The Regulatory Pulse

In conversation with the experts

A guide with regulatory insights on registration of microbial bioproducts

Metabolites in Agricultural Biologicals

Relevance, Risk Assessment and Key Considerations for Registrants

VOL. 4
APRIL 2026

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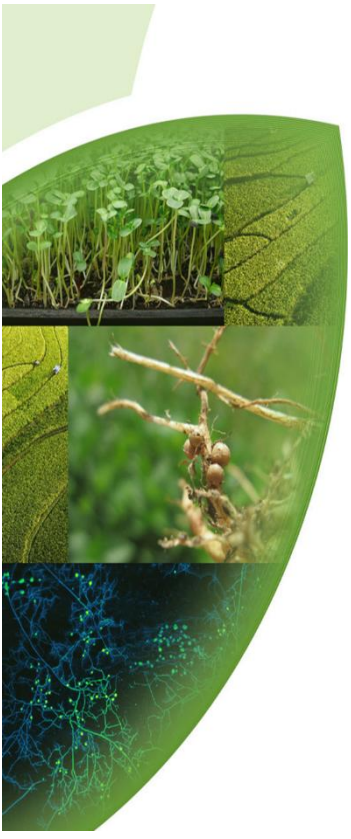
Acknowledgement

We sincerely thank Dr. Jacques Drolet for sharing his expertise and insights on metabolites for this edition. We also acknowledge the invaluable contributions of our research and publication team whose collaboration makes *The Regulatory Pulse* possible.

This publication is supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) through the ARTP program whose funding was provided to the Institute for Sustainable Horticulture to advance innovative agriculture solutions. The opinions expressed herein are those of the contributors and do not necessarily reflect the views of NSERC.

In This Issue



Editor's Note

Welcome to another edition of *The Regulatory Pulse*. This edition of our regulatory guide focuses on the critical metabolite chapter for microbial bioproduct registration, an area of increasing regulatory and scientific scrutiny. Given that these metabolites are the primary drivers of efficacy and safety, a rigorous approach to this chapter is crucial for securing regulatory approval. Understanding these tiny compounds and how they interact with their microbial hosts is critical for researchers and registrants navigating the path to market.

Our guest, Dr. Jacques Drolet, is a seasoned expert in microbial pesticide regulation, with years of experience in metabolite characterization and risk assessment. In this volume, he provides practical guidance, real-world examples and actionable insights on metabolite identification, characterization, risk assessment, data requirements and regulatory strategies. Whether you are a first-time applicant, an experienced registrant, or developing novel microbial strains, the insights shared here aim to make metabolite evaluation more approachable and support smoother, more predictable regulatory submissions.

We hope this edition serves as a practical reference, helping bridge the gap between science and regulatory practice while promoting the development of safe and sustainable microbial bioproducts.

Dr. Jaswinder Kaur

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Spotlight Interview - In Conversation with

DR. JACQUES DROLET

Government and Industry Advisor

Dr. Jacques Drolet is a biologist dedicated to advancing sustainable agriculture on a global scale. He supports food safety and fair, "eye-level" trade by helping companies gain international approvals for sustainable crop protection products, enabling growers to access these products and achieve international accreditation, and assisting regulatory bodies worldwide in implementing OECD harmonization tools.

With a lifelong career as a biotech founder, civil servant and international aid worker, Dr. Drolet also guides KAYAKAYO consultants in delivering services across diverse global contexts.

Questions & Answers - Insights from the expert

The following interview was coordinated and edited by Dr. Jaswinder Kaur, Publication Editor.

1. To start with the basics, when we talk about metabolites in microbial pesticides, what exactly are we referring to and how are these metabolites broadly classified?

Dr. Jacques Drolet: When we talk about metabolites in microbial pesticides, we are generally referring to non-physiological (secondary) metabolites produced by bacteria or fungi. These compounds play key roles in a microorganism's survival and function in its environment.

They can contribute to beneficial activities, such as biological control, competitiveness, and environmental adaptation, but they may also be associated with undesirable or toxic effects. Broadly, these metabolites support functions such as host or substrate penetration, toxicity, attraction or signaling, organism identification, soil or substrate optimization, and interactions with other organisms, including collaboration and mutualism.

2. That's interesting- these compounds can almost be thought of as tools that help microbes survive, thrive, and, in some cases, cause effects of regulatory concern. From a regulatory standpoint, how important is it to characterize these metabolites? Are there thresholds or specific concerns regulators focus on?

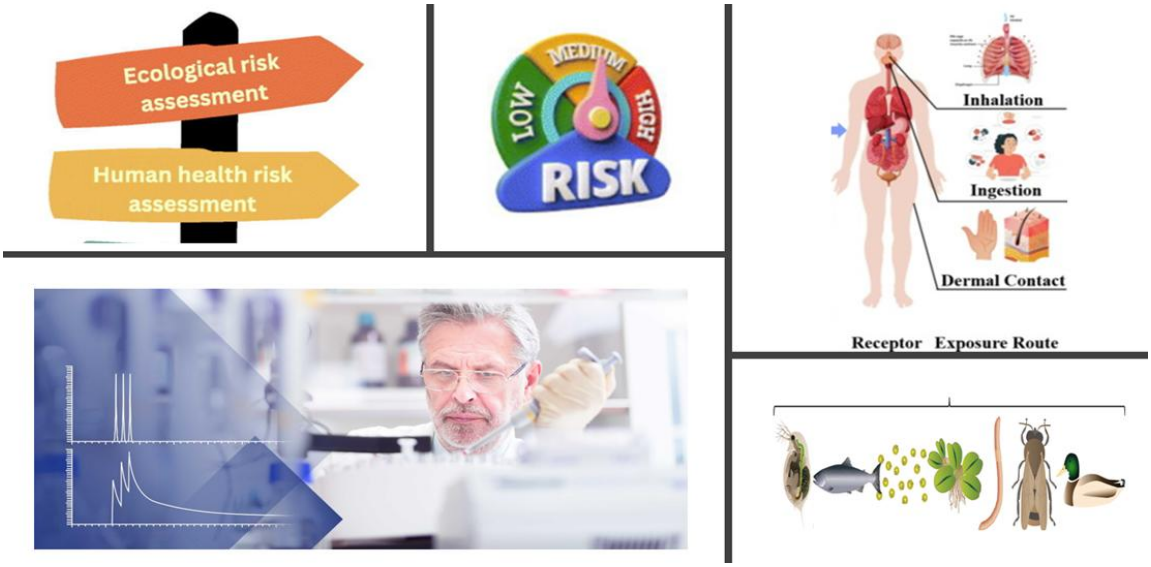
Dr. Jacques Drolet: From a regulatory perspective, the importance of characterizing metabolites is directly linked to risk, which is defined as toxicity multiplied by exposure. The primary objective is to identify metabolites that present the highest potential risk, based on this hazard–exposure relationship.

