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Modernizing the 12 principles of green chemistry: it's time

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This Perspective takes a look back at what the original 12 Principles were likely envisioned to be, where they are after over a quarter of a century relative to the original vision put forth by Anastas & Warner, and what changes are needed to make them a more demanding call to action given the events that have taken place in the world since their appearance in 1998.

Green foundation

1. It seems timely to "modernize" them to better reflect the current global situation. This Perspective, therefore, points to the current status of the 12 Principles, and how they need to be altered as a call to action, as time is running out.
2. This Perspective, while highlighting these original and fundamental Principles, focuses on responses to the original 12 Principles. These have led to a revised set of 12 Principles reflecting current times and the necessity of practitioners that now must pay greater attention to them, in revised format.
3. This updating should lead to (1) broader appreciation of their implications, and (2) greater attention being paid to green chemistry, as failure to do so by practitioners will have major consequences for society.

A. Introduction & background

The 12 Principles of Green Chemistry[1] represent a vision for making chemistry more environmentally responsible. Developed *ca.* 30 years ago by Anastas and Warner, these principles reflect aspirations for the future of chemistry, presumably, based on their experiences. The intention behind these guiding Principles was to promote the idea that, in the not-too-distant future, green chemistry would evolve into the standard practice within the field, embraced worldwide. However, while significant progress has certainly been made in this direction, it is evident that the extent of the transition envisioned at that time has yet to fully materialize. This is not to diminish the advancements achieved, but rather to recognize that the widespread adoption of green chemistry principles is still a work in progress. In particular, many research labs in universities, as well as sectors within the chemical enterprise, including the fine chemicals industry, such as pharmaceuticals, agrochemicals, and flavors & fragrances, have yet to completely, or in some cases even partially, integrate these Principles into their practices. Furthermore, it appears that many Contract Research Organizations (CROs) and Contract Manufacturing Organizations (CMOs) throughout chemistry are likely to be primarily focused on immediate economic considerations, rather than broader sustainability, which may limit their engagement with greener chemistry initiatives. Unfortunately, it remains (seemingly) unappreciated that embracing environmentally friendly practices could lead to more favorable economic outcomes, both in the short term and long run.[2] Continued dialogue and collaboration in this area should help bridge the gap and foster broader awareness, acceptance, and ultimately, the practice of these green chemistry principles across diverse sectors of this field.

Is it possible that the foundational Principles established decades ago may have anticipated more than what was achievable in a shorter timeframe? Given that green chemistry is often not perceived as a current reality,[3] it might be worth considering a thoughtful re-evaluation or "modernization" of the original Principles, informed by our current understanding. Put another way, should chemistry continue to evolve at a similar pace based on the same 12 Principles created during the last millennium, or is it time to re-assess them in light of the present state of chemistry? Perhaps it's an opportune moment to reflect on what we have learned and leverage this knowledge to refine our approach, acknowledging how significantly the landscape has evolved and is likely to continue to change.

To effectively modernize these Principles, it is important to understand what has actually changed over the past quarter of

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a century. Societal events, shifts in public awareness, and evolving circumstances today, probably more than ever demand attention. These factors collectively underline the necessity for incorporating new insights and perspectives. How can the 12 Principles be altered in such a way that they attract more attention; that the message they convey gets considered on a more frequent basis? This involves ensuring that the community does not simply acknowledge their existence, but also integrates their application into everyday decision-making and practices.

Over the past three decades since the 12 Principles were introduced, there have also been numerous advances, which are a positive step in the "right" direction. For example, several journals have appeared that cater exclusively to sustainability, and green chemistry, in particular.[4] But given the overall number of chemistry periodicals born during this time that bear either a direct or indirect relationship to the environment, has the needle been moved significantly towards the chemistry community becoming environmentally more conscious? Another example, among many, includes the level of support from various funding agencies throughout the world: have they come to fully recognize the importance of going green by financially investing more resources in creativity and innovation in sustainability, directing grant funds solely earmarked for increasing developments in this specific direction?[5] Have petroleum suppliers and consumers come to appreciate that, eventually, given that petroleum is a finite planetary resource, the day will eventually arrive when supplies are gone, and hence, society's reliance on their products, including some organic solvents, is in trouble and we may actually be, therefore, on "borrowed time"?[6,7] Have more universities worldwide, in any general way, demanded as they should (or have they even requested) that courses on green and sustainable chemistry be offered?[8] Has a Nobel Prize been awarded, regardless of recipients, in recognition of sustainability, calling much-needed attention to this topic? And while there are many additional questions along these lines that could be similarly queried, it should not come as a surprise that the answers to each of the above are the same: at best, maybe, or more likely, no.

