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# REGULATING MICROBIAL METABOLITE–BASED MYCOHERBICIDES IN INDIA: POLICY GAPS, RISK ASSESSMENT CHALLENGES, AND FUTURE DIRECTIONS

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## ABSTRACT

Weed management remains one of the most persistent challenges in Indian agriculture, contributing significantly to crop yield losses and increased reliance on synthetic herbicides. Mycoherbicides—fungal-based bioherbicides—have emerged as environmentally sustainable alternatives. A novel evolution in this domain involves the use of cell-free fungal broth formulations, consisting of extracellular metabolites and bioactive compounds without viable fungal propagules. While scientifically promising, regulatory pathways governing such products in India remain ambiguous due to overlapping jurisdiction between the Insecticides Act, 1968 and the Fertilizer (Control) Order, 1985 (FCO), particularly after recent amendments recognizing microbial and cell-free products under biostimulant categories. This review critically examines the regulatory landscape applicable to cell-free mycoherbicides in India, compares global regulatory approaches, identifies policy gaps, and proposes a structured framework for streamlined approval. Establishing dedicated guidelines for microbial metabolite-based herbicides will accelerate innovation while ensuring biosafety and environmental protection.

**KEYWORDS:** Mycoherbicide, Cell-free broth, Microbial metabolites, Biopesticide regulation, Insecticides Act 1968, Fertilizer Control Order, Sustainable weed management, India.

## 1. INTRODUCTION

Weeds constitute one of the most significant biotic constraints in agricultural production systems worldwide. In India, weed infestation accounts for an estimated 15–35% reduction in crop yields, frequently surpassing losses attributed to insect pests and plant diseases (Gharde et al., 2018; Rao et al., 2017). In major field crops such as rice, wheat, soybean, and cotton, unchecked weed competition during critical growth stages substantially reduces productivity and farm profitability. Consequently, chemical herbicides have become the dominant tool for weed management due to their rapid action, broad-spectrum efficacy, and labor-saving advantages.

However, extensive and repetitive use of synthetic herbicides has generated multiple agronomic and environmental challenges. These include the rapid evolution of herbicide-resistant weed biotypes, contamination of soil and water resources, persistence of chemical residues in food chains, adverse effects on non-target organisms, and disruption of soil microbial diversity (Heap, 2023; Duke & Powles, 2008; Sharma et al., 2019). India has reported increasing cases of resistance in *Phalaris minor*, *Amaranthus spp.*, and other problematic weeds, posing serious threats to cereal-based cropping systems (Chhokar et al., 2012). In addition, concerns over environmental sustainability and human health have intensified calls for reduced reliance on synthetic agrochemicals.

Sustainable agriculture frameworks—including Integrated Weed Management (IWM), organic farming initiatives, and climate-resilient agriculture policies—emphasize the integration of biological alternatives to minimize chemical inputs (FAO, 2019; Ministry of Agriculture & Farmers Welfare [MoAFW], 2022). Among biological strategies, mycoherbicides—fungal-based bioherbicides derived from phytopathogenic fungi—have emerged as promising eco-compatible tools for weed suppression. These agents exploit host-specific pathogenicity or phytotoxic metabolite production to selectively target weeds while minimizing collateral ecological damage (Charudattan, 2001; Bailey, 2014).

Traditionally, mycoherbicides have relied on the application of live fungal propagules, including spores and mycelial fragments. While effective under controlled conditions, live formulations face practical constraints such as limited shelf life, sensitivity to environmental fluctuations, biosafety concerns, and stringent regulatory scrutiny (Auld & Morin, 1995). Recent advances in microbial biotechnology have shifted attention toward cell-free culture filtrates—fermentation broths from which fungal biomass has been removed, retaining extracellular secondary metabolites and phytotoxic compounds responsible for herbicidal activity (Evidente et al., 2016). These metabolite-based formulations offer several

advantages, including improved storage stability, elimination of risks associated with environmental establishment of live pathogens, enhanced formulation flexibility, and potentially simplified biosafety evaluation.

Despite growing scientific evidence supporting the efficacy of cell-free fungal metabolites as bioherbicides, regulatory frameworks in India have not evolved specifically to address such products. Current governance mechanisms are primarily structured under the Insecticides Act, 1968, which regulates chemical pesticides and microbial biopesticides, and the Fertilizer (Control) Order (FCO), 1985, which recently incorporated microbial and cell-free products within biostimulant categories. However, neither framework explicitly defines or categorizes microbial metabolite-based herbicidal formulations, creating ambiguity in product registration pathways, data requirements, and risk assessment protocols.

Given the strategic importance of sustainable weed management and the policy momentum toward bio-based agricultural inputs, a comprehensive evaluation of the regulatory landscape governing cell-free mycoherbicides in India is timely and necessary. Therefore, this review aims to:

1. Analyze existing regulatory provisions governing microbial herbicides in India;
2. Examine classification and compliance challenges specific to cell-free broth formulations;
3. Compare international regulatory approaches to microbial metabolite-based pesticides; and
4. Propose policy recommendations for establishing a harmonized and science-based governance framework.

By addressing these dimensions, this paper seeks to bridge the gap between technological innovation and regulatory preparedness, thereby facilitating the responsible commercialization of cell-free mycoherbicides in Indian agriculture.

## 2. Scientific Basis of Cell-Free Broth Mycoherbicides

The growing interest in cell-free broth–based mycoherbicides arises from advances in fungal biotechnology and secondary metabolite research. As highlighted in the Introduction, biological weed control using fungi traditionally relied on live inoculum; however, understanding that phytotoxicity is often mediated by extracellular metabolites rather than physical colonization has shifted research focus toward metabolite-driven formulations (Charudattan, 2001; Evidente et al., 2016). Cell-free broth systems exploit this principle by

isolating and utilizing the active phytotoxic compounds produced during fungal fermentation, thereby separating herbicidal efficacy from microbial viability.

