Human Health and Environmental Impacts of Pesticides: Epigenetic Responsibility and a Quest for Justice

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Published By

MedCrave Group LLC

October 19, 2016

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Biography

Dr. Yehia Ibrahim is currently a Professor Emeritus of Pesticide Chemistry and Toxicology at Assiut University. While being a Deputy Chairman of the Agricultural Pesticide Committee (APC), Ministry of Agriculture and Land Reclamation, Egypt his contribution during the past ten years to policy and regulatory development is nationally and internationally recognized. He is the first Arab scholar to publish in the 'Science' magazine in the field of toxicology and the first toxicologist to write on the epigenetic responsibility of pesticides and the first Arab pesticide regulator to publish a review article on the carcinogenic potential of glyphosate following its classification by IARC/WHO in March 2015. He has been awarded the Rockefeller Foundation Fellowship and the National Academy of Science and Technology Prize twice for educational and research excellence. Following his Ph.D. Degree, he obtained a Harvard IEM Degree in Educational Management.

Dr. Ibrahim worked as a distinguished visiting and adjunct professor in six top U.S. universities (Cornell, UC-Davis, NCSU, Harvard, LSU and Ohio Weslyen). With 50-year experience in research and education he has served many research and educational institutes as a consultant or a board member, and helped many schools and universities in the Arab world to meet national and international quality standards. Besides, Dr. Ibrahim has been internationally certified in several psychological and organizational disciplines, simulations, methodologies and approaches including questionnaire design, evidence-searching tools and data evaluation.

As an internationally recognized master/senior trainer and HRD consultant, he has participated in training thousands of university professors, school teachers and principals, employees, managers, leaders, and trainers on many interdisciplinary fields (Leadership, Management, Lateral Thinking, Mind-mapping, Team Dynamics, Corporate Culture, Paradigm Shift, Habits of Effectiveness, Emotional Intelligence, Personality Types, REBT, NLP, Hypnosis, etc.) in many Arab countries. Dr. Ibrahim supervised dozens of students for their Master and/or Ph.D. degrees, authored and reviewed hundreds of books and training materials; published many articles on personal, interpersonal and organizational developments in leading conferences, journals and websites; and appeared on a number of TV programs.

Acknowledgement

The author has learned a lot of the science and art of toxicology since he joined the membership of the Agricultural Pesticide Committee (APC), Ministry of Agriculture and Land Reclamation, Egypt. Dr. Salah Soliman, Professor of Toxicology, Alexandria University, Egypt and Late Dr. Mostafa Tolba, Former Minister and Professor of Plant Pathology, Cairo University, Egypt had kindly nominated the author to be honored this membership. Mr. Amin Abaza, former Minister of Agriculture and Land Reclamation, Egypt signed the decree of the Committee Membership. Some years later, Dr. Mohamed Abdel-Megid, Professor of Plant Protection, Ain Shams University, Egypt and Chairman of the APC had presented the author's name to Dr. Salah Yousef, Former Minister of Agriculture and Land Reclamation, Egypt to become the Deputy Chairman of the Committee. During his ministerial term, Dr. Salah Yousef kindly granted the author full confidence, liberty, and support. The one who 'cannot not' be acknowledged is Dr. Mona K. Ibrahim whose support of the author goes beyond limits.

Abstract

The reasonable certainty of no harm is the ultimate principle upon which all pesticides should be registered and regulated. There is a multitude of reasons or causations that explains any appreciable human-health and environmental impact of pesticides beyond this principle. This review will only shed some light on these causations, but focus mainly on a misconception-based regulatory policy. The wrong assumption of treating adjuvants as inert materials leads regulatory authorities - worldwide - to assess the risk of exposure to 'pesticide formulation(s)' based on hazard data for its 'active ingredient alone'. Glyphosate is used in this review to prove the erroneousness and danger of this regulatory policy. Shortly, the regulatory-set acceptable daily intake (ADI) of glyphosate 'alone' is 4-5 orders of magnitudes more hazardous when used within the context of its formulation(s) to which people are actually exposed. This erroneous policy, in addition to the recent findings which indicate that glyphosate is an endocrine disruptor with an epigenetic potential, make regulatory authorities responsible and accountable for any epigenetic harms caused by this herbicide. Unfortunately, epigenetic cases are not genuinely covered by the current legal systems; thus harmed or disadvantaged people may not have recourse to legal action. For example, under the tort law pesticide-related epigenetic cases will be lost in the context of statutory limits, liability dilution, victim attenuation, and lack of documented proofs for the cause-effect relationship. The most serious crime of pesticide epigenesis is that people may lose their lives for no good reason except that they were the descendants of those who had been exposed some years or decades ago to epigenetically-active pesticides. It is important that the tort law be amended to properly handle future claims of regulatory miscalculated risk and epigenetic effects of pesticides. Equilibrium between harm discovery rules, statue limitations, and statute of repose must be reached to assure:

1. Litigation and stale claims of allegedly epigenetic harm over years or decades after memories have faded and witnesses have disappeared; and
2. Economic environment is reasonably secure to support vibrant development of plant protection business.

Keywords: Acceptable Daily Intake; Diethylstilbestrol; Endocrine Disruption; Epigenetic Inheritance; Epigenetic Responsibility; Glyphosate; Maximum Residue Limit; Moral Responsibility; No Observed Adverse Effect Level; Regulatory Authority; Roundup Ready Crops; Soft Inheritance; Tort Law; Transgenerational Inheritance

Abbreviations

AADI: Adjusted Acceptable Daily intake

ADI: Acceptable Daily Intake

DES: Diethylstilbestrol

EPA: Environmental Protection Agency

FDA: Food and Drug Administration

FQPA: Food Quality Protection Act

MRL: Maximum Residue Limit

NOAEL: No Observed Adverse Effect Level

RR crops: Roundup Ready crops

US-EPA: United States Environmental Protection Agency

Pesticide Regulation and Public Health

Pests compete with humans and cause discomfort to their daily life. They are harmful organisms that also compete with other beneficial organisms, transfer disease to economic or ornamental crops, humans and domestic and wild life animals. Therefore, pest management has become instrumental to people's life. With the increase in human population, the advent of green revolution and intensive agriculture, as well as other factors, we cannot depend anymore on mechanical tools of pest control. Pesticides have become the most effective and practical alternative of pest management for several reasons: they are mostly cost-effective with a high return on investment; they have high structural, toxicological and functional diversity; they offer multipurpose management options; they have wide-spectrum efficacy; and they allow high flexibility and better timing [1].

Pesticides are chemically designed to kill pests by interfering with some biological systems vital to their life. Since these systems are commonly functioning in humans and many of their beneficial organisms (e.g., domestic animals and honey bee), pesticides are hazardous to non-target organisms. Therefore, pesticides should never be registered and used without lengthy, detailed and costly toxicological tests to ensure their efficacy against target pests and their safety to non target organisms, especially humans. It is also important that the final pesticide registration eligibility decision is made by government representatives or pesticide regulatory authorities, e.g., the US Environmental Protection Agency (US-EPA) and the European Food Safety Authority (EFSA), the Canadian Pest Management Regulatory Agency (PMRA), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Chinese Institute for the Control of Agrochemicals, Ministry of Agriculture (ICAMA). Because they must base their pesticide registration eligibility decisions on the principle of 'reasonable certainty of no harm', pesticide regulatory authorities are indisputably responsible for protecting human-health and the environment and should be accountable for any wrong decisions that harm people's life.

Due to the hazard inherent in pesticides, manufacture, authorization, marketing, exportation, importation, handling, use, storage, and disposal are regulated by thematic legislations. Risk assessment and management decisions should always remain the sovereign right of individual countries. For many economic and/or technical reasons, however, many developing countries are using the decisions made by major regulatory authorities, especially the US-EPA and EFSA as a start-out in their local registration process. The key strategy of these legislations is to reduce the impact of pesticides on human-health and the environment [2]. Under this wholly strategy many specific objectives should be in place such as:

1. Establish a transparent system and introduce cut-off criteria to only register pesticides that exhibit minimum hazard and pose no appreciable risks to human-health and the environment;
2. Minimize the hazards and risks to human-health and the environment from any pesticide misuse;
3. Review the safety status of the registered pesticides either periodically or when needed to ensure their sustainable and undisputed safety;
4. Improve controls on the handling, use and distribution of pesticides and seek means to minimize the potential impact and reduce the risk of pesticides during these activities;
5. Encourage low input control by raising awareness and promoting good practices of pesticide-related activities;
6. Provide registration applicants with clear forms and accept financial instruments; and
7. Create offences, establish penalties, and provide enforcement powers to sustain the pesticide regulatory system(s).

