however is not great as a standalone metric

Atom economy high (≥ 62%)	Atom economy low
✔	Maximise incorporation of starting material into product (fewer wasted atoms). Choose leaving groups to be as small as possible, avoid large protecting groups..

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Reaction mass efficiency
Considers all reactants, stoichiometries and yield
The most efficient your reaction can be is if RME=AE

- Reaction Mass Efficiency (RME) gives a fuller picture of reactant use. It is mass based and incorporates yield and stoichiometry
- According to Andraos[citeneeded]: a reaction is only considered green when both the AE and RME are above 62%. In other words, if a reaction has an RME of ≥62% but an AE ≤62%, or vice versa, the reaction is **not green**.
- However, if your AE and RME are much greater than the current state of the art, then you are well on your way to improving the green credentials of such transformations.
- The AE provides the optimum efficiency your process can achieve; the closer the RME is to it, the closer the reaction is to its optimal efficiency.

RME (≥62%) ~ AE	RME << AE
✔	Try to reduce stoichiometric loading of reagents whilst monitoring yield

Solvents

- At reaction discovery stage is clearly important to allow for screening for as broad a range of solvents as possible
- This will help determine the best solvent and best solvent properties for the reaction
- Which will come in handy if the optimum solvent you have selected for the reaction is highly undesirable- restricted by OPRD and REACH- which will give you a red a flag
- In this situation, use of solvent maps could help you find a greener solvent alternative to screen for.

No highly undesirable solvents	Black listed solvents used
✔	Do not use! Use CHEM21 solvent replacement guides to identify a potential replacement

Health and safety
Red-flagged substances carry a serious physical, health or environmental risk

- Screening for a broad range of reagents is also necessary at this stage and give a lot of insight into the chemical transformation
- As such only the most severe hazard statements (red flag) are to be avoided at zero pass and must be substituted

No red flag	Red flag
✔	Use reagent replacement guides to identify a potential replacement If not possible, must be justified!

First pass in more detail

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The CHEM21 Metrics Toolkit is specifically structured with a series of 'passes' to cover everything from bench top research right through to industrial scale with increasing level of complexity. In this video Sarah Abou-Shehada at the Green Chemistry Centre of Excellence, University of York examines '*First Pass*' in more detail. First pass is a more comprehensive evaluation of research that has shown potential at Zero Pass and has been further optimised and scaled up (ca. hundreds mg/g scale).

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Transcript

So you've screened a variety of different substrates or catalysts and you So you've screened a variety of different substrates or catalysts and you So you've screened a variety of different substrates or catalysts and you finally come up with a promising transformation and your zero pass has given you the green finally come up with a promising transformation and your zero pass has given you the green light and said you can proceed now to first pass.

First pass should be used during the optimization stage of your reaction design and light and said you can proceed now to first pass.

First pass should be used during the optimization stage of your reaction design and light and said you can proceed now to first pass.

First pass should be used during the optimization stage of your reaction design and light and said you can proceed now to first pass.

First pass should be used during the optimization stage of your reaction design and light and said you can proceed now to first pass.

First pass should be used during the optimization stage of your reaction design and this is a lot more stringent than zero pass.

It's worth noting that zero pass is not your final metrics, it merely means you've avoided this is a lot more stringent than zero pass.

It's worth noting that zero pass is not your final metrics, it merely means you've avoided as many of the nasties as possible before moving on to optimisation.

And the idea with the as many of the nasties as possible before moving on to

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optimisation.

And the idea with the as many of the nasties as possible before moving on to optimisation.

And the idea with the first pass again is to try and get feedback from the metrics with respect to your optimisation and see if you can improve on it.

It's going to highlight further hotspots in your methodology - areas that might require further development to improve further hotspots in your methodology - areas that might require further development to improve further hotspots in your methodology - areas that might require further development to improve further hotspots in your methodology - areas that might require further development to improve its greenness.