Although the 12 Principles, as they currently stand,[1] make every attempt to inform and teach us what should be done, there is no connection as to what to expect if and when they are not followed. Examples of this disregard are plentiful, such as the continuing belief that Ni (and related Earth-abundant metals) must replace Pd in well-known cross-coupling reactions,[9] notwithstanding this metal's endangered status and greater toxicity than Pd, and that its use together with expensive and often toxic ligands in catalysis, involves organic solvents and hence, a guaranteed negative environmental consequence (*i.e.*, called waste).[9] And so, many years later, while most practitioners still opt to look the other way, traditional chemistry, for the most part, whether involving organic chemistry or other areas of consequence also under the blanket of sustainability, is still … chemistry. Due to this lack of global compliance, the resulting environmental issues have become truly daunting. None, however, has become more challenging than the existential problem of climate change, which is going to have major impacts on society as currently defined (*e.g.*, food supply, water quality, good health, immigration, *etc.*). Fortunately, this can be where synthetic chemistry can do its part; this is where chemists not only understand how this is happening, but also why. Doesn't the very first Principle state that waste should not be created, rather than forcing remediation once formed? Thus, in spite of the decades-old teachings of the ACS Green Chemistry Institute:[10] that the major (by far) source of organic waste derives from organic solvents being the medium for most reactions, their use remains common and has even been expanded. In fact, organic chemistry, even though it is one of several influential areas, continues to pay little attention to this major issue, and by doing so, may knowingly be contributing to climate change. To be fair, this dire situation could not have been imagined at the time that the 12 Principles were being scribed;[1] nonetheless, here we are, with the exact same 12 Principles, but in a very different world.

B. Discussion

So, what can be done? How do the concepts behind the original 12 Principles of Green Chemistry, which are today even more timely, become more effective? Whatever is proposed, or reviewed and updated,[11] must convey or, perhaps, remind practitioners of Nature; that Nature has been doing chemistry on Earth for over 4 billion years,[12] and yet, not a drop of petroleum in the ground has been touched. All of Nature's chemistry has been, and still is, done either neat or using water in an "on dirty water" or "in water" sense, the latter based on "soft matter"[13] (*e.g.*, membranes, vesicles, and micelles) for purposes of solubilizing water-insoluble compounds. Proof of this resides with us; in humans, believed to occupy the planet beginning a mere 300 000 years ago (or more),[12] documenting that Nature's chosen medium on which human life depends is water. And yet, modern organic chemistry, although it has generated an impressive number of transformations and hence, new and very important knowledge, spans a mere 250 years or so. During this time, it has become an unsustainable discipline, with most reactions across all subdisciplines typically performed in organic solvents, which generate enormous amounts of waste. Instead, there are "Green Solvent Guides", suggesting that "…there is no universal approach to solvent selection",[14] thereby encouraging readers, and students, in particular, to only consider "greener" organic solvents, all of which contain carbon and therefore, by definition, once burned, further climate change. This must change. Nature, being the perfect model, has already developed responses as to how to solve key questions being faced by the world, today. Nature defines efficiency on its own terms and not by rules created by a petroleum-based field of study. It is Nature that must be recognized and its teachings incorporated into our thinking. Hence, there seems to be a need to critically examine the original 12 Principles and to make changes based on Nature's teachings, and considering where the world is now; to modify them in a way that conveys a sense of urgency currently in play. It seems to be time that the 12 Principles, originally scribed mainly as nouns…become verbs…

Here are the original 12 Principles of Green Chemistry, as written by Anastas and Warner, as they appeared in 1998:[1]

1. Waste Prevention
2. Atom Economy
3. Less Hazardous Chemical Synthesis
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-Time Pollution Prevention
12. Safer Chemistry for Accident Prevention

A "modernization" must also consider a reordering, reflecting a shift in relative importance. Augmentation of selected Principles may also be needed in response to new technological developments. And finally, each and every one of the revised 12 Principles which follows must become, unequivocally, a call to action;[15] a call for the chemistry community to take notice; that these be treated as "orders" from Nature. We no longer have a choice.