In practice, this evaluation relies on established safety thresholds, particularly the reference dose - an estimate of daily oral exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of harmful non-cancer effects over a lifetime. The risk is compared against the reference dose to determine the level of concern for a metabolite. If the risk exceeds the reference dose, you will need to focus on that metabolite and decide if it is worth pursuing. As soon as you show that the metabolites with the highest risk are not of concern, the remaining metabolites (often present at very low concentrations) are generally considered irrelevant from a regulatory perspective.

3. How does a registrant determine if the metabolites are relevant for regulatory assessment?

Dr. Jacques Drolet: Risk is defined as toxicity multiplied by exposure. From a regulatory perspective, two broad areas are considered: human health and the environment. Human risk is typically assessed using mammalian model species, while environmental risk is evaluated using a selected set of non-target organisms that represent ecological systems.

For human health assessments, regulators focus on the metabolites present at the highest concentrations and evaluate their mammalian toxicity. For environmental assessments, a similar approach is taken using the key test organisms applied to conventional synthetic pesticides, although exposure calculations differ from those used in mammalian risk assessment. If exposure levels are well below the reference value—often by several orders of magnitude (e.g., more than 10,000-fold), the risk is generally considered acceptable. It is also important to note that regulators assess risk to individuals for humans, whereas population-level effects are the focus for environmental species. Domestic animals tend to fall between these two assessment frameworks.



4. Is there an established list or database of known hazardous metabolites used by PMRA or other regulatory agencies? If not, what are the best starting points or resources for identifying potentially relevant metabolites? I know that registrants could end up paying a lot of money to quantify things that PMRA may not be concerned with.

Dr. Jacques Drolet: There is no single, universal list used exclusively by PMRA or other regulators, but there are several well-established databases that compile known toxic microbial metabolites and are widely used as starting points for risk assessment.
Here just a few:

Bacteria: https://pmc.ncbi.nlm.nih.gov/articles/PMC10790787/
https://toxinome.pythonanywhere.com/
https://academic.oup.com/nar/article/51/D1/D452/6761730
https://libguides.sjf.edu/c.php?g=908256&p=6645213
https://cfs.nrcan.gc.ca/projects/119/2
https://data.ub.uni-muenchen.de/423/
Fungus: https://www.mycocentral.eu/

5. And in that context, are there any known toxic metabolites, like mycotoxins or antibiotics, that could trigger additional data requirements?

Dr. Jacques Drolet: Yes, but it is about the risk, not hazard alone as I mentioned earlier. Even compounds that are well known for their toxicity can be acceptable at sufficiently low levels. For example, aflatoxins are among the most potent mycotoxins, yet Health Canada permits them at low concentrations, with established limits such as 15 parts per billion (ppb) for total aflatoxins in certain products. What matters from a regulatory perspective is whether the metabolite's concentration and exposure scenario exceed acceptable risk thresholds.
If a known toxic metabolite is present at levels that could pose a risk, it may trigger additional data requirements; if not, further assessment is generally unnecessary.

6. Do the tolerances differ between countries? Or are they similar? Do they accept each other's tolerance limits? I know that some countries have different tolerance limits for some pesticide residues in food. So, could their tolerance different for naturally produced microbial metabolites in biopesticides too?

Dr. Jacques Drolet: Yes, tolerances can differ between countries, and this also applies to naturally produced microbial metabolites in biopesticides.
If a metabolite is considered a potential risk, regulators may need to establish a tolerance or maximum residue limit (MRL). These limits are based on several factors, including:

(i) the toxicity of the substance,
(ii) the level of exposure,
(iii) the sensitivity of the most sensitive species or in the case of humans on the sensitivity of the most sensitive organ,
(iv) the type of toxicity (e.g., acute, chronic, carcinogenic, endocrine-related),
(v) the already registered products if the risk cup for that substance is getting full,
(vi) environmental sensitivity (high ground water), and
(vii) the food basket of a region.

Toxicity as such is more or less universal (at a population level) but it is also clear that some of these influencing factors vary from region to region such as the already existing products, the food basket, environmental context, etc.

Countries have made tremendous efforts to harmonize tolerances, but it is a difficult grey area at the border of business, politics, and science. This is the reason that we say that one should consider seriously if the appetite is big enough to engage in the registration of a biological product involving a metabolite that may force the regulator to establish a tolerance (MRL).

7. What toxicity studies would be needed if a strain is producing a relevant metabolite?

Dr. Jacques Drolet: Relevance is determined by risk, not by the mere presence of a metabolite. If a metabolite presents a meaningful risk, the assessment framework is similar to that used for conventional synthetic chemicals, but with an important added dimension.

For microbial products, regulators also consider whether the organism producing the metabolite can multiply, persist, or spread in the environment, and under what conditions. This includes evaluating the organism's survival, replication potential and capacity to increase exposure over time. These biological characteristics can significantly influence both exposure scenarios and the overall risk assessment and therefore guide the type and extent of toxicity studies required.