Again it's a lot more stringent its greenness.

Again it's a lot more stringent so it looks at things in a lot more detail - things you might get away with at zero pass will definitely be flagged at first pass.

So you probably covered yield, atom economy, so it looks at things in a lot more detail - things you might get away with at zero pass will definitely be flagged at first pass.

So you probably covered yield, atom economy, and reaction mass efficiency at zero pass and you definitely need to consider the same conditions that I mentioned for zero pass, but these mass-based metrics alone aren't enough and at first pass we also include mass intensity the same conditions that I mentioned for zero pass, but these mass-based metrics alone aren't enough and at first pass we also include mass intensity the same conditions that I mentioned for zero pass, but these mass-based metrics alone aren't enough and at first pass we also include mass intensity the same conditions that I mentioned for zero pass, but these mass-based metrics alone aren't enough and at first pass we also include mass intensity and process mass intensity which will take into account and process mass intensity which will take into account solvent usage, the work-up stage as well, so it can really give you a good idea of where you're solvent usage, the work-up stage as well, so it can really give you a good idea of where you're using most of your material.

So if your process mass intensity is poor but using most of your material.

So if your process mass intensity is poor but your reaction mass intensity and atom economy are good, you need to look for the your reaction mass intensity and atom economy are good, you need to look for the cause.

Chances are your reaction stage is fine but there's something in the work-up or maybe your solvent use your reaction stage is fine but there's something in the work-up or

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maybe your solvent use that's causing an issue.

The metric tool kit has been designed so that it can actually break down your that's causing an issue.

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The metric tool kit has been designed so that it can actually break down your that's causing an issue.

The metric tool kit has been designed so that it can actually break down your process mass intensity data to the solvents used at the reaction stage and the solvents used and process mass intensity data to the solvents used at the reaction stage and the solvents used and the reagents used in the work-up stage so you can really use it to home in on where your material sinks are within your process.

The metric toolkit your material sinks are within your process.

The metric toolkit also analyzes reagent use, so these are the materials you've input into the reaction to also analyzes reagent use, so these are the materials you've input into the reaction to also analyzes reagent use, so these are the materials you've input into the reaction to facilitate it but don't actually form part of the final product.

facilitate it but don't actually form part of the final product.

I just wanted to stop for a bit and talk about catalysis, the use of enzymes or chemo-catalysis.

A lot of people will say that if they're developing I just wanted to stop for a bit and talk about catalysis, the use of enzymes or chemo- catalysis.

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A lot of people will say that if they're developing I just wanted to stop for a bit and talk about catalysis, the use of enzymes or chemo- catalysis.

A lot of people will say that if they're developing a catalytic process then by default it's green because as is with one of the principles of green chemistry a catalytic process then by default it's green because as is with one of the principles of green chemistry is that catalysis is always better.

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However we are getting to the stage where we need to start delving is that catalysis is always better.

However we are getting to the stage where we need to start delving is that catalysis is always better.

However we are getting to the stage where we need to start delving deeper into the catalyst that we're using - how green is a catalyst itself? We need to consider aspects such as turnover number, so how many moles of your substrate can you use with one mole of your catalyst to convert it to We need to consider aspects such as turnover number, so how many moles of your substrate can you use with one mole of your catalyst to convert it to the product before the catalyst becomes deactivated.

Space time yield - this is quite important the product before the catalyst becomes deactivated.

Space time yield - this is quite important the product before the catalyst becomes deactivated.

Space time yield - this is quite important when you're considering scaling up, so how much of the material can you produce per mole of catalyst and and how quickly can you do that.

Ideally want to produce as much of the per mole of catalyst and and how quickly can you do that.

Ideally want to produce as much of the product is possible, with as little of your catalyst as possible, in as little time as possible.