"Modernized" 12 Principles of Green Chemistry:

1. DO NOT CREATE WASTE! (was, and remains, Principle 1)

Rationale. The wording for this 1st Principle is made stronger than the originally penned "Waste Prevention", which now, hopefully, encourages the reader and/or practitioner to go beyond the words; to see what is meant, and why this concept has become so important. It is especially directed towards the fine chemical and pharmaceutical suppliers, since, as originally noted by Sheldon,[16] syntheses pharma area have done in the highest *E*-factors[17] given the multitude of steps involved in making most drugs. This is by no means an attempt to minimize the importance of these industries; indeed, how can it not be appreciated that the pharmaceuticals made are not lifesaving, or the herbicides and pesticides made by the agrochemical enterprise not be recognized for enabling the feeding of the planet. Nonetheless, and curiously, how is it that biocatalysis is regarded as an "up-and-coming" area[18] that utilizes widely accessible and native enzymes that have undergone improvements *via* directed evolution, and yet enzymatic catalysis takes place mainly in an aqueous reaction medium. Unfortunately, such a major point is rarely brought to light. Shouldn't this aspect of modern biocatalysis be highlighted and its use further encouraged as a green technology? And what about other key albeit waste-generating features of biocatalysis that must not be ignored. On the other hand, chemocatalysis is done mainly in organic solvents, many of which derive from our petroleum reserves and ultimately are burned. Considering the extensive number of "tools in the toolbox" that today offer many of the same types of bond constructions and can be even more effective from the synthetic perspective, it remains clouded as to why this approach to synthesis and its impact on sustainability is not being more widely employed, especially at the planning stages. Perhaps a directive to stop generating organic waste needs to be made, and enforced?

It should also not go unstated that there are several other industries that are also contributing to climate change, including mining (4–7%), and cement production (*ca.* 8%), *etc*. Nonetheless, the chemical industry is regarded as a major contributor (*ca.*14%) based on its use of fossil fuels. This is roughly equivalent to that associated with livestock farming.[19]

2. Use safer and recyclable solvents/reaction media (was Principle 5)

Rationale. The use of auxiliaries today is no longer common; it has become a minor contributor to waste, and hence, should be replaced by a more urgent and hence, timely Principle (*vide infra*). On the other hand, using safer solvents and reaction media must be strongly encouraged. And so, with this in mind, what is safer than water? Answer: no solvent. This implies that technologies such as mechanochemistry need to be more in focus. But if solvents are needed, then while alcohols are flammable, they are better than other choices (such as dipolar, aprotic solvents such as NMP, DMSO, and DMF). If recycling can be done, then alcohols and water are both wisely chosen, as is EtOAc. Even CPME and MTBE are recyclable if used as the sole reaction solvent, although in all cases, energy consumption for recycling purposes must be taken into account. Nature MUST be the guide here. Moreover, as succinctly stated by Roger Sheldon long ago (and could even be argued as a replacement Principle):[17]

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred.

3. Invest in catalysis, and telescope (was Principles 3 and 9; have been combined and augmented)

Rationale. If designed properly, a series of reactions *en route* to a target should include as many steps as possible being done with the 12 Principles in mind, focusing especially on catalysis. But also, with far better impurity profiles expected when following Nature's lead (given the milder conditions when reactions are run in water), telescoping needs to be the new norm, whether done using Nature's reaction medium or in a recyclable organic solvent. That is, telescoping implies that several steps can now be accomplished in a single pot. For example, this approach has recently been utilized leading to the anti-COVID 19 drug nirmatrelvir, the key ingredient in Paxlovid.[20] Processes should also be planned such that workups (*i.e.*, use of large amounts of water) are minimized, if needed at all, leading to gains in both time[21] and pot[22] economies. It need be appreciated that Nature does synthesis this way: easily, smoothly, and even executes multiple steps at the same time, routinely.

4. Focus on safer chemicals (was Principles 4 and 12)

Rationale. Since green chemistry, by definition, is safe chemistry, this remains an important Principle, being time-independent. And by doing so, this implies that there will be a minimization or avoidance entirely of accidents that are chemistry-based. Unfortunately, practitioners tend to go with what they know, or what has worked previously, rather than which reagent follows the 12 Principles and is the safest. Occasionally, cost factors may be determining, but usually not. New reagents that appear on a regular basis should be evaluated with safety in mind, and if they meet these criteria should not only be highlighted but their use encouraged.