8. That makes sense. It's not just about the metabolite itself, but also the organism's ability to multiply and spread, which certainly adds another layer of complexity. In cases where metabolites are likely to remain as residues in food or feed, do the registrants need to establish Maximum Residue Limits (MRLs) for these?

Dr. Jacques Drolet: Only if the risk assessment indicates it is necessary. In such cases, the metabolite is treated much like a conventional synthetic substance and MRLs would be required. However, when a microbial product reaches this point, it is often worth carefully reconsidering its overall suitability as a biopesticide.

9. Are there some examples of when a metabolite has been considered too risky?

Dr. Jacques Drolet: Whether a metabolite is considered too risky really depends on the regulatory context, which can vary between countries. There are several examples where metabolites or microbial products have been assigned maximum residue limits (MRLs) because regulators saw a potential risk. For microbial pesticides: *Bacillus thuringiensis* (Bt), *Trichoderma* species, and various baculoviruses have been given an MRL by some countries. The same applies to biochemical/botanical pesticides such as Neem oil, citronella oil, pyrethrins, and plant extracts, and to mineral-based pesticides such as Kaolin clay, iron phosphate, and insecticidal soaps. Similarly, fermentation-derived compounds like Spinosad often have a specific, low-level MRLs in many jurisdictions.

The key point is that metabolites are not automatically assumed safe. If exposure or toxicity data suggest any potential risk, regulators will set limits or require additional assessment.

10. Is there ever a situation where the benefit of a product might outweigh the fact that one of its metabolites is technically above a risk threshold? Could you please provide a few examples?

Dr. Jacques Drolet: Yes, there are situations where the benefits of a product can outweigh the fact that one of its metabolites is technically above a risk threshold. A classic example is Spinosad, where its efficacy against key pests justified regulatory acceptance despite low-level exposures. Other examples include:

- Abamectin (Avermectins): Secondary metabolites from *Streptomyces avermitilis* used as miticides and insecticides.
- Bacillus metabolites: Strains of *Bacillus subtilis* and *Bacillus amyloliquefaciens* produce antifungal compounds like surfactin and fengycins, registered for biocontrol.
- Gibberellins (Gibberellic Acid): Produced by fungi such as *Gibberella fujikuroi*, these plant growth regulators can induce systemic resistance.
- Rhamnolipids: Glycolipids from *Pseudomonas aeruginosa* and other bacteria, acting as biofungicides against pathogens like *Botrytis cinerea*.
- Fermentation products: Lysates or inactivated cells from organisms like *Willaertia magna* or *Burkholderia rinojensis*, used as nematicides or fungicides.
- Plant defense elicitors: Microbial-derived compounds like jasmonic acid and salicylic acid that trigger induced systemic resistance.
- Microbial viruses and bacteriophages: Certain baculoviruses, such as *Cydia pomonella* granulovirus, are registered with minimal residue concerns.

The key is that regulatory acceptance depends on a weight-of-evidence approach, balancing demonstrated efficacy and societal benefit against potential risks. While regulatory harmonization would help, decisions can still differ between countries**.**

11. Are there any tolerance exemptions for certain classes of metabolites that are considered inherently low risk?

Dr. Jacques Drolet: Low risk considerations are no exemption. We have to go away from the concept of exemption or waivers. If the assessed risk to mammals and the environment is well below acceptable thresholds, the metabolite is considered acceptable, not because it is exempt, but because further study is scientifically unnecessary. Once it is clearly demonstrated that exposure is far below the reference value, the regulatory concern is effectively resolved. Some regulators, such as those in the EU, have introduced tools like the Qualified Presumption of Safety (QPS) framework to streamline this process for both regulators and applicants.

12. You mentioned that when risk is well below the Rf, further study simply does not make sense. Could you share a few practical examples where low-risk determinations were accepted without triggering further testing?

Dr. Jacques Drolet: There are many practical examples where low-risk determinations were accepted without triggering additional testing, particularly for well-characterized microbial active ingredients. From an organism perspective, several have been registered without the need for MRLs, including *Beauveria bassiana* (e.g., GHA strain), *Trichoderma harzianum*,

Ampelomyces quisqualis, *Simplicillium lamellicola*, *Bacillus subtilis* (e.g., QST713, GB0365, M27), *Bacillus thuringiensis* subspecies *aizawai* and *kurstaki*, *Bacillus amyloliquefaciens*, *Paenibacillus polymyxa*, as well as baculoviruses such as *Cydia pomonella* granulovirus (CpGV), *Spodoptera exigua* multiple nucleopolyhedrovirus (SeMNPV), and *Helicoverpa* armigera nucleopolyhedrovirus (HearNPV). Their registration without MRLs reflects the conclusion that exposure and hazard profiles of these did not warrant concern.

From a metabolite perspective, this implies that even the "worst-case" or most biologically active compounds associated with these organisms were not considered to pose unacceptable risks. For example:

- *Beauveria bassiana*: metabolites such as beauvericin, bassianolide, tenellin, and oosporein
- *Trichoderma harzianum*: peptaibols, terpenoids, polyketides, and lactones
- *Ampelomyces quisqualis*: hydrolytic enzymes (e.g., chitinases, β-1,3-glucanases, proteases) and volatile compounds such as squalene and fatty acids
- *Simplicillium lamellicola*: compounds like verlamelin and mannosyl lipids (e.g., halymecins)
- *Bacillus subtilis*: lipopeptides (surfactin, fengycin, iturin), polyketides (bacillaene, difficidin), siderophores, and VOCs
- *Bacillus thuringiensis*: Cry, Vip, and Cyt proteins, along with other metabolites such as zwittermycin A and certain enterotoxins
- *Bacillus amyloliquefaciens*: similar lipopeptides and polyketides (e.g., macrolactin, difficidin, bacillaene)
- *Paenibacillus polymyxa*: polymyxins, fusaricidins, enzymes, phytohormones, EPS, and VOCs

For insect viruses, the situation is different—they do not produce secondary metabolites in the traditional sense. Instead, their replication in host insects results in proteins such as metalloproteases, cathepsins, chitinases, and apoptosis inhibitors, along with normal cellular metabolites like amino acids and vitamins. These have likewise not triggered concern under typical exposure scenarios.