### 2.1 Mechanism of Action

Phytopathogenic fungi synthesize a diverse array of bioactive compounds during host interaction and in vitro fermentation. These compounds contribute to weed suppression through multiple biochemical and physiological mechanisms. The major categories include host-specific toxins, non-specific phytotoxins, hydrolytic enzymes, organic acids, and structurally diverse secondary metabolites (Andolfi et al., 2014; Cimmino et al., 2015).

**Host-Specific Toxins (HSTs)**

Host-specific toxins selectively affect particular weed species by targeting unique metabolic pathways or membrane receptors. These toxins often determine pathogen virulence and specificity. For example, *Alternaria* spp. and *Cochliobolus* spp. produce HSTs that disrupt chloroplast function or ion transport mechanisms in susceptible hosts (Walton, 1996). Such specificity enhances the potential for selective weed management without affecting crop plants.

**Non-Specific Phytotoxins**

Non-specific toxins exhibit broader phytotoxic effects by interfering with essential physiological processes such as photosynthesis, respiration, and membrane integrity. Compounds such as tentoxin and trichothecenes inhibit chloroplast ATP synthesis and protein synthesis, respectively (Evidente et al., 2016). These compounds can induce rapid necrosis, chlorosis, or growth inhibition in targeted weeds.

**Cell Wall-Degrading Enzymes**

Fungi produce extracellular enzymes including cellulases, pectinases, and xylanases that degrade plant cell walls, facilitating tissue maceration and pathogen penetration (Kubicek et al., 2014). Even in the absence of viable fungal cells, residual enzymatic activity in culture filtrates can contribute to phytotoxicity by weakening structural integrity of plant tissues.

**Organic Acids**

Certain fungi secrete organic acids (e.g., oxalic acid, citric acid, gluconic acid) that lower pH, disrupt cellular homeostasis, and enhance membrane permeability. Oxalic acid, produced by several pathogenic fungi, plays a critical role in host tissue degradation and oxidative stress induction (Cessna et al., 2000).

**Secondary Metabolites**

Secondary metabolites represent the most important group of bioactive compounds in cell-free mycoherbicides. Examples include:

- **Fusaric acid** (from *Fusarium* spp.) – inhibits mitochondrial respiration and ion transport
- **Tentoxin** (from *Alternaria alternata*) – disrupts chloroplast ATP synthase
- **Trichothecenes** – inhibit eukaryotic protein synthesis
- **Colletotrichins** (from *Colletotrichum* spp.) – induce necrosis and membrane disruption

These compounds interfere with key plant metabolic pathways, leading to oxidative stress, photosynthetic inhibition, electrolyte leakage, and eventual plant death (Cimmino et al., 2015; Evidente et al., 2016).

**Cell-Free Broth System: Process and Biological Rationale**

In cell-free broth–based systems:

- Fungal cultures are grown under controlled fermentation conditions.
- The culture medium accumulates extracellular metabolites.
- Biomass (spores and mycelia) is removed via filtration or centrifugation.
- The resulting filtrate contains active phytotoxic compounds but no viable propagules.

This approach eliminates the risk of unintended fungal establishment in agroecosystems while preserving herbicidal activity. Since the biological effect is metabolite-driven rather than infection-driven, environmental persistence and host-range concerns may be more predictable compared to live inoculum applications (Bailey, 2014).

Furthermore, absence of viable organisms reduces the likelihood of horizontal gene transfer, unintended mutation, or ecological displacement—issues sometimes raised in regulatory risk assessments of live microbial agents (OECD, 2019).

**2.2 Advantages Over Live Mycoherbicides**

While live fungal formulations have demonstrated efficacy, their commercial adoption has been limited by environmental sensitivity and regulatory scrutiny (Auld & Morin, 1995). Cell-free broth formulations offer several technical and regulatory advantages, as summarized in Table 1.

**Table 1. Comparative Characteristics of Live Mycoherbicides and Cell-Free Broth Formulations.**

| Parameter | Live Fungal Mycoherbicide | Cell-Free Broth Formulation |
|---|---|---|
| **Viability requirement** | Essential for infection and efficacy | Not required |
| **Shelf life** | Limited; sensitive to temperature and humidity | Extended; dependent on metabolite stability |
| **Ecological establishment risk** | Possible colonization of non-target habitats | Minimal; no viable propagules |
| **Biosafety concerns** | Moderate; requires pathogenicity and infectivity testing | Reduced; evaluated as metabolite-based product |
| **Regulatory pathway** | Registered as microbial biopesticide | Ambiguous; may fall under metabolite or biochemical category |
| **Field stability** | Variable; influenced by environmental conditions | Formulation dependent; can be optimized |
| **Risk of resistance evolution** | Lower than chemicals but possible | Similar to natural-product herbicides; manageable through rotation |

**Scientific and Regulatory Implications**

The metabolite-based approach aligns with the sustainability goals discussed in the Introduction by:

1. Reducing ecological uncertainty associated with live pathogens.
2. Enhancing product standardization and batch consistency.
3. Potentially simplifying toxicological profiling compared to living organisms.

However, challenges remain in standardizing metabolite concentration, identifying active fractions, and defining regulatory thresholds for environmental safety (Cimmino et al., 2015). Additionally, complex metabolite mixtures may require advanced analytical tools such as LC-MS/MS for quality control and residue analysis.

In the Indian context, where regulatory classification under the Insecticides Act currently emphasizes either chemical or microbial categories, the unique biological nature of cell-free broths creates interpretive ambiguity. Scientifically, these products function as natural-product herbicides; regulatorily, they straddle the boundary between biochemical pesticides and microbial biopesticides—an issue explored in subsequent sections of this review.

**3. Regulatory Framework in India**

The commercialization of cell-free broth–based mycoherbicides in India must be examined within the broader statutory framework governing pesticides and agricultural inputs. As

discussed in the preceding sections, these products occupy an intermediate position between microbial biopesticides and natural-product herbicides. However, Indian regulatory instruments were originally designed for either synthetic chemical pesticides or live microbial agents, creating interpretive ambiguity for metabolite-based formulations. The two principal regulatory instruments relevant to this discussion are the Insecticides Act, 1968 (and associated Rules, 1971) and the Fertilizer (Control) Order, 1985 (FCO), including recent amendments related to biostimulants.