When a company desires to register a pesticide, it will be responsible for testing this pesticide, and providing the regulatory authority with an honest, clear, complete, well-organized and transparent dossier that includes comprehensive data on the mammalian and environmental hazard of this pesticide. Based on its hazard and the expected residue levels following its recommended application, the pesticide risk under field-use scenarios is assessed by the regulatory authority. The authority writes an evaluation report or monograph with a conclusive registration eligibility decision. When the decision is in favor of pesticide registration, the company is granted the authorization of marketing and selling this pesticide to retailers or users. The Organisation for Economic Cooperation and Development (OECD) runs a program on chemical safety under the Environment, Health and Safety (EHS). This safety program covers many areas of work, one of which is the Working Group on Pesticides (WGP) which developed a new Vision for Future 2024 encompassing a global approach to the regulation of agricultural pesticides [3]. Guidelines and criteria for the evaluation of dossiers and for the preparation of reports by regulatory authorities in OECD countries were prepared by the WGP [4]. Data providers and registration decision makers are - by no doubt - sharing the collective responsibility of any future risk that is based on inaccurate data, lack of critical information, or misinterpretation of the data upon which risk assessment and safety measures are calculated. When the risk is due to wrong policy and miscalculation of safety measures, the regulatory authority is the sole responsible and accountable party.

In almost all the countries worldwide, pesticides

must be approved for production, sale and use by a government agency [5]. To achieve their mission regulatory authorities should follow some principles, policies, and processes mandated by national/federal and sometimes international laws. For example, the US-EPA is responsible for regulating pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Food Quality Protection Act (FQPA) [6]. These two acts regulate pesticides to ensure that they do not pose adverse effects to humans or the environment. In completion to the registration requirements, a label is created to contain instructions, directions and safety restrictions for the proper use of the newly-registered pesticide. Studies must be conducted by pesticide companies to establish the conditions in which the material is safe to use and the effectiveness against the intended pest(s). In addition to the US-EPA, the United States Department of Agriculture (USDA) and the United States Food and Drug Administration (FDA) set standards for the level of pesticide residue that is allowed on/in crops [7]. Similar to other major regulatory authorities, the US-EPA uses the National Research Council's four-step process for human-health risk assessment:

A. Hazard Identification,

B. Dose-Response Assessment,

C. Exposure Assessment, and

D. Risk Characterization [8].

The aforementioned objectives along with the main strategy are more or less the same worldwide and the registration of pesticides seems to be under semi-harmonization philosophy. However, reaching a decision regarding such registration is different from country to the other depending on many factors. Among these factors is the data required for making any registration eligibility decision, especially the risk assessment data.

Do Safe Active Ingredients Mean Safe Formulations?

To start with the end in mind, it is fairly said that any toxicologist would never give this question a blind yes answer as will be explained in this and the following section. There are two critical measures that should be available for a pesticide to be registered and earn its pass to the market and field. The first and most important toxicological measure is what is called the acceptable daily intake (ADI). According to the medical Dictionary, ADI can be simply defined as: "An estimate of the amount of a substance (such as a food additive) that can be safely consumed on a daily basis over a person's lifetime without posing a health risk" [9]. ADI is usually measured in milligrams of the substance, per kilogram of bodyweight of the exposed person, per day (mg/kg/day). The second measure is what is called maximum residue limit (MRL). This measure is a legal, rather than, a toxicological measure. According to WHO/FAO [10], "The Codex MRL is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or ìg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food." Pesticides for which no specific MRLs are experimentally set, a default value of 0.01 mg/ kg is used [11 and references therein].

The problem of assuming that any pesticide active ingredient exerts the same risk when used alone as when used in formulation or mixtures is a complete fallacy. The formulation and mixture toxicology is a dark field that challenges the regulatory decisions regarding the registration of pesticides based on the risk of their active ingredient(s) in isolation. Currently, methods and terminology for evaluating the toxicity of pesticide formulations and mixtures are poorly established and chemical legislation rarely considers exposure to multiple chemicals [11]. The toxicokinetics and toxicodynamics of a pesticide that involves a primary toxicant and its co-formulants or involves a second toxicant plus these co-formulants are not the same as those of the primary toxicant alone and are extremely hard to model. Co-formulants may change the mammalian and environmental toxicity, as well as the persistence of the primary toxicant. Altogether, this will increase or decrease the adverse effects of the primary toxicant several-folds. One would expect that more often than not a pesticide formulation or mixture will be more toxic than what is expected from the toxicity of individual components or active ingredients. At present, the mammalian and ecological toxicity caused by pesticide formulations and mixtures are given little consideration in the regulatory process. The fact that the registration of all pesticides is based on the hazard of their individual active ingredients indicates clearly that the risk assessed is always underestimated or underrated and leads to false safety or safety misconception. The data gap in mixture and formulation toxicology is due to many reasons, e.g.,