5. Design energy efficient processes (was Principle 6)

Rationale. Although there is a very modest change in wording from the original Principle, this important concept spells out what the process chemistry needs to seriously consider. Energy is not a major driver on their spreadsheet in North America, but in Europe and other parts of the globe (such as in Asia), it certainly is or can be, depending upon scale. Therefore, in general, this important Principle must be accentuated for all processes, whether based on chemo-, bio-, and/or chemoenzymatic catalysis, and regardless of the product being manufactured. In the future, the availability of, and access to, inexpensive sources of energy may greatly impact the "greenness" of a process at scale, and hence, such a consideration places an even greater dependence on this particular Principle. But until that day arrives, when energy is freely available, its use (mainly in the form of heating reaction mixtures over time) should be taken into account. Moreover, an awareness must be developed that includes the interplay of energy and how its use (*e.g.*, how much?) is impacted by other factors (*e.g.*, choice of medium, functional group compatibility, time,[21] and pot[22] economies, *etc.*).

6. Find "Gifts" from Nature (was Principle 7; has been augmented)

Rationale. As organic chemistry, unfortunately, continues to consume limited planetary resources, an awareness of the many gifts that Nature has waiting to be discovered, as well as the ones that have already become known, including "renewables", must be further developed. Previously, the focus has been solely on finding additional ways to utilize, in particular, bio-renewables. Nonetheless, it is also important to expand the pie and to appreciate that there are several natural resources ripe for discovery. The keyword here is "awareness"; we need to start "looking" for these treasures that exist; they may be hidden, usually within other, less interesting, and oftentimes, far less valuable items. Nonetheless, they are there, but unfortunately, the general practitioner is not in the habit of noticing or even thinking along these lines.

For example, and there are several, where a precious metal, such as palladium, is being made available by Nature, albeit in masked form. Consider the rare case where Pd is present in the iron ore being mined (in this case) in one country and processed in another. After chlorination (*i.e.*, conversion to very inexpensive $FeCl_3$), there is enough Pd present such that nanoparticles created *via* addition of MeMgCl affords a catalyst capable of effecting Suzuki–Miyaura couplings under mild conditions.[23] Thus, while other sources of iron ore, and the resulting $FeCl_3$ derived therefrom were ineffective (*i.e.*, contained too little Pd to catalyze the same couplings), finding and then testing this source revealed new technologies ripe for development,[24] not to mention that this Pd (within the $FeCl_3$) was essentially, free. What else are we missing that Nature has provided?

7. Design products for facile degradation (was Principle 10)

Rationale. The original concept remains as a fundamental Principle of Green Chemistry, as examples of new problems that reflect the importance of this approach to product design keep appearing; *e.g.*, PFAS, or "forever" materials.[25] These new developments must be part of the planning process!

8. Ensure pollution prevention (was Principle 11; has been augmented)

Rationale. This revised Principle underscores the urgent need to integrate innovative, holistic, and sustainable thinking into the design process en route to a product that society recognizes as vital. It calls for a proactive approach, where the environmental consequences of producing materials are carefully evaluated from the outset. As the world grapples, *e.g.*, with the issue of pollution caused by the buildup of plastics, it is imperative that we learn from past missteps and prioritize eco-friendly practices to safeguard our planet for future generations.

9. Be mindful of toxicological issues (newly added)

Rationale. The prospect that any product is, or might become (in time) a pollutant needs to be considered at the design stage. And if so, what are the potential dangers to mankind and any life form that is part of the equation? Modern society now recognize that this can be a very real issue; for example, if a product becomes part of an aqueous waste stream, how can it be easily and cost-effectively decomposed into simpler materials that are harmless to all living species? This is a very real example of a new Principle that reflects a current reality that has become non-trivial.[26]

10. Don't forget metrics! (newly added)

Rationale. If there is one and only one take-home lesson learned these past decades, it is that what is being claimed as "green" or "sustainable" may not be, and in reality, may actually be quite the opposite (*i.e.*, environmentally harmful). The only way to show that these Principles are playing a role is to do the math; make the calculations showing that the chemistry, indeed, is green. There are today many options, commonly referred to as metrics, for proving the extent of "greenness" associated with work done: *E*-factors, process mass intensity (PMI), life cycle assessment (LCA), innovation Green Aspiration Level (iGAL), *etc.* Whichever is chosen is relatively important; however, at least one that is holistic must be selected if the work being presented is truly sustainable. Otherwise, the chemistry literature will continue to feature unsubstantiated claims that can mislead readers and, even worse, encourage the use of environmentally damaging processes.