### 3.1 The Insecticides Act, 1968

The **Insecticides Act, 1968**, enacted to regulate the import, manufacture, sale, transport, distribution, and use of insecticides in India, remains the primary legislation governing pesticides, including herbicides and biopesticides (Government of India, 1968). The Act aims to prevent risks to human beings and animals and to ensure the availability of safe and effective pest control products.

#### Regulatory Authority

The implementation of the Act is overseen by:

- **Central Insecticides Board (CIB)** – Advisory body
- **Registration Committee (RC)** – Responsible for product registration
- Collectively administered under the **Central Insecticides Board & Registration Committee (CIB&RC)**, Ministry of Agriculture & Farmers Welfare

No insecticide can be manufactured or marketed in India without registration under Section 9 of the Act.

#### Registration Provisions

Products are generally registered under:

- **Section 9(3)** – Full registration (complete data package)
- **Section 9(3B)** – Provisional registration (limited period, typically two years, pending full data submission)

Currently, several microbial biopesticides—such as *Trichoderma spp.*, *Beauveria bassiana*, *Metarhizium anisopliae*, and *Bacillus thuringiensis*—are registered under these provisions as microbial insecticides or fungicides (CIB&RC, 2023).

### Key Data Requirements for Registration

The Registration Committee requires submission of comprehensive dossiers including:

- **Chemistry data** (identity, composition, manufacturing process)
- **Bioefficacy trials** (multi-location field trials as per ICAR guidelines)
- **Toxicological studies** (acute oral, dermal, inhalation, irritation studies)
- **Ecotoxicology data** (effects on birds, fish, bees, non-target organisms)
- **Shelf-life and stability validation**
- **Label claims and packaging details**

Data requirements are guided by technical protocols issued by CIB&RC and aligned partially with OECD standards.

### Regulatory Ambiguity for Cell-Free Mycoherbicides

Although microbial biopesticides are recognized under the Act, the statutory definition of "insecticide" under Section 3(e) broadly includes substances intended for preventing, destroying, repelling, or mitigating pests, including weeds. However, the Act does not explicitly define:

- Microbial secondary metabolites devoid of viable organisms
- Cell-free fermentation broths
- Biochemical herbicides derived from microbial sources

This omission creates regulatory uncertainty. Cell-free mycoherbicides could potentially be interpreted as:

1. **Biopesticides** – If considered derivatives of microbial origin
2. **Chemical herbicides** – If treated as purified or semi-purified chemical substances
3. **Novel products requiring case-specific regulatory interpretation**

The classification pathway significantly affects data requirements, cost of registration, and time to market. For instance, classification as a conventional chemical herbicide may require extensive chronic toxicity and residue studies, while microbial registration protocols focus more heavily on infectivity and pathogenicity testing (OECD, 2019). Since cell-free broths contain no viable propagules, infectivity testing may be scientifically redundant, yet chemical-level toxicological profiling may be disproportionately burdensome.

Thus, the Insecticides Act, while comprehensive, lacks a dedicated regulatory category for microbial metabolite-based herbicides, necessitating either interpretive guidance or legislative amendment.

### 3.2 Fertilizer (Control) Order, 1985 (FCO)

The **Fertilizer (Control) Order, 1985**, promulgated under the Essential Commodities Act, regulates the manufacture, quality, sale, and distribution of fertilizers and related agricultural inputs in India (Government of India, 1985). Traditionally focused on nutrient-based fertilizers, the FCO has undergone significant amendments in recent years to accommodate emerging biological products.

#### Introduction of Biostimulant Category

Recent amendments introduced a formal **biostimulant category under Schedule VI**, recognizing:

- Live microorganisms (excluding biofertilizers already covered under Schedule III)
- Microbial consortia
- Cell-free microbial products, including metabolites and signaling molecules

These amendments reflect the government's acknowledgment of microbial and metabolite-based agricultural innovations (Department of Agriculture & Farmers Welfare, 2021).

#### Scope and Limitations

Under the FCO framework:

- Biostimulants are defined as substances that enhance plant growth, nutrient uptake, stress tolerance, or crop quality.
- Registration requires submission of safety data, efficacy data, and product composition details.

However, a critical limitation arises:

Biostimulants are legally intended to promote plant growth, whereas mycoherbicides are designed to suppress or destroy weeds. Herbicidal activity directly contradicts the statutory purpose of biostimulants.

Therefore:

- A cell-free microbial metabolite formulated for weed control cannot legitimately be registered under FCO as a biostimulant.
- Doing so would create regulatory inconsistency and potential legal vulnerability.

This regulatory divergence highlights a structural gap: while the FCO recognizes cell-free microbial products, it does so exclusively in the context of plant growth promotion—not weed suppression.

**Regulatory Intersection and Policy Gap**

The juxtaposition of the Insecticides Act and FCO creates a policy paradox:

| Regulatory Instrument | Recognizes Microbial Metabolites | Recognizes Herbicidal Use | Clear Category for Cell-Free Mycoherbicide |
|---|---|---|---|
| Insecticides Act, 1968 | Implicitly | Yes | No |
| FCO, 1985 (Amended) | Yes | No | No |

Thus, cell-free broth–based mycoherbicides fall into a regulatory gray area. Scientifically, they function as biochemical herbicides. Legally, they lack explicit categorization. This gap may deter innovation, increase compliance uncertainty, and delay commercialization of sustainable weed management technologies.

A harmonized and science-based interpretive framework—possibly through amendment of the Insecticides Act or issuance of specific CIB&RC guidelines—would be essential to ensure regulatory clarity while maintaining biosafety standards.