Other aspects that we look at is recoverability and reuse, and this is to do with whether you're using a supported catalyst or not, because Other aspects that we look at is recoverability and reuse, and this is to do with whether you're using a supported catalyst or not, because Other aspects that we look at is recoverability and reuse, and this is to do with whether you're using a supported catalyst or not, because a supported catalyst can be recovered and reused, although when you're developing a a supported catalyst can be recovered and reused, although when you're developing a a supported catalyst can be recovered and reused, although when you're developing a a supported catalyst can be recovered and reused, although when you're developing a novel methodology that's not always straightforward, to move straight on to catalyst support, novel methodology that's not always straightforward, to move straight on to catalyst support, novel methodology that's not always straightforward, to move straight on to catalyst support, but if you bear that in mind when you're developing a methodology and this can but if you bear that in mind when you're developing a methodology and this can but if you bear that in mind when you're developing a methodology and this can but if you bear that in

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mind when you're developing a methodology and this can help you on your way to developing a catalytic methodology where your catalyst help you on your way to developing a catalytic methodology where your catalyst help you on your way to developing a catalytic methodology where your catalyst can be reused and recovered.

Another aspect is the use of critical elements.

A lot of the catalytic systems we depend on can be reused and recovered.

Another aspect is the use of critical elements.

A lot of the catalytic systems we depend on can be reused and recovered.

Another aspect is the use of critical elements.

A lot of the catalytic systems we depend on can be reused and recovered.

Another aspect is the use of critical elements.

A lot of the catalytic systems we depend on nowadays do use platinum-group metals based catalysts.

do use platinum-group metals based catalysts.

In the metric toolkit, you will be given a red flag if you're not using a catalyst and using your reagents in stoichiometric quantities, but you'll be given a green flag if you are using a catalyst, but other things you want to In the metric toolkit, you will be given a red flag if you're not using a catalyst and using your reagents in stoichiometric quantities, but you'll be given a green flag if you are using a catalyst, but other things you want to In the metric toolkit, you will be given a red flag if you're not using a catalyst and using your reagents in stoichiometric quantities, but you'll be given a green flag if you are using a catalyst, but other things you want to In the metric toolkit, you will be given a red flag if you're not using a catalyst and using your reagents in stoichiometric quantities, but you'll be given a green flag if you are using a catalyst, but other things you want to consider is its recoverability and whether you are using a critical element, and finding alternatives if you are.

consider is its recoverability and whether you are using a critical element, and finding alternatives if you are.

consider is its recoverability and whether you are using a critical element, and finding alternatives if you are.

Things to consider on recoverability are shown in the blue box, to consider Things to consider on recoverability are shown in the blue box, to consider Things to consider on

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recoverability are shown in the blue box, to consider either supporting it using a biphasic solvent system or membranes.

Solvents is either supporting it using a biphasic solvent system or membranes.

Solvents is addressed in first pass but it becomes a lot more stringent.

The solvents are now addressed in first pass but it becomes a lot more stringent.

The solvents are now separated into three categories - preferred, problematic and hazardous - which would each be given a green, amber or red separated into three categories - preferred, problematic and hazardous - which would each be given a green, amber or red separated into three categories - preferred, problematic and hazardous - which would each be given a green, amber or red separated into three categories - preferred, problematic and hazardous - which would each be given a green, amber or red flag respectively.

flag respectively.

Because solvents do form the bulk of the material used in a process, it is very important at this Because solvents do form the bulk of the material used in a process, it is very important at this stage to try and use a preferred solvent.

So if you are stage to try and use a preferred solvent.

So if you are using either problematic or hazardous solvents, try using solvent maps to find a number of different candidates for a solvent screen.

Not only will you hopefully find number of different candidates for a solvent screen.

Not only will you hopefully find number of different candidates for a solvent screen.

Not only will you hopefully find a solvent alternative, it could indicate the kind of physical properties you need to a solvent alternative, it could indicate the kind of physical properties you need to a solvent alternative, it could indicate the kind of physical properties you need to facilitate your reaction.

The metric toolkit also considers energy.