i. Experimental studies on mixtures are very costly and time consuming;

ii. Two misconceptions of regulatory authorities:

   a. Co-formulants are considered inert materials;

   b. The active ingredients and its formulation have the same impacts on human-health and the environment.

Unfortunately, the abovementioned gap leads to uncalculated or underrated risk and become the sole responsibility of policy-makers, in this case the regulatory authorities. Furthermore, though MRL is set in view of the consumption pattern and the human exposure to the active ingredient in the context of its formulation blend,

its calculation is based on an ADI value that is originally estimated for the active ingredient alone. If there is bestowed toxicity induced by co-formulants, both the ADI and MRL values will be considered overestimated for the formulation and the risk will be certain even within the scope and magnitude of label instructions.

Inaccurate ADI values lead to safety misconception

To assess the risk of any pesticide to human-health and the environment, one should take two principal factors into consideration:

I. Its innate or potential hazard; and

II. Its actual level of exposure to humans and the environment.

The first factor is more or less based on fixed and experimentally-defined toxicological safety measures, e.g., the no observed adverse effect level (NOAEL) or the ADI level, while the second one depends on actual human and environmental exposure stemming from how much pesticide is being applied in a region on a given crop, collectively across all crops, and in other places. If perfectly determined, the potential hazard is static for each toxicological endpoint, while the experienced exposure is momentarily dynamic. This section contains a literature-based justification approach for the importance of refining ADI values measured for the active ingredient 'alone' using glyphosate as an exemplary model. It is supported by a novel illustration (Figure 1) that clearly shows how erroneously overestimated ADI value leads to enormously underrated risk, especially in the era of RR biotechnology (i.e., after the adoption of genetically-engineered glyphosate-resistant crops, commercially known as Roundup Ready (RR) Crops. This adoption has escalated glyphosate use to unprecedented volumes, especially in the US and some South American countries [12].

