Environmental Sciences Europe

REVIEW

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Scientists' warning: we must change paradigm for a revolution in toxicology and world food supply

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Abstract

We propose a new paradigm, as **toxicology** currently lacks the proper perspective. From the 1950s to the 1970s, at least one-third of all toxicological testing in the United States, including for chemicals and drugs, was misleading scientists, and this worldwide issue persists today. Moreover, petroleum-based waste and heavy metals have been discovered in pesticide and plasticizer formulations. These contaminations have now reached all forms of life. Widespread exposure to chemical mixtures promotes health and environmental risks. We discovered that pesticides have never undergone long-term testing on mammals in their full commercial formulations by regulatory authorities or the pesticide industry; instead, only their declared active ingredients have been assessed, contrary to environmental law recommendations. The ingredients of these formulations are not fully disclosed, yet the formulations are in general at least 1000 times more toxic at low environmentally relevant doses than the active ingredients alone under conditions of long-term exposure. A similar lack of comprehensive toxicological evaluation applies to plasticizers. Their regulatory authorisations might have been obtained by incomplete, misleading and potentially false input data. This has profound implications not only for scientific knowledge, but also for public and environmental health. We propose pragmatically a paradigm shift in regulation: 1/to lower the ADI of polluting substances by at least a factor of 100 for already authorized products; 2/for new compounds, the obligation to test the full pesticide formulations in vivo chronically at environmentally relevant levels. This is necessary because pesticides are synthesized from petroleum, which can contain heavy metals. Moreover, formulated pesticides can contain plasticizers. The declared active substance, as an isolated compound of this mixture chosen by the company, will not have to be tested by itself alone. Compensation could be organized for pesticide use reduction, this will save health and environmental degradation; 3/the complete toxicological raw data for individual animals should be published on the Internet,

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including the precise protocols by which they were obtained, and they must be accessible for the scientific community, including students. There is no reason to keep these data secret. Implementing these changes would also support the advancement of agroecological alternatives.

Keywords New paradigm, Toxicology, Pollutants, Environmental health, Mixtures, Pesticides formulations, Plasticizers, Petroleum byproducts, Glyphosate-based, Agroecology

Background

The so-called Green Revolution began in the 1960s with the goal of feeding the world and reducing hunger. Unfortunately, it failed on both fronts. In India, its effects included increased human and livestock diseases, as well as soil toxicity [1]. A review of the Green Revolution's effects noted the decreased cultivation and availability of traditional nutritious foods, as well as adverse impacts on health from increased exposure to toxic pesticides [2]. [3] considers that "poverty and food insecurity persisted" or developed, in part since "traditional crops that were important sources of critical micronutrients (such as iron, vitamin A, and zinc) were displaced in favor of the higher-value staple crops" [4] document the "alarming decline in the nutritional quality of foods" in the 60 years since the Green Revolution and, more broadly, the global rise in chemically based farming. The authors term this decline "the biggest challenge for future generations 'health" and link it to weakened food security and local economies.

Today, the production of meat and vegetables tainted by pesticides, undeclared petroleum residues found at tens or hundreds of micrograms per kg [5], and medical/veterinary drugs, does not support optimal health.

At the same time, environmental degradation has accelerated, leading to an increase in pollution-related diseases, and not only by air but also by water, sea, soil, and food [6, 7].

We propose a new paradigm because at present we lack the proper perspective in both toxicology and economics to effectively guide policymakers and economic decisions. However, today by contrast, cascading social–ecological benefits of biodiversity in agriculture have been confirmed [8]. Unfortunately, economic models continue to be calculated using outdated 18th or 19th century principles [9], failing to account for externalities, such as environmental and public health costs.

Moreover, the industrial secrecy is barring access to raw toxicological data, this means that there is no independent scientific oversight over industry-led risk assessments (RAs), creating a distorted view of product safety [10]. The regulatory framework has been built on the false assumption that laboratory-based RAs are sufficient, but these assessments are not representative of real-world scenarios, and their acceptance as authoritative is deeply flawed [11]. In other words, the RAs, as given authority by policy, legal, and media bodies, are not remotely scientific. This is particularly true for the mixture exposures to which we are all exposed.

Those who have experience in regulatory agencies expertise often admit that there is a broader system of influence, in which the agencies, pressured by industry interests, continue to endorse these RAs without questioning their validity or scientific accuracy [12].