## 4. Regulatory Gap Analysis and Risk Assessment Challenges

The preceding sections established that cell-free broth–based mycoherbicides occupy an intermediate scientific and regulatory position between microbial biopesticides and biochemical herbicides. While the Insecticides Act, 1968 governs pesticide registration in India and the Fertilizer (Control) Order (FCO), 1985 recognizes certain microbial metabolites under biostimulants, neither framework explicitly addresses microbial metabolite–based herbicidal formulations. This structural omission gives rise to significant regulatory gaps and risk assessment challenges that must be addressed to facilitate responsible commercialization.

### 4.1 Regulatory Classification Ambiguity

#### 4.1.1 Absence of a Defined Legal Category

Under the Insecticides Act, products are generally categorized as:

- Chemical pesticides
- Microbial biopesticides
- Botanical pesticides

However, cell-free fungal metabolites do not neatly fit into any of these classifications. They are:

- Not living organisms (thus not classical microbial biopesticides),
- Not synthetic chemical molecules in the conventional sense,
- Not plant-derived botanicals.

This classification ambiguity leads to case-by-case interpretation by the Registration Committee (RC), potentially resulting in inconsistent regulatory outcomes. In regulatory science, predictability and clarity are critical for innovation investment (OECD, 2019). The absence of an explicit category increases uncertainty for developers and investors in bioherbicide technologies.

### 4.1.2 Risk of Over- or Under-Regulation

Misclassification may lead to:

- **Over-regulation**: If treated as synthetic chemical herbicides, cell-free products may be subjected to extensive chronic toxicity, carcinogenicity, reproductive toxicity, and long-term environmental persistence studies—requirements that may not be scientifically proportionate for biodegradable microbial metabolites.
- **Under-regulation**: Conversely, if evaluated under microbial biopesticide frameworks without appropriate metabolite-specific toxicological assessment, potential chemical toxicity risks may be inadequately addressed.

A risk-proportionate regulatory model is therefore essential.

## 4.2 Data Requirement Challenges

### 4.2.1 Complexity of Metabolite Mixtures

Unlike single-molecule synthetic herbicides, cell-free broth formulations typically contain complex mixtures of:

- Multiple secondary metabolites
- Residual enzymes
- Organic acids
- Fermentation by-products

This raises several regulatory questions:

1. Should each metabolite be chemically identified and quantified?
2. Must toxicological testing be conducted on purified compounds or whole filtrate?
3. How should “active ingredient” be defined?

Current CIB&RC chemistry data requirements are structured around single active ingredients with defined purity standards (CIB&RC, 2023). Applying this framework to multi-component biological extracts poses analytical and regulatory difficulties.

Advanced analytical techniques such as LC-MS/MS, GC-MS, and metabolomic profiling may be required for standardization and quality control. However, regulatory guidelines for acceptable compositional variability in biological extracts are not clearly defined in India.

### 4.2.2 Standardization and Batch Consistency

A critical issue in biological product regulation is ensuring batch-to-batch consistency. Variability may arise from:

- Fermentation conditions
- Strain variability
- Nutrient media composition
- Downstream processing methods

Without clear regulatory standards defining acceptable variation ranges for metabolite concentration, product approval may be delayed or rejected on quality grounds.

International guidance documents for microbial pest control agents emphasize identity, biological properties, and manufacturing controls but offer limited direction on metabolite-only formulations (OECD, 2019).

## 4.3 Toxicological Risk Assessment Challenges

### 4.3.1 Acute and Chronic Toxicity Testing

Cell-free broth products would likely require:

- Acute oral, dermal, and inhalation toxicity studies
- Skin and eye irritation tests
- Ecotoxicological testing (birds, fish, bees, earthworms)

However, uncertainty remains regarding:

- Whether chronic toxicity studies are necessary for biodegradable metabolites
- Whether Maximum Residue Limits (MRLs) must be established

Since fungal metabolites vary widely in toxicity—from relatively benign organic acids to potent mycotoxins such as trichothecenes—risk assessment must be compound-specific (Cimmino et al., 2015). Blanket classification is scientifically inappropriate.

### 4.3.2 Environmental Fate and Persistence

Risk assessment must consider:

- Soil degradation rate
- Photodegradation
- Leaching potential
- Bioaccumulation

Most fungal metabolites are biodegradable and environmentally labile, but empirical degradation data are required to support regulatory decisions. Current pesticide guidelines emphasize persistence thresholds and half-life values, yet standardized methodologies for microbial metabolite degradation studies are limited in India.

### 4.3.3 Non-Target Plant Effects

Unlike highly specific host-selective toxins, non-specific phytotoxins may affect crops under certain exposure conditions. Therefore:

- Crop safety studies
- Drift simulation trials
- Selectivity index calculations

Are essential components of bio-efficacy and risk assessment.

Balancing herbicidal efficacy with crop safety represents a major regulatory evaluation criterion.

## 4.4 Residue and Food Safety Concerns

If cell-free mycoherbicides are applied in food crops:

- Residue detection in harvested produce becomes relevant.
- Analytical methods must be validated for detection limits.
- Dietary exposure assessment may be required.

Currently, India's pesticide residue framework is primarily designed for synthetic molecules with defined chemical structures. Establishing MRLs for complex metabolite mixtures presents methodological challenges.

In cases where metabolites are naturally occurring and rapidly degraded, a waiver system based on scientific justification may be appropriate, similar to biochemical pesticide exemptions in certain jurisdictions (EPA, 2022).

### 4.5 Institutional and Procedural Gaps

#### 4.5.1 Lack of Inter-Agency Harmonization

The coexistence of:

- Insecticides Act (pesticide regulation)
- FCO (biostimulant regulation)

creates jurisdictional overlap. Clear coordination mechanisms between:

- CIB&RC
- Department of Agriculture & Farmers Welfare
- State Agriculture Departments

are necessary to avoid regulatory duplication or conflict.

#### 4.5.2 Limited Technical Capacity

Evaluation of metabolite-based products requires expertise in:

- Microbial biochemistry
- Natural product chemistry
- Toxicology
- Environmental modeling

Capacity building within regulatory agencies is essential for evidence-based decision-making.