The common thread across these examples is that regulators were satisfied—based on available data, exposure considerations, and weight-of-evidence arguments—that risks were well below levels of concern. In such cases, requiring additional studies simply did not add scientific or regulatory value.

13. You mentioned QPS, a tool being used by EU regulators. Could you briefly explain how QPS works and how it helps both regulators and applicants in assessing risk?"

Dr. Jacques Drolet: EU regulators establish a Qualified Presumption of Safety (QPS) list. The four Pillars of QPS Assessment used are:

a) The Taxonomic Identity: The microbe must be unambiguously defined, usually at the species level.

b) The Body of Knowledge: A sufficient history of use in the food/feed chain or elsewhere must be documented.

c) The Safety Concerns: The microorganism should not possess traits that pose a hazard to human or animal health, or the environment.
d) The End Use: The assessment considers whether the microorganism is added as a live strain (e.g., probiotic) or used for production (e.g., enzyme production).

Once a species is listed on the QPS list, risk assessment can be fast-tracked. Applicants benefit from reduced data requirements, meaning they often don't need to submit full toxicological studies for that species. However, strain-level verification remains essential: the applicant must confirm the identity of their specific strain and demonstrate it meets the QPS qualifications. This ensures safety while reducing redundant testing for well-known microorganisms.

14. How do these metabolites behave in the environment? Is persistence, leaching, or bioaccumulation issues regulators are watching for?

Dr. Jacques Drolet: Yes, regulators do consider persistence, leaching, and bioaccumulation—but only when the potential risk is significant and approaches the reference value. In such cases, the same environmental fate parameters used for conventional chemical pesticides are applied to microbial metabolites.

That said, many microbial metabolites tend to have relatively short half-lives in the environment, although there are exceptions. Regulators also look closely at the biology of the organism itself. If a microbial agent can readily multiply or spread, attention shifts to the potential risk associated with an increasing environmental load over time.

A strong regulatory rationale typically addresses metabolite half-life, the environmental conditions required for microbial survival and multiplication, the amount present per unit area or on harvested commodities, and toxicity to key non-target organisms. In most respects, this assessment mirrors that of conventional pesticides unless rapid degradation of the metabolite clearly limits exposure.

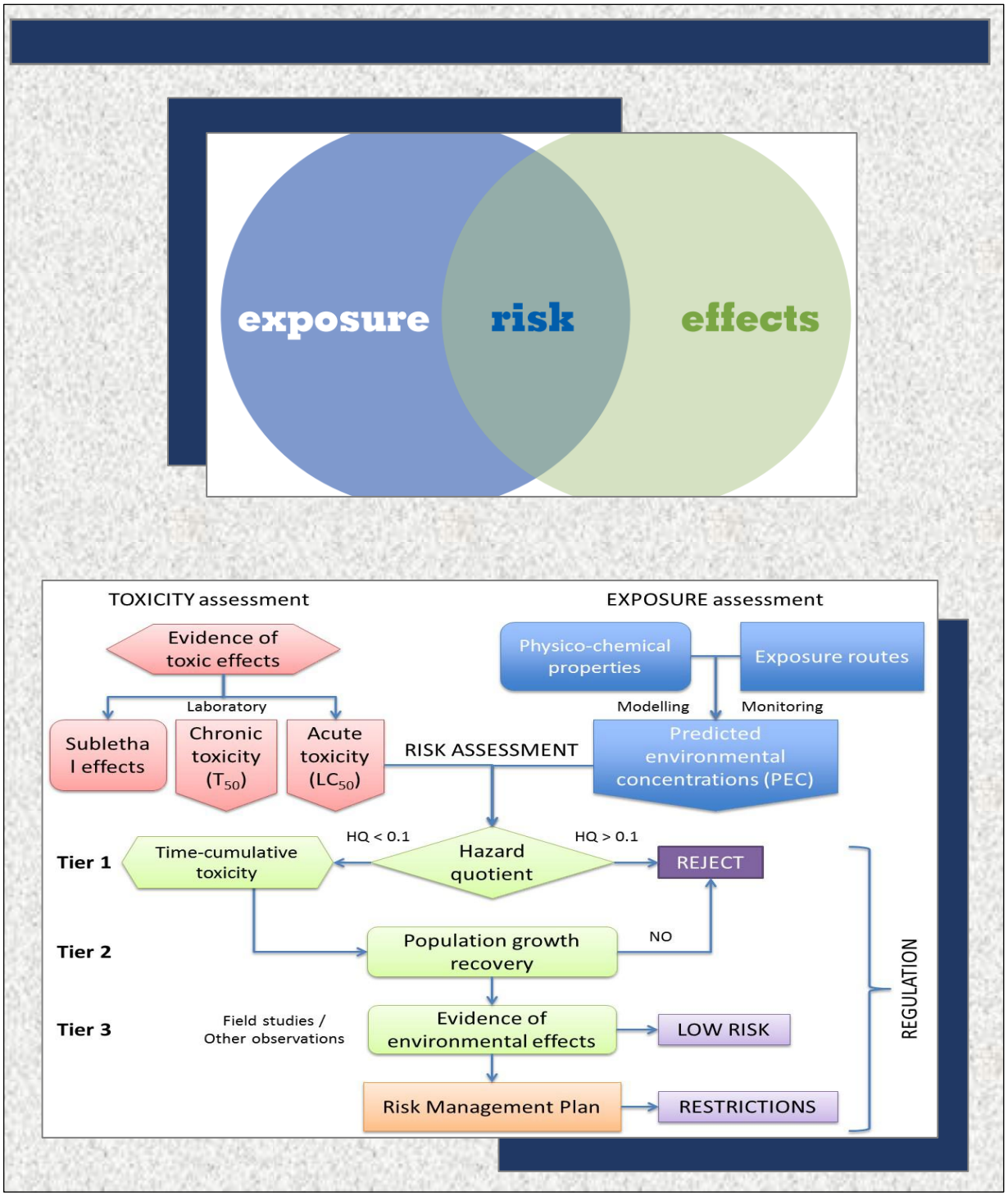
15. Could these compounds potentially harm beneficial insects, aquatic life, or other non-target organisms?