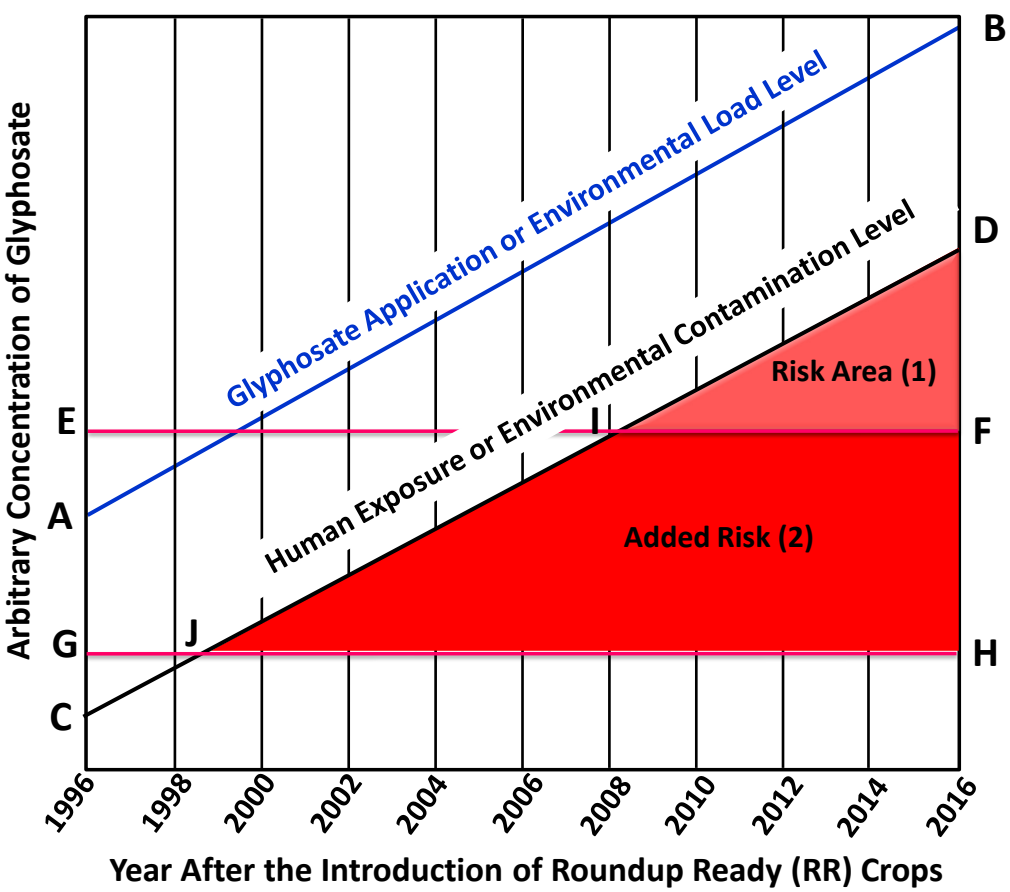

Figure 1: A hypothetical illustration shows how overestimated ADI value (line EF) leads to an underestimation of the risk imposed by exposure to glyphosate. With the adjusted or miniaturized ADI value (line GH), there is no safety misconception and the risk is accurately determined.

There are several reasons that led the author to question and challenge the reliability and validity of the currently-known and regulatory-certified ADI values of glyphosate and its end-use formulations. The same and other reasons have encouraged the author to seek ways to refine the currently-accepted but evidently-overestimated ADI values [13]. For the sake of this review article these reasons will be briefly reported.

1. ADI values have been determined by testing the active principle or ingredient 'alone' on laboratory animals; yet the regulatory authorities enforce these values on all used glyphosate-based formulations; barely known for the identity and toxicity of their individual components. That is in spite of the fact that people and the environment are genuinely exposed to formulations, not just their isolated active ingredient(s). Several Studies confirmed that glyphosate formulations administered to rats and pigs at levels - deemed safe for glyphosate active ingredient alone - were extremely harmful to treated animals [14-18].

2. ADI values are based on studies conducted on adult animals mostly failed to test or observe the effects of exposure during vulnerable windows of development, e.g. foetal development and unexposed descending generations. The issue of transgenerational or epigenetic inheritance of adverse human-health and environmental effects of endocrine disrupting pesticides was strongly emphasized when the well-known fungicide vinclozolin was given at a single time to mice with testis in a critical period of development [19]. Vinclozolin produced an adverse effect on the developing testis that was passed on to the following three generations of mice. The epigenetic inheritance was also found with other pesticides and pesticide mixtures. For example, it was clearly shown that the epigenotoxic effects of an insecticidal mixture (permethrin + DEET) lasted for three successive generations [20]. Generally, a subtle endocrine disruption during early life can modify the morphologies and functions of many organs and eventually cause reprotoxicity and cancer [21].

3. The regulatory-accepted risk assessment protocols are based on the 15th century old adage of Philippus von Hohenheim (globably known as Paracelsus, the father/founder of toxicology) who stated that: "the dose makes the poison" and implied that the higher the dose, the greater the degree of toxicity [22,23]. Although it fully applies to acute toxicity and related endpoints, this adage does not fully apply to some chronic toxicity, especially what is related to endocrine-disruption, wherein the dose-response relationship is not always monotonic and safe levels cannot simply be extrapolated from high doses [21,24-26]. Ultra-low concentrations of some endocrine-disrupting pesticides are more toxic than NOAELs which are commonly expected or extrapolated from higher concentrations. Besides, NOAEL itself may still cause serious response or damage on the same or different endpoints, if the dose matches the vulnerability window(s) and/or exhibits a biphasic or concaved relationship with its response. In the light of the endocrine-disrupting potential of glyphosate and other pesticides [27,28], the author prefers to rephrase the well-known Paracelsus toxicology principle to make it more applicable to any pesticide chemicals, regardless of the shape of its dose-response curve (monotonic or non-monotonic). The rephrased principle states that "the dose unfolds the actual risk of its potential or tacit hazardousness." The dose required for some toxicological outcomes or endpoints does not have to be only in the range of high doses.