### 4.6 Innovation and Commercialization Implications

Regulatory uncertainty directly impacts:

- R&D investment
- Patent commercialization
- Startup participation in bio-agriculture
- International collaboration

India's policy emphasis on sustainable agriculture and bio-input promotion (MoAFW, 2022) may be undermined if regulatory ambiguity discourages technological adoption.

A clearly defined regulatory pathway would:

- Reduce approval timelines
- Lower compliance costs
- Encourage domestic innovation
- Improve global competitiveness

### 4.7 Toward a Risk-Proportionate Regulatory Model

To address these gaps, a **tiered risk assessment framework** is recommended:

**Tier I: Screening**

- Chemical characterization
- Acute toxicity
- Preliminary environmental fate

**Tier II: Expanded Testing (If Required)**

- Sub-chronic toxicity
- Detailed ecotoxicology
- Residue analysis

**Tier III: Post-Market Surveillance**

- Environmental monitoring
- Resistance management
- Periodic safety review

Such a model aligns regulatory burden with actual risk, ensuring biosafety without stifling innovation.

The regulatory gap surrounding cell-free broth–based mycoherbicides in India arises from classification ambiguity, insufficient metabolite-specific guidelines, and limited risk assessment frameworks tailored to biological extracts. Addressing these challenges requires statutory clarification, scientific guideline development, and institutional strengthening. Without such reforms, the commercialization of environmentally sustainable bioherbicides may remain constrained despite strong scientific justification.

## 5. Comparative Global Regulatory Perspective

Given the regulatory ambiguity identified in the Indian framework, it is instructive to examine how other major jurisdictions regulate microbial and metabolite-based pesticide products. Both the United States and the European Union have developed structured pathways for biological and biochemical pesticides that may provide useful reference models for India. These systems emphasize risk-based assessment, proportional data requirements, and differentiated treatment of low-risk biological substances.

### 5.1 United States: Environmental Protection Agency (EPA)

In the United States, pesticide regulation is governed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The U.S. Environmental Protection Agency (EPA) is responsible for pesticide registration and classification.

**Regulatory Classification**

Under FIFRA, pesticides are broadly categorized into:

1. Conventional chemical pesticides
2. Microbial pesticides
3. Biochemical pesticides

Biochemical pesticides include naturally occurring substances that control pests by non-toxic mechanisms, such as pheromones, plant extracts, and certain microbial metabolites (EPA, 2022). Importantly, microbial metabolites that act as pest control agents without involving viable organisms may be classified as biochemical pesticides, provided they demonstrate low toxicity and minimal environmental risk.

This distinction is significant because biochemical pesticides are generally subject to:

- Reduced data requirements
- Waivers for certain toxicological studies
- Expedited review timelines

**Risk-Based Assessment Approach**

The EPA employs a risk-based assessment model, focusing on:

- Toxicological profile
- Exposure potential
- Environmental persistence
- Non-target effects

If a microbial metabolite demonstrates:

- Low mammalian toxicity
- Rapid environmental degradation
- Minimal bioaccumulation potential

It may qualify for streamlined registration or tolerance exemption from residue requirements (EPA, 2022).

The EPA also allows conditional data waivers when scientific evidence supports low risk. This flexible, science-driven approach encourages innovation in biological pest management technologies while maintaining safety standards.

For cell-free mycoherbicides, this model offers an example of how metabolite-based products can be regulated separately from both synthetic chemicals and live microbial agents.

### 5.2 European Union

In the European Union (EU), pesticide regulation is governed under Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market.

**Two-Tier Approval System**

The EU regulatory process follows a two-step structure:

1. **Active Substance Approval at EU Level**
2. **Product Authorization at Member State Level**

Microbial agents and their metabolites are evaluated under specific data requirements outlined by the European Food Safety Authority (EFSA).

**Low-Risk and Basic Substances**

The EU framework includes provisions for:

- **Low-risk active substances**
- **Basic substances**

Microbial metabolites of natural origin may qualify as low-risk substances if they:

- Are not persistent, bioaccumulative, or toxic (PBT)
- Do not disrupt endocrine systems
- Show minimal ecotoxicological risk

This designation allows simplified and faster authorization procedures (European Commission, 2009; EFSA, 2013).

Additionally, the EU emphasizes:

- Clear identification of active compounds
- Defined impurity profiles
- Comprehensive environmental fate data

However, the risk assessment remains proportionate to the hazard profile. Biological origin alone does not guarantee regulatory leniency; scientific evidence determines regulatory burden.

### 5.3 Comparative Insights

A comparison of regulatory approaches is presented in Table 2.

**Table 2. Comparative Regulatory Approach for Microbial Metabolite-Based Pesticides.**

| Parameter | United States (EPA) | European Union | India (Current Status) |
|---|---|---|---|
| Governing Law | FIFRA | Regulation (EC) No 1107/2009 | Insecticides Act, 1968 |
| Specific category for microbial metabolites | Yes (Biochemical pesticides) | Implicit (Low-risk substances) | No explicit category |
| Risk assessment model | Risk-based, proportionate | Hazard + risk-based | Primarily hazard-oriented |
| Fast-track mechanism | Available | Available for low-risk | Limited |
| Data waivers | Possible | Possible | Limited clarity |

### 5.4 Lessons for India

The comparative analysis highlights several policy insights relevant to India.

**1. Establish a Dedicated Category**

India could introduce a clearly defined regulatory classification such as:

**"Microbial Metabolite-Based Bioherbicides"**

This category would distinguish:

- Live microbial agents
- Synthetic chemical herbicides
- Biological metabolite-based products

Clear classification would reduce interpretive ambiguity under the Insecticides Act.