Notably, several journals catering to green chemistry have recently introduced various ways of convincing the Editors that the work being submitted meets these requirements; that truly green chemistry is involved. As cases in point, Green Chemistry now features a Green Foundation Box that must accompany each submission, and appears prominently at the beginning of each paper.[27] Also, ACS Green Chemistry & Engineering has very recently put out a detailed statement as to what it expects and how to evaluate greenness and sustainability as a whole for each manuscript prior to its consideration for publication.[28] These examples serve to make it abundantly clear that the use of some "metric" will be essential for convincing editors, referees, and the readership that the work being described is truly "green".

11. Innovate following Nature's lead (newly added)

Rationale. Forget the boundaries imposed by current thinking. Invent solutions that address the important question: How would Nature solve this problem? The more that chemists find ways that Nature would, or already has, come up with a solution, the closer green chemistry gets to being "chemistry". We need to encourage (and reward!?) every practitioner to think along these lines at the outset; to increase awareness of this environmentally important approach to targets, using alternative means of achieving the same goals, but doing so in ways that are "green". For example, using chemistry that takes place with equal effectiveness in an aqueous medium at ambient temperatures, rather than using dry (and waste-generating) THF at low temperatures (which below −20 °C is costly).

12. Evaluate! (newly added)

Rationale. It is imperative that practitioners develop the habit of critically evaluating their own proposed work from an environmental standpoint before undertaking any project. Questions such as: Has the proposed plan taken measures to respect Nature, both short and long term? If the chemistry goes precisely according to plan, what's the overall impact on the environment? What is the anticipated backup scenario, and does it also align, to the extent possible, with the 12 Principles of Green Chemistry?

Previously included among the original Principles were both "atom economy" and the idea that a series of reactions should include a reduction in associated derivatives. These have been left out among the revised 12 Principles for the following reasons:

Atom economy (was Principle 2). This concept is certainly still valid, and yes, this critical mode of thinking is important to highlight when applicable. But time has shown that there are relatively few cases of this concept having become reality. For example, C–H activation can be a highly atom-efficient cross-coupling reaction, but it involves several other components that, overall, negatively impact its green metrics. More importantly, atom economy is not as indicative of a process being green compared with the other metrics that now exist. This concept, along with "step economy" that also falls into this category, are both extremely important conceptually, but have yet to be pursued to the extent initially anticipated.

Reduce derivatives (was Principle 2). This Principle implies that there is a need for extra steps that result in more time to be invested, as well as losses of material, such as in the case of protecting group chemistry. Over the years, this concept has dramatically gained in appreciation, although such acceptance may be mainly due to the implied impact on chemical yields. Nonetheless, with processes that already reflect this original Principle today, it is no longer considered a major environmental issue.

C. Implementation

Ultimately, "modernization" of the fundamental 12 Principles is about translating, and quickly, these words into actions. One approach is to ensure that they are seen by future chemists, especially younger students who will inherit worldly problems, existential or otherwise, that now exist and continue to be created by the limited pace at which green and sustainable chemistry is being advanced. For this to happen, more talks advocating this subject are needed, as is a greater infusion of green chemistry into curricula within our educational system.[29] Also needed is a level of awareness of the issues that can be met with a greater investment in the sustainability needs of society, conveyed to both elected officials[30] and agencies that decide on funding criteria. And lastly, although there remain several additional pathways for action, industrial processes should be identified as leading to appropriate benefits, both of an economic and environmental nature,[31] and evaluated for future use knowing that by going green, the likelihood of realizing these benefits is usually high.[32]

D Conclusions

Overall, revising the 12 Principles of Green Chemistry is meant to both acknowledge and appreciate where chemistry was originally envisioned to be, as put forth by the Anastas and Warner team;[1] that green chemistry must, and soon, become the prevailing, overarching way that chemists think about, and then carry out reactions. And while there are definitely visible elements of change in the right direction, some "green chemistry" claims appear merely as verbiage; words that seem in harmony but offer no clear path forward, resulting in slow progress. Together, we need action, and they are needed NOW. The major difference between "then and now", however, is that time is running out. The pace at which actions use these overriding, and now, modernized Principles must be accelerated; our survival is at stake. Fortunately, Nature continues to provide the hints, guidance, as well as the materials needed. The question that remains, however, is: Are we paying attention?

Conflicts of interest

There are no conflicts to declare.

Data availability

There is no data supporting this article since it is a perspective and none is required.

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