RAs must also go beyond controlled laboratory environments and should include field-based data of the trials carried out prior to the registration of a pesticide and for renewal of authorizations, which can account for the complexity of real-world interactions between chemicals, the environment, and human health.

It has been a long time since the establishment of international health and food agencies following World War II. These agencies were initially created to promote consumer safety and standardize trade regulations. However, large multinational corporations and industries have played a major role in shaping many of these regulations in the OECD, among other organizations [13] including establishing the rules for toxicological testing, particularly in cases where countries lacked the financial resources to regulate pesticides for intensive agriculture. Many of these chemicals originated from wartime explosives and toxicants repurposed for agricultural use [14, 15].

A notable historical example of the destructive effects of industry influence on safety testing is Industrial Bio-Test Laboratories (IBT), which conducted research for Monsanto and other major corporations from the 1950s to the 1970s. IBT was an American industrial product safety testing laboratory [16] and one of the largest of its kind. It was responsible for more than one-third of all toxicology testing in the United States, including for pharmaceuticals and industrial chemicals.

However, in 1981, IBT was exposed for engaging in widespread scientific fraud and misconduct, leading to the indictment of its president and several top executives [17]. The fraudulent practices included switching test animals, failing to expose them to actual toxicants, and even fabricating biochemical results.

After these revelations, international regulatory authorities instituted Good Laboratory Practice (GLP),

which systematizes the processes and conditions under which industry testing is carried out, with the aim of combatting fraud, as well as the OECD protocols, which set out specifications for the testing of chemicals. However, these measures have not ensured a transparent, verifiable, and reliable system. For instance, there is no scientific transparency of raw data, and many chemical products continue to be accepted worldwide without extensive re-evaluation or verification considering new scientific evidence. Moreover, frauds and scientific manipulations have continued into the present time—for example, as documented by legal proceedings in the case of glyphosate described below.

Numerous cases have demonstrated how industrial malpractices were overlooked for decades, despite scientific evidence of harm. One such example is the deliberate manipulation of environmental assessments related to per- and polyfluoroalkyl substances (PFAS), commonly known as "forever" chemicals, which have been recognized as pollutants since the 1950s [18–20]. From DDT to bisphenol A, toxicological fraud remains common [21–23]. Many of these substances, including petroleum byproducts, heavy metals, pesticides, and plasticizers, are among the most persistent pollutants worldwide. Another issue is that conflicting scientific conclusions between academic research and regulatory tests are quite common [24, 25].

Furthermore, the dishonest use and recycling (not declared) of petrochemical products in pesticides [26, 27] often conducted without proper toxicological evaluation of the mixtures or transparent declarations—has become a widespread issue, exacerbating environmental and public health risks.

Toxicology of pesticides and plasticizers contaminate all present-day forms of life

Pesticide formulations, as sold and used in the environment, have never been subjected by industry to long-term testing on mammals. The only such tests have been carried out by academic scientists in independent studies [28, 29], not even for a single pesticide, despite legal requirements mandating tests on formulations. These tests should have been conducted, as recently reaffirmed by the European Court of Justice [30, 31]. The same issue applies to plasticizers, which, as previously noted, are also petroleum derivatives. It may be argued that long-term exposure to intact formulated products in the real environment is unlikely, due to various conditions that would lead to dissipation and degradation of the components. However, for instance, a biomonitoring study based in the US found the pesticide surfactant polyoxyethylene tallow amine (POEA), which is commonly used in glyphosate-based herbicides marketed in the US, in the urine of pregnant women; this surfactant is also used in other pesticides and products [32]. Moreover, the dissipation and degradation argument does not apply to the petroleum waste, heavy metals, and plastic nanoparticles present in pesticides.

Long-term regulatory tests are conducted only on the purified, isolated declared active ingredients of pesticides. Long-term testing is not carried out on the full commercial formulations as sold and used in agriculture. However, pesticides are always applied as formulations, which have been shown to be at least 1000 times more toxic than the declared active ingredient alone, both in long-term studies and even after a few days in vitro [33].