4. The potential endocrine-disruption by glyphosate and its commercial formulations [29,30] indicates that the standard long-term animal studies and traditional endpoints required by regulatory authorities and executed by pesticide companies are inadequate to accurately determine valid and reliable ADI values. In a comprehensive review including 314 references [31], the authors compiled and discussed the uncertainties and unknowns that regulators may face when considering the risk assessment of endocrine disruptors and indicated clearly that there is no definitive risk assessment tool for these chemicals; a situation that will enforce regulators to accept data from loosely designed testing protocols and poorly defined, even distant or irrelevant, endpoints.

5. Several studies demonstrated additive or synergistic effects of different types of endocrine disruption, e.g., estrogenic, antiandrogenic, or thyroid-disrupting agents, when used in mixture at concentrations far below their NOAELs. A dramatic enhancement of endocrine effects not predicted from tests on individual compounds has been observed for some estrogenic chemicals [32-34]. When three estrogenic test systems were used, similar outcomes on mixtures of endocrine-disrupting pesticides were confirmed [35]. The additive/synergistic behavior of endocrine disruptors is likely to be the case with glyphosate and the additives in its formulations.

6. Commercially used formulations of glyphosate contain additives (adjuvants or co-formulants), which are either toxic in their own right and/or increase the toxicity of glyphosate [36]. Altogether this section indicates conclusively that when the safety measures are miscalculated and ADI is overestimated, the on-paper unexpected risk will be actually expected, and the blame should then go thoroughly to the pesticide regulatory authorities.

Do glyphosate ADI values require adjustment?

The six reasons mentioned in the previous section, along with the solid research evidence that supports them lead us to challenge the validity and reliability of regulatory-enforced ADI values on one hand, and to emphasize the importance of refining these values, on the other hand. These values seem to be highly overestimated and the risk of exposure assessed with reference to them is significantly underestimated. These reasons have encouraged the author to make some adjustment of the currently overestimated ADI values by introducing some safety factors [13]. Due to the high danger of ADI overestimation and the consequently exaggerated safety, the author will summarize a part of his in press study in this subsection. Two safety factors were introduced to adjust or scale down glyphosate ADI values. The first factor (10X) is to compensate for the likely harm in the light of the elevated environmental and human exposure following the adoption of glyphosate-resistant crops [12,37], and the repeated epidemiological incidences of glyphosate-related health effects [38]. The second factor (1000X) is to compensate for the bestowed toxicity of glyphosate in the presence of co-formulants. The introduction of the adjuvant or co-formulant safety factor is extremely important due to the fact that even though ADI is determined for glyphosate alone, people are exposed to the whole formulation simply because glyphosate alone can never be used by itself for weed control. In the following paragraph there will be a research-based justification for the importance and magnitude of the two safety factors. The first safety factor is similar to that of the US-FQPA and will be referred to here as the 'FQPA safety factor'. FQPA requires the US-EPA to assure that a pesticide can be used if only its residues demonstrate "A Reasonable Certainty of No Harm." This assurance requires the EPA to introduce a tenfold (10X) safety factor when setting and reassessing tolerances unless adequate data are available to support a different factor [39-40]. This factor is also used to compensate for dietary exposures and higher risk of glyphosate or any pesticide to extra-sensitive groups in the population, e.g., pregnant women, infants, children, and elderly people living in or nearby heavily exposed areas. According to researchers, cell damage and/or cell death, especially, embryonic, placental and umbilical cord cells, can occur at residue concentrations commonly found on Roundup-treated crops, yards, lawns, parks and gardens for weed control [41]. Considering the 'uncertain safety of safety measures' set for glyphosate-based formulations, and of the continual and high exposure of pesticide applicators, farm workers and bystanders in residential areas close to RR fields, one can introduce, for partial adjustment of glyphosate ADI, a safety factor of 10X, similar to that of the 1996 mandate of US-FQPA Act.