**2. Adopt a Tiered Risk Assessment Framework**

Both the EPA and EU apply proportionate data requirements based on hazard profile and exposure potential. India could similarly implement:

- Tier I: Basic toxicology and environmental screening
- Tier II: Expanded studies if risk thresholds are exceeded
- Tier III: Post-registration monitoring

This would ensure safety while avoiding unnecessary regulatory burden for low-risk biodegradable metabolites.

### 3. Enable Fast-Track Approval for Low-Toxicity Natural Metabolites

Natural fungal metabolites with:

- Low mammalian toxicity
- Rapid degradation
- No bioaccumulation

could qualify for expedited review, similar to biochemical pesticide pathways in the United States.

Such reform would:

- Promote domestic innovation
- Encourage sustainable weed management solutions
- Align with national bioeconomy and sustainable agriculture goals

### 4. Strengthen Analytical and Regulatory Capacity

Adopting global best practices requires:

- Advanced analytical infrastructure
- Clear impurity profiling guidelines
- Training of regulatory evaluators in natural product toxicology

Institutional strengthening is therefore integral to regulatory modernization.

The regulatory frameworks of the United States and European Union demonstrate that microbial metabolite–based pesticides can be governed under structured, risk-proportionate systems without compromising safety. India currently lacks an explicit category for such products, creating uncertainty for developers of cell-free mycoherbicides. By adopting international best practices—particularly dedicated classification and tiered risk assessment—India can foster innovation while maintaining robust environmental and public health safeguards.

### 6. Proposed Regulatory Framework for India

The emergence of cell-free mycoherbicides necessitates a structured and scientifically robust regulatory pathway tailored to microbial metabolite–based bioherbicides. Given the limitations identified in the current Indian regulatory system, a dedicated framework is required to ensure safety, efficacy, and innovation support while avoiding misclassification under chemical pesticide regulations.

This section proposes a regulatory pathway aligned with international best practices but adapted to Indian institutional structures, particularly under the Central Insecticides Board & Registration Committee (CIB&RC).(Fig 1).

**Stepwise Regulatory Model:**

Research Validation

↓

Metabolite Characterization

↓

Toxicological Screening (Tier I)

↓

Environmental Fate Assessment

↓

Field Bioefficacy Trials (Multi-Location)

↓

Submission to CIB&RC (Dedicated Metabolite Category)

↓

Conditional Registration

↓

Post-Market Surveillance

**Figure 1. Proposed Regulatory Pathway for Cell-Free Mycoherbicides**

**Explanation of Regulatory Stages**

**a. Research Validation**

Initial validation should establish:

- Herbicidal mode of action
- Selectivity toward target weed species
- Absence of viable propagules in the formulation
- Reproducibility across laboratory trials

This stage should generate proof-of-concept data before formal regulatory submission.

**b. Metabolite Characterization**

Regulators must require detailed analytical profiling, including:

- Chemical identity of active metabolite(s)

- Structural elucidation (HPLC, LC-MS/MS, NMR)
- Impurity profile
- Batch-to-batch consistency
- Stability data

Unlike live microbial agents, cell-free products require clear definition of the active compound(s) to avoid variability and regulatory ambiguity.

**c. Toxicological Screening (Tier I)**

A tiered risk assessment model should be adopted.

**Tier I studies may include:**

- Acute oral toxicity
- Acute dermal toxicity
- Acute inhalation toxicity
- Skin and eye irritation
- Basic genotoxicity screening

If Tier I results indicate low toxicity and rapid degradation, higher-tier chronic studies may be waived or minimized under a risk-proportionate approach.

**d. Environmental Fate Assessment**

Given the ecological complexity of Indian agroecosystems, environmental data should address:

- Soil degradation kinetics
- Water solubility and leaching potential
- Photodegradation
- Non-target organism safety (earthworms, beneficial insects, aquatic organisms)

For biodegradable fungal metabolites, accelerated degradation and minimal bioaccumulation should qualify the product for simplified environmental evaluation.

**e. Multi-Location Field Bioefficacy Trials**

Field validation should be conducted across:

- Agro-climatic zones
- Different soil types
- Diverse cropping systems

Data parameters should include:

- Weed control efficiency

- Crop selectivity
- Yield impact
- Phytotoxicity to non-target plants

These trials should be supervised or validated by accredited institutions such as ICAR or SAUs.

**f. Submission to CIB&RC under Dedicated Category**

A new classification titled:

**"Microbial Metabolite-Based Bioherbicides"**

should be introduced under the amended Insecticides Act.

Separate application forms, data templates, and review committees with expertise in microbial biotechnology and natural product chemistry should be established to prevent misinterpretation as synthetic chemical herbicides.

**g. Conditional Registration**

Similar to international practices, conditional registration may be granted based on:

- Demonstrated low toxicity
- Positive field efficacy
- Acceptable environmental risk

This would allow controlled commercialization while requiring additional confirmatory data.

**h. Post-Market Surveillance**

Robust monitoring mechanisms should include:

- Residue surveillance
- Environmental impact monitoring
- Farmer feedback systems
- Adverse event reporting

This ensures adaptive regulatory oversight and strengthens public trust.

**6.1 Recommended Policy Measures**

To operationalize the proposed framework, the following policy reforms are recommended:

**a. Amend the Insecticides Act to Define Microbial Metabolite Products**

The Act should explicitly define:

"Microbial metabolite-based pesticide products derived from microbial fermentation processes containing no viable organisms."

Clear statutory recognition will eliminate interpretative uncertainty and prevent arbitrary classification.

**b. Develop Separate Data Submission Guidelines**

CIB&RC should publish:

- Specific dossier requirements
- Tiered toxicology guidelines
- Analytical standards for metabolite profiling
- Environmental assessment protocols

This will improve transparency and reduce approval delays.

**c. Establish Maximum Residue Levels (MRLs) for Fungal Metabolites**

Where relevant, scientifically derived MRLs should be notified under:

- Food Safety and Standards Authority of India (FSSAI)
- Export compliance frameworks

Given that many fungal metabolites degrade rapidly, residue exemptions may be justified under risk-based evaluation.