To cite just one type of pesticide as an example of the inadequacy of this approach, recent reviews of the literature on the terrestrial and aquatic ecotoxicity of glyphosate-based herbicides found that in the majority of cases, the toxicity of the formulated herbicides exceeds the toxicity of glyphosate alone and concluded that their continued high use "cannot be considered ecologically sustainable" [34]. All forms of life are exposed to the formulations, not the isolated declared active ingredient, and exposures to glyphosate-based herbicides have been linked with numerous adverse health outcomes, including carcinogenicity, liver disorders, metabolic syndromes, and reproductive and endocrine-related effects [35]. For ethical reasons, this would save animals' lives to test only the major existing commercial product, which is always a mixture, which is preferable to test only one of its isolated components. Regulatory assessments typically include only short-term tests on formulations, conducted by chemical companies and limited to dermal and ocular exposure. This approach is both legally insufficient and scientifically inadequate for pesticide approval, yet these remain the only animal tests performed with formulations. Similarly, no long-term toxicological studies have been conducted for plasticizers. For instance, for flufenacet or other supposingly declared active substances (there could be some of its metabolites like PFAS among other compounds), model formulations were not tested over the long term in vivo. Instead, conclusions on safety were deduced from a theoretical background, which also is not transparent nor scientifically available because of the secrecy surrounding raw data.

This secrecy extends to the full chemical composition of formulations, raw bioanalytical data from toxicological studies on test animals, and even the detailed study protocols themselves. We are then reliant on trusting the reported findings on the endpoints, with which the independent experiments disagree. Such opacity is more akin to a ritualized industry practice than a scientific standard. This lack of transparency, including scientific cheats, were exposed in US courts. This was documented

in the so-called Monsanto Papers (2016), which surfaced during lawsuits against the company, resulting in unanimous convictions by popular juries for fraud after long court trials. It ended in favor of 100,000 patients and more presently who explained a link between exposure to glyphosate-based herbicides and their cancers [36–38]. This has led Bayer, owning now Monsanto to pay more than ten billion dollars in settlements. However, the products are still on the world market. Similarly, the toxicity of PCBs was deliberately hidden for decades, as has been the case with PFAS, which has recently gained widespread media attention. While some products have been removed from the market, a lack of transparency persists and never extends to the release of toxicological raw data.

Thus, it could be concluded that pesticides are, in fact, being marketed illegally. Scientifically, it is now well established that chronic toxicity can be several thousand times greater than the officially assessed toxicity of the declared active ingredient alone, due to the presence of undeclared formulants.

Despite this, legal toxicity thresholds for isolated active ingredients continue to be used as the primary measure of commercial product safety. This practice has persisted since World War II and is still widely accepted by scientists, medical professionals, regulatory authorities, journalists, and environmental advocates. This issue has crucial scientific implications. Toxicological reference values, such as the no observed adverse effect level (NOAEL) and acceptable daily intake (ADI), are primarily determined through experiments conducted by manufacturers. In some cases, independent scientists verify these values, but the testing is done using isolated, purified, and quantified chemical compounds, such as glyphosate (G) in the case of glyphosate-based herbicides (GBH), which are the most widely used herbicides in the world.

However, in real-world applications, GBH formulations—not pure glyphosate—are used in the field and natural environments. Studies have shown that GBH formulations exhibit 1000–100,000 times greater toxicity than glyphosate alone both in vitro [39], and in vivo [28]. The tumorigenicity and carcinogenicity of GBH was confirmed recently in a comprehensive long-term study [29]. This reasoning extends to other pesticides as well [33].

Therefore, long-term toxicity tests should be conducted, for instance, on full GBH formulations rather than with just glyphosate alone. The current ADI values, even after applying the conventional safety factor of 100, remain severely overestimated. To reflect scientific reality and the true toxicity of formulations, these thresholds should be reduced by a factor of at least 10^5 to 10^8. This is particularly important because commercial pesticide formulations are the actual mixtures that enter the market and environment, not only their isolated active ingredients, as previously explained. G represents about 40% of some commercial formulations used, thus pesticide spraying data overlooks at least 60% of the quantities applied, which, combined with already widely underestimated national and international data, presents a completely distorted picture of the global pesticide applications and their impacts [40].

The recognition that pesticides and plasticizers have unintended side effects on non-target species has been established for decades [14] and is now well documented, especially for pesticides [41]. Even as early as the 1950s, it was known that pesticides were contaminated with petroleum residues, but only recently have these residues been fully characterized as undeclared byproducts of petroleum distillation tower waste [27]. We group pesticides and plasticizers together for several reasons: pesticides, like plasticizers, are made from petroleum; no long-term studies are conducted in vivo by applicants for authorisation of the product as sold and used; moreover, petroleum residues and plasticizers have been found in pesticide formulations [42]; and plasticizers even in nanoparticle form have been authorized in pesticides.