Now it's very difficult to measure the energy input The metric toolkit also considers energy.

Now it's very difficult to measure the energy input into your reaction at lab scale but the metric toolkit provides a few guidelines on how you can limit at lab scale but the metric toolkit provides a few guidelines on how you can limit the energy intensity of your

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process.

A green flag will be denoted if your reaction is running between 0 and 70□□C and a yellow A green flag will be denoted if your reaction is running between 0 and 70□□C and a yellow A green flag will be denoted if your reaction is running between 0 and 70□□C and a yellow flag will come up if you're using flag will come up if you're using your reaction between -20 and 140□□C.

your reaction between -20 and 140□□C.

Any reaction temperatures outside of these ranges will give a red flag.

Any reaction temperatures outside of these ranges will give a red flag.

If your methodology is running outside these ranges try to investigate developing a process to within the green reaction range or developing a process to within the green reaction range or as close as possible.

Another thing that came out of our discussions in the as close as possible.

Another thing that came out of our discussions in the CHEM21 consortium is the fact that if you're running reaction at reflux you are resulting in a six-fold increase in the energy requirements of your process.

So try to investigate you are resulting in a six-fold increase in the energy requirements of your process.

So try to investigate using your reaction at 5□□C below the reflux temperature of your solvent, make sure that you're not making any compromises with respect to your other metrics.

Alternatively sure that you're not making any compromises with respect to your other metrics.

Alternatively sure that you're not making any compromises with respect to your other metrics.

Alternatively try using a solvent that has a higher boiling point so that you can run your try using a solvent that has a higher boiling point so that you can run your reaction at that temperature without reaching a solvent's reflux.

reaction at that temperature without reaching a solvent's reflux.

reaction at that temperature without reaching a solvent's reflux.

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We also address batch and flow in the metrics toolkit, and this We also address batch and flow in the metrics toolkit, and this is done so that we can encourage people to use continuous flow processes so if you're using a batch process an amber flag will be produced, if you're using a flow process a green flag is given.

Now we realise it's not possible to run a process in flow, especially if your group doesn't specialise in it but if you've been making the right corrections to your methodology with respect to all the other metrics, such as using a supported catalyst, limiting the use of stoichiometric reagents, etc, then you are well on your way to developing methodology with respect to all the other metrics, such as using a supported catalyst, limiting the use of stoichiometric reagents, etc, then you are well on your way to developing methodology with respect to all the other metrics, such as using a supported catalyst, limiting the use of stoichiometric reagents, etc, then you are well on your way to developing methodology with respect to all the other metrics, such as using a supported catalyst, limiting the use of stoichiometric reagents, etc, then you are well on your way to developing methodology with respect to all the other metrics, such as using a supported catalyst, limiting the use of stoichiometric reagents, etc, then you are well on your way to developing a methodology that should be compatible with continuous flow processes.

As Louise mentioned in her a methodology that should be compatible with continuous flow processes.

As Louise mentioned in her a methodology that should be compatible with continuous flow processes.

As Louise mentioned in her presentation on the metrics toolkit, we do need to consider the downstream processes of your reaction.

It's not enough to think of your methodology processes of your reaction.

It's not enough to think of your methodology as the chemical transformation in isolation.

If you really want to make a real impact and as the chemical transformation in isolation.

If you really want to make a real impact and develop a green methodology, you do need to consider the work-up and isolation steps.

develop a green methodology, you do need to consider the work-up and isolation steps.

Mass-based metrics such as mass intensity can capture the material usage that encompasses work-up and isolation so Mass-based metrics such as mass intensity can capture the material usage that encompasses work-up and isolation so you do need to take a critical look at what methodologies you're using and solvents you're using at this stage.

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Various work-up you do need to take a critical look at what methodologies you're using and solvents you're using at this stage.