**d. Encourage Public–Private Regulatory Consultation**

Structured consultation platforms involving:

- ICAR
- Biotechnology researchers
- Biopesticide industry stakeholders
- Regulatory authorities

would ensure science-informed policymaking and practical feasibility.

**e. Introduce Expedited Review for Eco-Friendly Bioherbicides**

Products demonstrating:

- Low mammalian toxicity
- Rapid biodegradation
- Minimal non-target risk

should qualify for:

- Fast-track evaluation
- Reduced registration fees
- Innovation incentives

Such policy support would align with:

- National Mission on Sustainable Agriculture
- Organic farming initiatives
- Bioeconomy development goals

India stands at a regulatory crossroads in addressing cell-free mycoherbicides. By establishing a dedicated metabolite-based category, adopting tiered risk assessment, and integrating post-market monitoring, India can foster innovation while maintaining environmental and public health safeguards. The proposed framework balances scientific rigor with regulatory flexibility, positioning microbial metabolite-based bioherbicides as a sustainable alternative within Indian agriculture.

## 7. Policy Roadmap and Implementation Strategy (5–10 Year Outlook)

The successful integration of cell-free mycoherbicides into Indian agriculture requires a phased, multi-stakeholder policy roadmap. Regulatory reform alone is insufficient; coordinated institutional strengthening, scientific validation, industry participation, and farmer-level adoption strategies are equally essential. This section outlines a 5–10-year implementation framework aligned with India's sustainable agriculture, bioeconomy, and climate-resilient farming objectives.

### 7.1 Phase I (Years 1–2): Regulatory Recognition and Framework Development

The initial phase should focus on establishing legal clarity and institutional preparedness.

**a. Legislative Amendments**

- Introduce explicit definitions of "microbial metabolite-based pesticide products" in the Insecticides Act (or its successor legislation).
- Notify a separate registration category under CIB&RC.
- Clarify jurisdictional boundaries between CIB&RC, FCO (biostimulants), and FSSAI (residue standards).

**b. Development of Technical Guidelines**

CIB&RC, in collaboration with ICAR and leading agricultural universities, should publish:

- Tiered toxicology testing protocols
- Environmental fate data requirements
- Analytical standards for metabolite identification
- Shelf-life and formulation validation criteria

This step reduces regulatory uncertainty and enhances investor confidence.

**c. Capacity Building within Regulatory Agencies**

- Specialized training for regulatory scientists in microbial metabolite toxicology and natural product chemistry
- Creation of an expert advisory panel on biological and metabolite-based pesticides
- Upgrading analytical laboratories for advanced metabolite detection

**Expected Outcome (Year 2):**

A legally recognized and technically structured regulatory pathway for cell-free mycoherbicides.

**7.2 Phase II (Years 3–5): Pilot Approvals and Evidence-Based Scaling**

The second phase should focus on controlled commercialization and scientific validation at scale.

**a. Conditional Registrations**

Grant limited, region-specific approvals for:

- Low-toxicity fungal metabolites
- Products with demonstrated biodegradability
- Bioherbicides validated through multi-location trials

This allows real-world performance evaluation while minimizing risk.

**b. National Field Demonstration Programs**

Under ICAR and State Agricultural Universities:

- Establish demonstration plots across agro-climatic zones
- Compare performance against chemical herbicides
- Assess weed resistance management benefits

Data generated will support long-term policy refinement.

**c. Residue and Environmental Monitoring Framework**

Develop national surveillance mechanisms to track:

- Soil residue persistence
- Impact on beneficial organisms
- Water contamination risks

Data transparency will strengthen public trust and export compliance.

**d. Public–Private Innovation Platforms**

Encourage collaboration through:

- Biotechnology incubation grants
- Start-up support under agri-biotech missions
- Joint regulatory-scientific workshops

**Expected Outcome (Year 5):**

Validated safety and efficacy data, improved farmer awareness, and early-stage market penetration.

### 7.3 Phase III (Years 6–10): Mainstream Integration and Global Alignment

The final phase should aim at systemic integration and international competitiveness.

**a. Integration into National Weed Management Programs**

Incorporate metabolite-based bioherbicides into:

- Integrated Weed Management (IWM) guidelines
- Organic and natural farming schemes
- Climate-smart agriculture initiatives

This would reduce reliance on synthetic herbicides and mitigate herbicide resistance.

**b. International Harmonization**

Align Indian regulatory standards with:

- OECD microbial pesticide guidelines
- Codex Alimentarius residue frameworks
- Major export market standards (EU, USA)

Harmonization will facilitate export opportunities for Indian-developed bioherbicides.

**c. Incentive Structures**

Introduce policy incentives such as:

- Reduced GST rates for eco-friendly bioherbicides
- Green certification labels
- Carbon-credit linked incentives for reduced chemical herbicide usage

Such measures will accelerate farmer adoption and private investment.

**d. Digital Traceability and Post-Market Governance**

Leverage digital agriculture platforms for:

- Product traceability
- Adverse effect reporting

- Real-time monitoring of field performance

AI-enabled surveillance systems may enhance regulatory responsiveness and adaptive management.

### 7.4 Cross-Cutting Strategic Enablers

Successful implementation requires supportive institutional mechanisms:

**A. Research and Development Funding**

Dedicated grants under DBT, ICAR, and DST for:

- Metabolite discovery
- Mode-of-action studies
- Formulation stabilization

**B. Intellectual Property Facilitation**

Streamlined patent examination for microbial metabolite technologies to protect domestic innovation.

**C. Farmer Awareness and Extension**

Capacity-building programs through:

- Krishi Vigyan Kendras (KVKs)
- Digital advisory platforms
- Farmer Producer Organizations (FPOs)

**D. Environmental Safeguard Framework**

Continuous evaluation of long-term ecological impacts to prevent unforeseen environmental risks.