Dr. Jacques Drolet: Yes. But you must assess the toxicity of your most prevalent metabolites and their concentration per surface area of application. Risks to mammals (human representatives) are different than risk assessment for the environment. Risk to the environment deals with more species but at a population level, not at an individual level. This notion is key. However, remember that in general, low toxicity and exposure are biopesticides salvation, but nevertheless it depends on the quality of your rationales.

16. So, what kind of ecotoxicity data should registrants generate to support their environmental risk assessments?

Dr. Jacques Drolet: Registrants should begin by defining a realistic worst-case exposure scenario and determining whether it presents a potential environmental concern. If a concern is identified, ecotoxicity testing should then be targeted and strategic. This means selecting relevant non-target organisms based on the expected exposure pathways and ecological

relevance and choosing the most appropriate study design—whether laboratory, greenhouse, or field-based. The goal is to generate data that are both scientifically meaningful and directly applicable to risk assessment, avoiding unnecessary testing while still addressing potential risks effectively.



Framework of Ecological Risk Assessment

Source: 10.4066/2529-8046.100025)

17. You mentioned that registrants should assess whether a metabolite represents a potential concern. How do you determine what qualifies as a potential concern in practice? Are there specific criteria used to prioritize which metabolites or exposure routes need more attention? Could you share an example?

Dr. Jacques Drolet: In practice, determining a "potential concern" comes down to evaluating whether a metabolite could plausibly pose a risk based on its exposure and toxicity profile.

The starting point is usually the list of non-target organisms provided by regulators. If such guidance is not available, the scientific literature should be used to identify relevant and representative species. From there, prioritization focuses on metabolites for which both environmental concentrations and inherent toxicity could be of concern. A few practical principles help guide this process:

- Focus on worst-case exposure routes (e.g., dietary, contact, inhalation), depending on the use pattern.
- Consider the most sensitive life stage of the organism (or, for humans, the most sensitive organ or system).
- Start with simple, conservative laboratory studies to screen the effects before moving to more complex designs.

For example, if a metabolite is expected to accumulate in soil following application, and there is some indication of toxicity, initial laboratory studies might focus on soil invertebrates under worst-case exposure conditions. If no adverse effects are observed at concentrations exceeding realistic environmental levels, the metabolite would typically not be considered a concern, and no further testing would be required.

There are also established frameworks in the literature that help guide the selection of appropriate non-target species and refine testing strategies.

- https://www.semanticscholar.org/paper/Selection-of-non-target-species-for-host-testing-of-Kuhlmann Schaffner/4f0339a60595e7fe12f956ea52a1c1c2210122c8?utm_source=direct_link
- https://doi.org/10.1186/s12302-025-01085-x
- https://link.springer.com/article/10.1186/s12302-025-01085-x
- https://www.sciencedirect.com/science/article/pii/S1049964424002226

18. Once one has selected the appropriate test system as you mentioned lab, greenhouse, or field, what exactly is mimicked in those trials? Is it simulating the worst-case exposure, realistic use patterns, or something else?

Dr. Jacques Drolet:
This is an important question. From a regulatory perspective, it is most of the time the worst-case scenario that is desired, but from a practical standpoint, 10x the recommended use pattern is a good rule of thumb and will be accepted. This approach provides a margin of safety while remaining scientifically meaningful.

19. Are there some protocols for conducting these studies? Where can registrants find these testing protocols?

Dr. Jacques Drolet: Yes. But they are always specific to an organism or even a metabolite. Registrants can refer to detailed guidelines from the EPA, EFSA, and OECD such as

- Series 885 - Microbial Pesticide Test Guidelines
- EFSA Threshold of Toxicological Concern
- EFSA 2011 Toxicological Framework
- OECD Working Document on the Risk Assessment of Secondary Metabolites of Microbial Biocontrol Agents

The registrants also refer to these protocols to determine that ecotoxicity or human toxicity studies are compliant with current regulatory standards.

20. And are there accredited laboratories that specialize in this type of testing? How can registrants identify reliable labs for these studies?

Dr. Jacques Drolet: You really have to conduct your own search. Honestly, most of them are valid, the big ones more expensive but not necessarily better; consider asking universities but give them a precise mandate. Governmental labs may be ok but make sure you are very precise on what you want them to do. In over-developed countries, they tend to love fundamental and applied studies instead of regulatory studies, and you end up paying for the advancement of sciences.

In many countries, governments will only accept data from certified labs. Best is to look for laboratories that are GLP certified. For the laboratories that are not certified, one must ask the regulator before contracting out the study.

21. Let's touch on analytical methods. Are there validated methods to detect and quantify metabolites in different matrices (soil, water, plants)? Do you know of any labs that conduct such studies? Or where a registrant could go to find these labs?

Dr. Jacques Drolet: If validated methods aren't readily available in the literature, registrants will need to search for both suitable methods and labs, think of it as a bit of shopping for the right tools. For example, the EPA has a Test Methods Index that helps locate its official methods. In Europe, the EquATox consortium publishes detailed guidance on microbial toxins, covering detection, identification, structure, and function, which can be a valuable reference when designing studies.

22. There might be some detection limits required by the regulators e.g., PMRA, EPA, EU? What are those limits and where can one find these?

Dr. Jacques Drolet: Detection limits are specific to each toxin. However, most microbial pesticide toxins are relatively new, so published limits are scarce. Registrants often need to rely on available literature, regulatory guidance or case-by-case consultation to determine appropriate detection thresholds.