Why formulations are more potent and harmful than declared active ingredients alone

Pesticide formulations are designed to penetrate biological barriers, such as plant cuticles, insect exoskeletons, and cell membranes [42]. Unlike declared active ingredients, which may have specific modes of action, formulations interact with organisms in diverse and unpredictable ways. They can affect fungi, bacteria (both symbiotic gut microbiota and pathogens), and human cells through mechanisms that always cannot be explained by a single uniform toxicological model.

Mass spectrometry analyses of commercially available pesticide formulations have revealed that they contain hundreds of unidentified compounds, distributed along Gaussian curves [43]. This confirms that adjuvants are not only numerous and variable, but also contain a mixture of residual industrial chemicals, many of which are toxic, originating from petroleum waste—and they are not declared. The toxicity has been observed in human placenta toxicity studies [44]. This is true for multiple pesticides, such as neonicotinoids including other fungicides [33]. Thus, relying on the ADI of a purified declared active ingredient is scientifically flawed, yet it remains the standard toxicological reference.

Fraud and regulatory failures in pesticide assessments

In addition to flawed testing methodologies, fraudulent declarations further compromise toxicological assessments. The inadequacy of regulatory frameworks in

evaluating chronic toxic effects has been confirmed by omics-based studies in living organisms [45, 46], conducted by independent researchers, since these studies revealed undeclared toxicities and their mechanisms.

This issue is not simply a matter of solubility of the declared active ingredient, because this has been proposed. The declared active ingredient in a pesticide product is mixed with numerous other substances, including known and unknown, and declared and undeclared adjuvants, forming what is collectively referred to as the formulation. It has been proven that any formulation contains co-formulants that, in some cases, may be more toxic than the declared active ingredient itself. The assumption that the declared ingredient is the most toxic component is thus not really accurate.

Furthermore, adjuvants and formulants often have their own unassessed toxicity, whether alone or in mixtures. Long-term toxicological evaluations by industry, regulatory bodies, and international safety agencies remain insufficient, leaving significant uncertainties regarding the composition and safety of pesticides. Many formulations contain undeclared components, some of which are not even known to regulatory authorities due to industrial secrecy and constant modifications in commercial batches [27].

Heavy metals and petroleum derivatives in pesticides

It is now evident that G is not the most or the only active toxic component in GBH formulations, even in plants [47]. Many formulations contain heavy metals and metalloids, including arsenic, nickel, and lead [47], which originate from petroleum-based adjuvants. Even in low concentrations, these elements exert combined toxic effects and are also able to act on their own but are not accounted for in standard regulatory assessments.

Other common compounds in pesticide formulants include polycyclic aromatic hydrocarbons (PAHs), which are petroleum residues. PAHs have been recognized for their pesticidal properties since 1787, and their toxicity and carcinogenicity have been acknowledged since 1953 [27]. Despite this, their presence in pesticide formulations has largely been overlooked in regulatory evaluations.

The true toxicity of pesticide formulations can be orders of magnitude higher than what is currently acknowledged in regulatory assessments. Furthermore, the lack of transparency, fraudulent declarations, and presence of undisclosed industrial chemicals further undermine the safety of these products.

As explained, a scientifically sound approach to pesticide regulation should include comprehensive long-term testing on full commercial formulations at environmentally relevant levels, rather than isolated active ingredients. This would also be more ethical. Until such reforms are implemented, pesticide toxicity will continue to be severely underestimated because it is not assessed as it really exists, putting both human health and ecosystems at risk.

What are the solutions?

In the meantime, a precautionary approach is necessary. In our opinion, for older, already approved pesticides and plasticizers, toxicity thresholds should be reduced pragmatically by at least by a factor of 100 to account for unassessed formulation toxicity, without requiring additional animal testing. For new pesticides, regulatory authorities should eliminate testing on isolated active ingredients and instead require tests on the full commercial formulations, at least a real model one, which reflects actual exposure. Traditional active ingredient testing is unnecessary, wasteful, and relies heavily on animal experimentation, which should be minimized. The mechanism of toxicity of each molecule is a subject of scientific research, not just a regulatory concern. However, regulatory agencies have never mandated comprehensive long term toxicological testing on full commercial pesticide formulations, even for some model formulations. This failure is largely due to industry lobbying, as we experienced, which aims to obscure the true toxicity of pesticides and blocks necessary reforms in toxicology. There is a recent debate on the mixture assessment or allocation factor (MAF, a tool used in risk assessment to account for the potential risks associated with the combined effects of chemical mixtures). It is still under discussion [48], but our proposal goes far beyond that.