### 7.5 Anticipated Impacts Over 10 Years

If implemented effectively, the proposed roadmap may result in:

- 20–30% reduction in synthetic herbicide dependence in select cropping systems
- Improved soil microbiome health
- Reduced herbicide resistance development
- Increased domestic biopesticide industry growth
- Enhanced global competitiveness of Indian agri-biotechnology

The regulatory evolution of cell-free mycoherbicides in India requires a phased, science-driven policy approach. Over the next decade, coordinated legal reform, institutional strengthening, and innovation incentives can transform microbial metabolite-based bioherbicides from a regulatory gray zone into a mainstream sustainable weed management

solution. By aligning safety assurance with innovation support, India can position itself as a global leader in next-generation biological crop protection technologies.

## 8. Conclusions and Future Research Directions

### 8.1 CONCLUSIONS

Cell-free mycoherbicides, derived from fungal fermentation broths containing bioactive secondary metabolites but no viable propagules, represent a significant advancement in biological weed management. Unlike conventional microbial biopesticides, their pesticidal activity is mediated through chemically defined metabolites, positioning them at the interface of biochemical pesticides and natural product–based herbicides (Copping & Menn, 2000; Glare et al., 2012).

India's regulatory system, governed primarily by the **Insecticides Act, 1968**, does not explicitly define microbial metabolite-based products. Current registration pathways under Section 9(3) and 9(3B) address microbial agents such as *Trichoderma*, *Beauveria*, and *Bacillus thuringiensis*, but do not distinguish between live microbial formulations and cell-free metabolites (CIB&RC, 2023). This creates regulatory ambiguity in classification, toxicological data requirements, and residue assessment.

International regulatory systems provide a clearer framework. In the United States, microbial metabolites may be regulated as **biochemical pesticides** under FIFRA, with data requirements proportionate to risk (U.S. EPA, 2022). Similarly, the European Union regulates microbial and low-risk biological substances under Regulation (EC) No 1107/2009, incorporating hazard- and risk-based criteria (European Commission, 2009; EFSA, 2013). These systems emphasize:

- Tiered toxicological evaluation
- Environmental fate assessment
- Conditional approvals
- Reduced data requirements for low-risk natural metabolites

Scientific literature supports the generally favorable environmental profile of many fungal secondary metabolites, particularly those that exhibit rapid degradation and low mammalian toxicity (Köhl et al., 2019; OECD, 2019). However, biological origin does not inherently guarantee safety, necessitating structured risk assessment (EFSA, 2013).

Given India's commitment to sustainable agriculture and reduction of chemical pesticide dependence under national missions on natural farming and climate-resilient agriculture,

regulatory modernization for microbial metabolite–based bioherbicides is both scientifically justified and strategically aligned with policy goals.

### 8.2 Future Research Directions

**1. Mode of Action and Molecular Mechanisms**

Understanding molecular targets of fungal metabolites is critical for:

- Predicting weed selectivity
- Assessing resistance risk
- Supporting regulatory toxicology

Secondary metabolites such as phytotoxins often interfere with photosynthesis, membrane integrity, or enzymatic pathways (Duke et al., 2010). Advanced transcriptomic and metabolomic studies are needed to characterize these mechanisms in Indian agroecosystems.

**2. Standardization and Analytical Characterization**

Batch variability remains a significant concern in fermentation-derived products. Regulatory acceptance requires:

- Defined chemical identity
- Impurity profiling
- Quantitative metabolite fingerprinting

Advanced analytical tools such as LC-MS/MS and NMR are recommended for ensuring reproducibility (OECD, 2019). EFSA guidance emphasizes precise characterization of microbial-derived substances to differentiate active metabolites from contaminants (EFSA, 2013).

**3. Environmental Fate and Non-Target Risk**

Although many fungal metabolites degrade rapidly in soil, comprehensive environmental fate studies are necessary to assess:

- Soil persistence
- Leaching potential
- Impact on non-target organisms

OECD microbial pesticide guidance highlights the importance of tiered environmental assessment based on exposure potential (OECD, 2019). Long-term soil microbiome studies are particularly relevant in tropical agroecosystems such as India’s.

### 4. Residue and Food Safety Assessment

Residue behavior of microbial metabolites in edible crops remains underexplored in India. International practice demonstrates that low-risk biochemical pesticides may qualify for tolerance exemptions where dietary exposure is negligible (U.S. EPA, 2022). However, India requires localized data for:

- Degradation kinetics
- Crop uptake and translocation
- Dietary exposure modeling

This evidence is essential for establishing Maximum Residue Levels (MRLs) under FSSAI guidelines.

### 5. Resistance Management Research

Overreliance on synthetic herbicides has led to widespread herbicide resistance globally (Heap, 2023). Incorporating metabolite-based bioherbicides into integrated weed management (IWM) systems could diversify modes of action and delay resistance evolution (Duke, 2012). Long-term rotational field trials are therefore recommended.

### 6. Socio-Economic and Adoption Studies

Adoption of biological weed management tools depends on:

- Cost competitiveness
- Farmer awareness
- Extension support

Studies indicate that farmer perception significantly influences uptake of biopesticides (Glare et al., 2012). Economic feasibility analyses under Indian smallholder conditions are therefore essential.

### 7. Alignment with Climate-Smart Agriculture

Biological weed control technologies may reduce environmental externalities associated with synthetic herbicides, including soil degradation and greenhouse gas emissions linked to chemical production (Pretty & Bharucha, 2015). Quantitative life-cycle assessment studies should evaluate the carbon and ecological footprint of cell-free mycoherbicides.

### 8.3 Final Perspective

Cell-free mycoherbicides represent a convergence of microbial biotechnology, natural product chemistry, and sustainable crop protection. International regulatory precedents

demonstrate that risk-proportionate frameworks can successfully govern microbial metabolites while fostering innovation. For India, integrating scientific rigor with adaptive regulatory reform can position microbial metabolite-based bioherbicides as a cornerstone of next-generation weed management systems.

Future interdisciplinary collaboration among microbiologists, toxicologists, regulatory authorities, and policymakers will determine the pace and success of this transition.

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