23. When you say these toxins are 'new,' do you mean they're newly discovered, or just new to regulatory scrutiny?

Dr. Jacques Drolet: In reality, it can be both. From a regulatory perspective, however, what truly matters is whether the compound is new to regulatory scrutiny. That is the point at which it must be properly assessed, regardless of how long it has been known in scientific literature.

24. How early in product development should researchers begin characterizing metabolites especially if they aim for regulatory approval?

Dr. Jacques Drolet: Characterization should start from the very beginning. Conduct thorough literature reviews including all published studies on your organism to assess whether it's worth proceeding. If potential concerns are identified, address them as early as possible, since they can affect feasibility decisions for your project. HPLC and other analyses should be performed early, unless you are working with a well-characterized strain. It is important to complete this initial assessment before planning any additional studies.

25. Now, moving to data requirements, what are the key data requirements for metabolite assessment under PMRA in Canada? How do these requirements compare with those in the U.S., the EU, or other jurisdictions?

Dr. Jacques Drolet: Registrants are expected to:

- Provide the full genetic code as a part of characterization of microbial strain. If there are gene sequences that code for toxins in other microbes might trigger more detailed research to ensure that the microbe in question, under specific environmental conditions, does not produce these toxins.
- Identify and characterize relevant metabolites (especially those with potential toxicity).
- Conduct or reference toxicology studies for metabolites of concern.
- Assess environmental fate and ecotoxicity, particularly for persistent or mobile compounds.
- Provide exposure estimates for humans (e.g., dietary intake) and non-target species.

Essentially there are no differences in data requirement of Canada, US or EU. Science is science. In other words, a good rational in English is international.

26. For researchers working with natural vs genetically modified strains, how does the metabolite profile typically differ and how might that impact the regulatory outlook?

Dr. Jacques Drolet: There are four forms: indigenous, introduced, precisely genetically modified (CRISPR-SKIP) and broad random modification (conventional gene-editing). These are all very different. Regulators will need less from indigenous, more safety arguments for the introduced. For the CRISPR, there are very few registered uses, regulators are still wary of introducing genetically modified microbials. As far as I know there are no registration for the conventional gene editing products (only field trials for a modified virus have been attempted about 25 years ago).

27. You mentioned that CRISPR-modified microbes are still rare in regulatory submissions, and that regulators are cautious. Given this, do you have any advice for registrants—like researchers working with CRISPR-edited strains, on how to build a strong case for safety and acceptance?

Dr. Jacques Drolet: Right now, CRISPR-modified microbes are still new, so regulators and the public are cautious. We don't yet have much real-world experience, which makes it harder to fully assess long-term safety.

Because of this, the strongest cases are those that address a clear and urgent need, such as major public health challenges like Zika. When the problem is serious, the benefits of using a new technology are easier to justify.

It's also important to show that the modified microbe is well controlled. For example, it should not persist indefinitely in the environment and should disappear if it is no longer applied. At the same time, care should be taken to avoid introducing any additional risks, such as the production of harmful metabolites.

Finally, some argue that the level of urgency is not always high enough, since we are still just beginning to explore the wide range of naturally occurring microbes that could be used instead.

Overall, success in this area will depend on building a clear, evidence-based case that balances demonstrated need, controlled behavior, and a robust safety profile.

28. Is there a separate assessment for metabolites required, even if they are not pesticidally active or are safe to human and non-targets? Can existing literature or previously published data be used to support safety conclusions?

Dr. Jacques Drolet: Absolutely. Literature is always the first resource and, in most cases, is sufficient if you provide a strong rationale. I often refer to these rationales as "stories" because, like a good novel, they should be logical, fact-based, and well-structured. For regulators, what matters is whether a metabolite could pose any risk, not whether it contributes to pest control. Your job is to demonstrate that metabolites are safe for humans and the environment. Never assume the regulator knows what you think; even if they do, they cannot make the case for you. Think of it as a judge needing the defense attorney to present the argument, everything must be clearly laid out. Finally, pesticidal activity is only relevant to efficacy assessments. For disciplines such as mammalian toxicology or ecotoxicology, whether a metabolite has pesticidal properties is not a consideration—only its potential risk profile matters.

29. If metabolites are of concern, what risk mitigation measures should we include on the label? e.g., PPE, buffer zones etc.?

Dr. Jacques Drolet: If the toxicity and concentrations of the metabolites indicate that the product may require an MRL or could pose a risk to certain species, there are generally two options: either manage it as you would a conventional chemical, or reconsider using the product. If you proceed, the label should include standard mitigation measures: for humans, things like pre-harvest intervals (PHI) and protective clothing; for non-target species, measures such as buffer zones and timing of application. Additionally, if the microbial agent is alive, you will need to demonstrate that its field persistence is limited and that it will not spread beyond the treated area.

30. Based on your experience, what are the most common pitfalls in metabolite assessments for microbial pesticides?

Dr. Jacques Drolet: Registrants do too many studies and/or the wrong studies or present too much or the wrong literature. Rationales that sound like a marketing spree are particularly damaging. Imagine you are the regulator and things should go well. Yes, you must spell out facts, but these should add value to your story. Nothing more, nothing less.

31. Could you please walk us through a step-by-step approach a registrant should follow when planning to generate metabolite related data?

Dr. Jacques Drolet: Here's a practical approach:

1. Know the literature inside out. Review all published information thoroughly, it is the foundation of your rationale.
2. Identify metabolites of potential concern. Focus on those that pose the highest risk, considering both hazard and exposure.
3. Develop your rationale. if there is cause for concern. Include factors like the potential for the microbial agent to multiply or spread if applied live.
4. Identify data gaps. Writing your rationale will reveal which studies are needed to support a robust regulatory submission.
5. Consult with your regulator. Before conducting studies, ensure your good lab practices (GLP) protocols meet their expectations and nothing unnecessary is done.
6. Propose studies internally. Present the plan to your supervisor, keeping the focus on what adds value to the submission. Remember, regulatory science is about practical justification, not fundamental research.
7. Finalize your submission. Based on study results, either complete your rationale, conduct additional targeted studies if needed, or reconsider the strain if a better alternative is available.