The widespread presence of pollutants in food and the environment

Every species is exposed not only to full commercial pesticide formulations, but also to a complex mixture of industrial pollutants. These include residual pesticides, plasticizers of various sizes (including nanoparticles used in adjuvants), heavy metals, metalloids, additives, preservatives, and petroleum-derived chemicals. These persistent industrial residues have accumulated rapidly over recent decades, contaminating all forms of life as they disperse throughout the environment, participating in the development of chronic environmental diseases including endocrine and nervous ones [49], and acting as "spams" (like for electronic messages) or inhibitors for cellular communications.

Recent studies emphasize the real-life impact of these chemical mixtures [50, 51]. Their long-term effects are far greater than just the sum of their individual toxicities. This complex cocktail effect could explain the rise in chronic diseases in humans, animals, plants, microbiota

and even microbial ecosystems, contributing to a severe loss of biodiversity, also known as the sixth global extinction [52].

For instance, microbial communities have been shown to be disrupted by exposure to mixtures of pesticides, heavy metals, and other industrial chemicals, which could subsequently alter their structure and favor resilient or harmful species, as well as promoting the proliferation of opportunistic pathogens and/or antibiotic-resistant bacteria [53].

The persistent presence of these chemicals in the environment exerts selective pressure, encouraging bacteria to develop resistance mechanisms and adversely impacting the immunity of macroorganisms. As a result, microbial ecosystems become less diverse, and harmful pathogens with antibiotic resistance spread more rapidly (even if this process is also driven by other phenomena), threatening not only biodiversity, but also public health [54].

The need for a paradigm shift in pesticide regulation

The world's most widely used pesticides, such as GBHs, are at the center of debate across all continents. However, they are not the only concern. Other hazardous pesticides, such as neonicotinoids, must also be reevaluated. Addressing this issue will elevate human and environmental health to its rightful status, integrating food security and safety, soil and water quality, biodiversity, and ecosystem functions. It will also promote the advancement of agroecology as a sustainable alternative to chemically intensive agriculture.

Agroecology: a path to reducing chemical contamination

Better approaches are possible. Agroecological food production, free from synthetic pesticides, contains significantly lower levels of petroleum and metal residues, a fact supported by scientific evidence [5].

In this century, agroecology has proven to be a viable, resilient alternative capable of sustaining the world's food supply [55]. Evidence suggests that abundant, sustainable food production is achievable [56], albeit with a necessary reduction in meat and fish consumption. Numerous agroecological practices reduce pesticide use. For example, we should adopt biodiversity technologies, such as intercropping, cover cropping, crop rotation, soil health management, fertility enhancement, rice-fish [57] or rice-duck co-cultures, to biologically control pests [58–60]. Permaculture [61] can also significantly reduce reliance on chemical inputs.

The future of food must be reimagined [62], to achieve food security and reduce poverty. Agricultural development should prioritize growing a diversity of vegetables for consumption, rather than advancing industrial agriculture, such as raising mostly pigs, cows and chickens in factories and intensive feedlots for rich developed countries, also a major driver of exceeding planetary boundaries. Intensive farming increases pollution and contamination of products by artificial chemicals, contributing to chronic illnesses.

As scientists, we call for a complete and transparent assessment of all pollutants and pesticides before they are approved for market use. Today, the fetus is considered as a privileged target for pesticides and other pollutants, which have emerged as key players in a global health, social, economic, legal, environmental and ethical scandals. Moreover, the transgenerational effects jeopardize future generations. It is time for regulatory policies to align with current scientific knowledge, ensuring that human health and environmental sustainability take precedence over industrial interests.

Acknowledgements

We actively thanks Spark-Vie for financial support only for pages charges. No other financial support. No funding.

Author contribution

G.E.S. initially wrote the manuscript, G.J. was the main co-author, others by alphabetical order slighty modified, completed and approved it.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The review was not published elsewhere; we consent to publish.

Competing interests

The authors declare no competing interests.

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Received: 2 April 2025 Accepted: 24 September 2025
Published online: 04 November 2025

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