Various work-up and isolation steps were examined for the metrics toolkit and you'll get a green flag for the recommended work-up methods and isolation methods would be quenching, filtration, centrifugation, and isolation methods would be quenching, filtration, centrifugation, crystallisation and low temperature distillation, evaporation or sublimation, and by low-temperature we mean <140□□C at atmospheric pressure.

So when you're developing a methodology, you should be really looking at using these isolation and work-up methods first.

An amber flag is given if you are using solvent isolation and work-up methods first.

An amber flag is given if you are using solvent isolation and work-up methods first.

An amber flag is given if you are using solvent exchange or quenching to aqueous media.

Methods that you should really try to avoid are chromatography, high temperature exchange or quenching to aqueous media.

Methods that you should really try to avoid are chromatography, high temperature distillations, evaporations and sublimations - when we say high temperature, we mean >140□□C at atmospheric pressure.

Multiple recrystallisations distillations, evaporations and sublimations - when we say high temperature, we mean >140□□C at atmospheric pressure.

Multiple recrystallisations and ion exchange will also give you a red flag.

Health and safety, as with solvents, has a more stringent assessment at first pass.

The H codes that will and ion exchange will also give you a red flag.

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Health and safety, as with solvents, has a more stringent assessment at first pass.

The H codes that will either give a red or amber flag are shown on this slide, and ideally you want to look either give a red or amber flag are shown on this slide, and ideally you want to look at replacing reagants that fall within either of these categories where possible.

Something to note is that sometimes you're going to be at replacing reagants that fall within either of these categories where possible.

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Something to note is that sometimes you're going to be using a chemical entity that you've made in the lab - it's fairly novel and doesn't have an MSDS using a chemical entity that you've made in the lab - it's fairly novel and doesn't have an MSDS using a chemical entity that you've made in the lab - it's fairly novel and doesn't have an MSDS datasheet.

This doesn't mean your reagent is safe, and your metrics will not automatically be green as a result.

Generally the metrics toolkit will produce an amber flag for datasheet.

This doesn't mean your reagent is safe, and your metrics will not automatically be green as a result.

Generally the metrics toolkit will produce an amber flag for chemical entities that don't have an associated MSDS datasheet..

First pass interactive tool

Coming soon!

Morpholine exercise

To test your understanding, you can work through the exercise below using the CHEM21 metrics toolkit spreadsheet and following data sheets :

- Morpholine example: Method 1 data
- Morpholine example: Method 2 data

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When you have completed, compare your answers with the model answers below:

- Morpholine example: Completed spreadsheets and model answers

Scroll down the pages of the PDF below to see all questions.

Large scale example

Page coming soon

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Summary and further reading

This page reproduces content from L. Summerton and A. Constandinou, Beyond Mass-based Metrics: Evaluating the Greenness of Your Reaction, 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. 4, pp. 41-53.

Metrics will not provide a definitive answer to the question ‘is my reaction green?’ - this is never a straightforward yes or no answer, as there are numerous factors to take into consideration. It should however help to answer probably the most important question, 'is my reaction greener?' As with all things, a balance must be struck and a number of considerations should be incorporated into the decision making process.

An approach that encompasses more than mass based metrics has been studied in this module. This, alongside a greater understanding of the issues surrounding sustainability, and the ability to interpret the metrics results, should provide evidence to suggest where improvements could be made, and where methodologies are performing well.

Ultimately, the use of metrics bridges the gap between discovery and larger scale/process chemistry by highlighting issues at an earlier stage.

Recommended reading:

S. Abou-Shehada, P. Mampuys, B. U. W. Maes, Clark and L. Summerton , An evaluation of credentials of a multicomponent reaction for the synthesis of isothioureas through the use of a holistic CHEM21 green metrics toolkit, *Green Chem.*, 2016, **19**, 249–258.

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.

L. Summerton and A. Constandinou, Beyond Mass-based Metrics: Evaluating the Greenness of Your Reaction, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon,

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L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 4, pp. 41-53.

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.

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