32. As we wrap up our discussion, I would love to hear any advice you might have for researchers who are just starting to work with novel microbial strains, particularly when it comes to metabolite profiling.

Dr. Jacques Drolet: My advice is simple: immerse yourself in the literature**.** Read everything you can about your organism and its metabolites, both primary and secondary. The deeper your understanding, the stronger and more persuasive your regulatory rationale will be. Think of writing your rationale like crafting a novel, revise it repeatedly, refine your arguments and present the story in a way that engages and convinces the regulator. Clear, well-structured, evidence-based reasoning is key to a successful submission. I would also emphasize the importance of engaging with regulators early in the process. Data requirements serve as valuable guidance for product development. Aligning your research with these expectations from the outset can significantly strengthen your overall submission as well as reduce the overall costs.

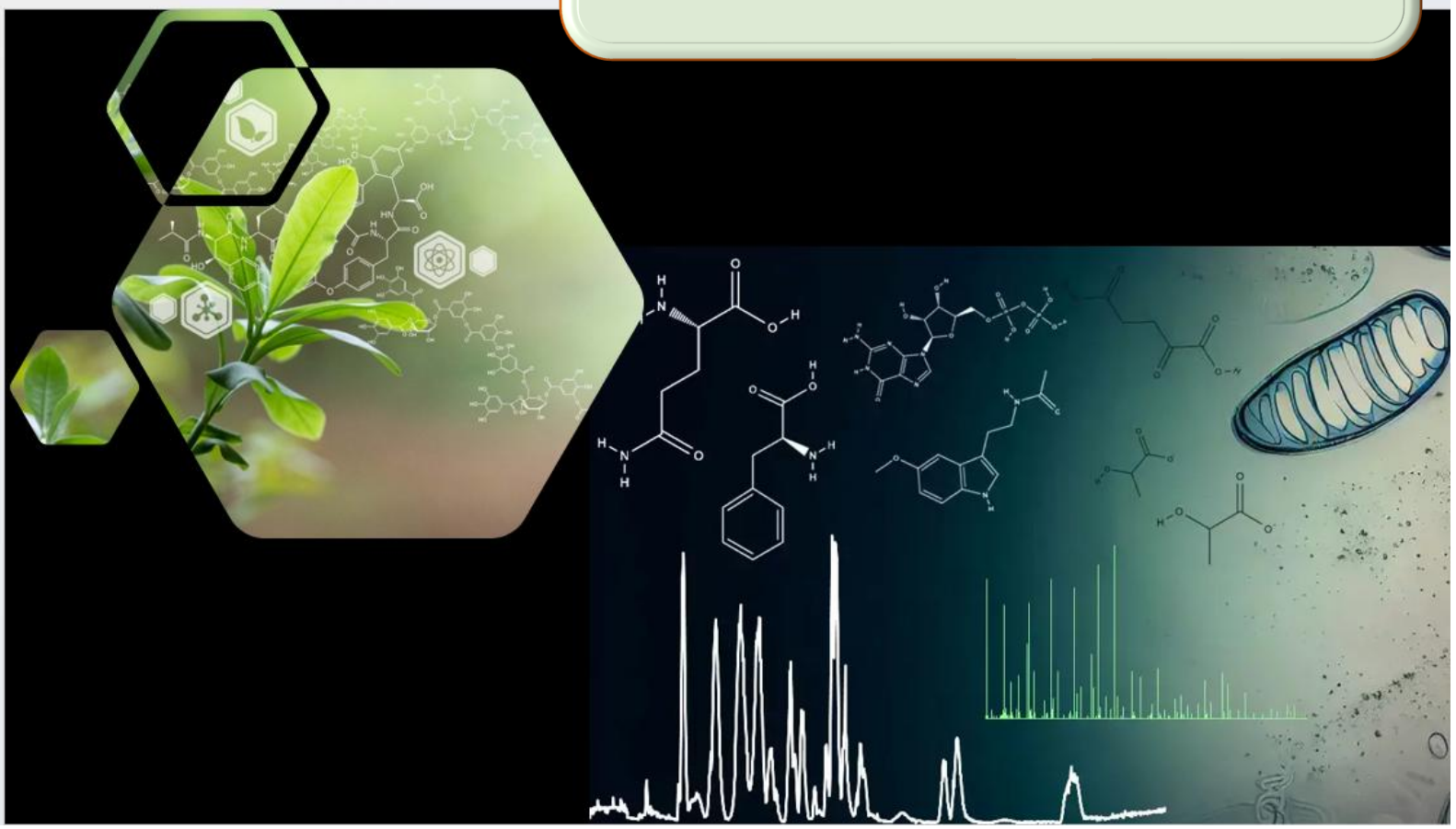
33. With the advances in metabolomics, bioinformatics and predictive modelling, how do you see the role of metabolite data evolving in future regulatory frameworks?

Dr. Jacques Drolet: Metabolomics in medicine is far more advanced than what we currently see in integrated pest management, and it provides a useful blueprint for future "risk assessment" approaches. The time is not far off when AI will write the rationale structure based on metabolite profiles linking HPLC data, concentrations, and toxicity. However,

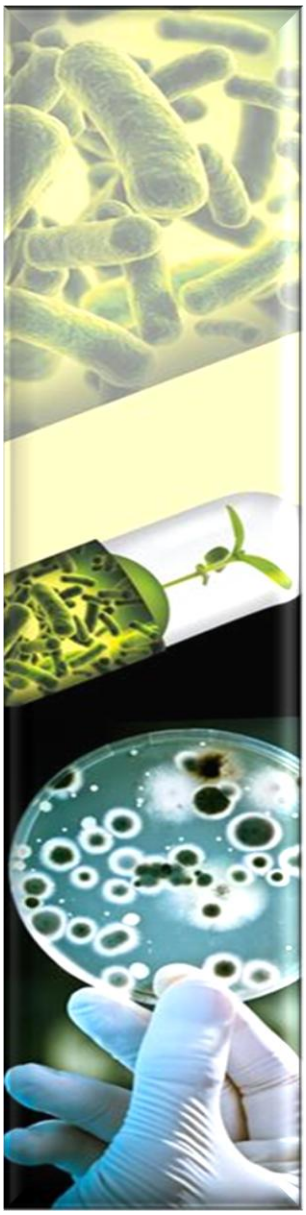
knowledgeable experts will always be required to review, correct, and refine AI-generated outputs.

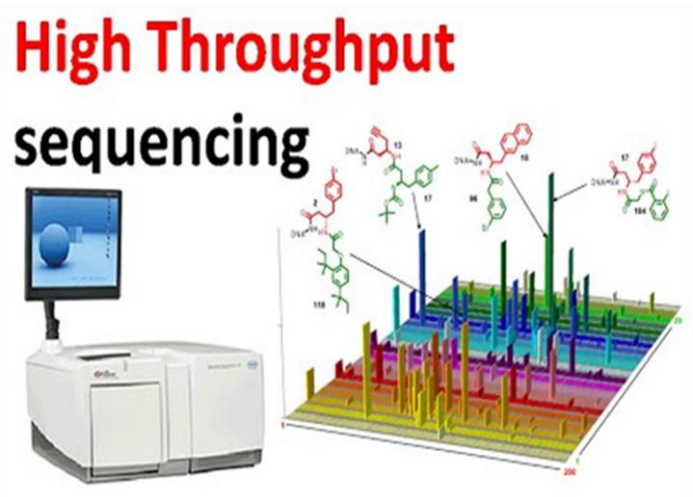
The challenge I foresee is that truly experienced experts may become rare, which could lead to companies submitting information that is inaccurate or poorly interpreted. If regulators then rely on the same AI outputs without critical oversight, flawed approvals could occur. Then, in 15 years, emerging technologies like quantum computing may help correct these errors, incorporating human review into more robust predictive frameworks. Beyond that, much will depend on how society values expertise, oversight, and responsible governance in regulatory science.

Stay ahead of requirements - Plan for metabolites, not just active ingredient



Where big data meets the tiny molecules





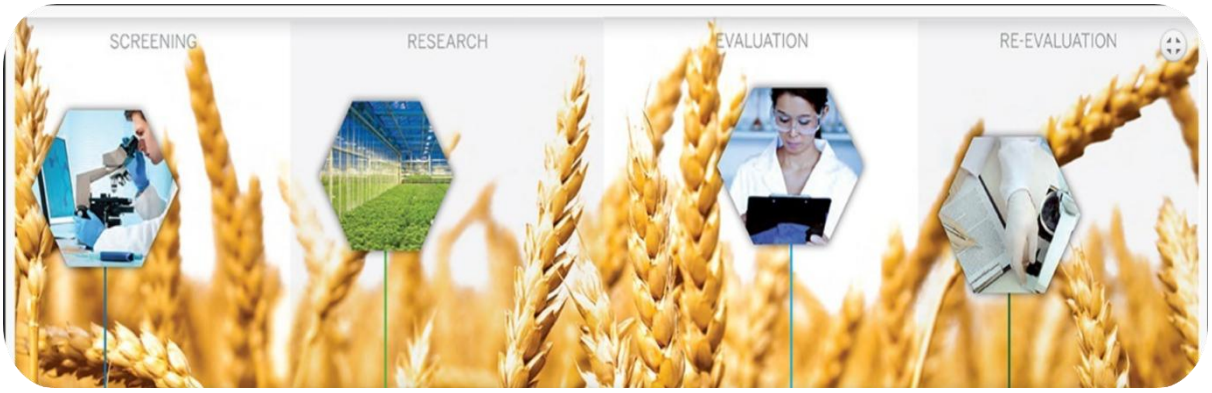
High–throughput sequencing reveals the genetic blueprints of microbes allowing researchers to predict the metabolites they can produce. By linking biosynthetic genes to chemical products, new bioactive compounds can be identified faster and more efficiently than traditional culturing methods. This genome to metabolite approach is accelerating natural product discovery.

Key Takeaways

- Regulatory assessment focuses on metabolites that pose real risk, defined by toxicity multiplied by exposure.
- Metabolite characterization should begin early in product development, supported by thorough literature review.
- Strong, evidence-based rationales are essential to demonstrate safety for humans and the environment.
- The microbial agent's ability to persist, multiply, or spread influences exposure and study requirements.
- Data generation should follow a structured approach: identify metabolites of concern, develop rationale, consult regulators, and perform targeted studies.
- Advances in metabolomics, AI, and predictive modeling will enhance risk assessment, but expert oversight remains critical.

Resources

- https://www.oecd.org/chemicalsafety/pesticides-biocides/biological-pesticides.htm
- https://www.oecd.org/en/publications/oecd-guidance-to-the-environmental-safety-evaluation-of-microbial-biocontrol-agents_9789264221659-en.html
- https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en
- https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach
- https://www.fao.org/pesticide-registration-toolkit/registration-tools/data-requirements-and-testing-guidelines/study-detail/en/c/1186773/
- https://www.mpi.govt.nz/agriculture/agricultural-compounds-vet-medicines/maximum-residue-levels-agricultural-compounds
- https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/risk-management-pest-control-products.html
- https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/approach-environmental-risk-assessment.html
- https://pubmed.ncbi.nlm.nih.gov/38188093/
- https://openknowledge.fao.org/items/533c310e-dd22-427d-9b0d-ab764a76f607



Next Issue

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Published by

The Institute for Sustainable Horticulture
Kwantlen Polytechnic University, Langley Campus
Langley, British Columbia, Canada