The second safety factor is called the 'Adjuvant or Co-formulant Safety Factor'. Based on a diversity of recent studies, a factor of 1000X was introduced to further adjust the thought- and also found-to-be overestimated ADI values. This factor compensates for the bestowed toxicity of glyphosate induced by adjuvants or co-formulants which are mistakenly believed to be inert additives. It has been recently mentioned that certain glyphosate-formulating adjuvants cause human cell toxicity, adding to the hazards inherent in the active principle (glyphosate) [42]. A study of the effects of glyphosate and its adjuvants on hepatic (HepG2), embryonic (HEK293) and placental (JEG3) cell lines, indicated that the toxicity of commercial formulations was due to adjuvants rather than the active ingredient itself, and the toxicity was proportional to the concentration of these adjuvants [36]. This has also been found to the case with other herbicides, as well as some insecticides and fungicides [43]. The formulations in almost all the tested pesticides were up to 1000 times more toxic than their active ingredients to human cells in vitro. Polyethoxylated tallowamine (POEA), a major surfactant in Roundup formulations, has been shown to be 1,200 and 2,000 times more cytotoxic than glyphosate [44]. The bestowed toxicity of the formulated vs. active principle of glyphosate is emphasized not only for human-health outcomes but also for environmental disruption [45,46]. For example, glyphosate at 50 ppb was shown to have significant negative impacts on the aquatic invertebrate, Daphnia magna [37,47]. This concentration is orders of magnitude lower than the range of the Maximum Contaminant Level or eco-toxicological threshold (700-27000 ppb) assigned by regulatory authorities in the USA and Canada [48]. Based on the aforementioned studies, a safety factor of 1000X was used to compensate for the bestowed toxicity of glyphosate induced by its co-formulants.

Altogether the two safety factors count 10,000 and has been used to miniaturize or scale down the overestimated ADI value(s) by four orders of magnitude. A group of scientists led by Dr. Michael Antoniou has compiled evidence supporting a miniaturized ADI value of 0.025 mg/kg bw/day [15]. Although this value is 12-70 times lower that the EU and EPA reference values, it is still four orders or magnitude higher than what was found to inflict gene disturbance or epigenetic disorder/havoc in rats [49]. Therefore, Antoniu's ADI value requires further refinement. When this value was taken as a baseline for adjustment, and divided by the combined safety factors of 104X, an Adjusted ADI (AADI) value of only 2.50 ng/kg bw/day was obtained for glyphosate in the context of its formulated blends. A recent finding clearly showed that genes in kidney and liver of rats treated with glyphosate at 4.0 ng/kg bw/day were functionally disturbed [49]. The fact that this dose is only 1.6 times that of the AADI value indicates that this value is reasonably calculated and

conservatively adjusted and refined. If this is the case with glyphosate, it is impossible to find out a responsible party but the concerned regulatory authority for any consequences resulting from overestimating ADI values and exaggerating this herbicide's safety. This authority sets the wrong policy by requiring the safety measures to be estimated only for the pesticide active ingredient, when in fact the pesticide-based formulation is:

I. The one that is actually applied in the field; and

II. Four to five orders of magnitude more toxic than the active ingredient alone.

The tort law or its modified or amended version, as will be explained later in this review, can be applied to handle the cases of people who have been harmed or will be harmed by this compound. It is so sad that many developing countries rely heavily on western regulatory authorities by following their policies regarding pesticide registration. Some of these policies may not be accurate, and those countries import what save their plants and harm their life concurrently. The author believes that there should be an international, epigenetic tort law to deal with any hidden or yet undiscovered imported/exported harm that threatens people life regardless of their location on the map.

The relationship between ADI overestimation and the safety zone perceived by pesticide users is conceptually; yet arbitrarily, illustrated in Figure 1. Before discussing the conceptual design of this figure it is important to mention that it is within our understanding that the relationship between the exposure level to any pesticide and its used quantity is not perfectly straight - but certainly correlated. It is also understood that the interface of pesticide use, human and environmental exposure, biologically-responsive system(s) and adverse outcomes is very complex. Obviously, the nature and severity of these outcomes vary depending on the overall health of the exposed organism, its physiological and psychological state, the level, timing and duration of exposures, the tissues exposed, their vulnerability, the consequent human-health outcomes, to count just a few. In particular, the timing of pesticide exposure that temporally and spatially matches the sensitivity window is a key determinant, especially with endocrine-disruption and epigenetically-mediated outcomes [50]. In Figure 1, there are two horizontal lines which present the inaccurate or overestimated ADI value (line EF) and the adjusted or possibly accurate ADI value (line GH). Hypothetically, there should be no risk for any 'exposure' below the 'ADI' value and left to the intersection of their lines. Any area below the ADI value and right to the intersection with the exposure line is considered to be a safety zone. However, any area above the ADI line and right to the intersection with the exposure line is considered to be a risky zone. In the case of inaccurate ADI values the risky zone is only the triangular IDF and the safety zone is the area under the JIFH shape. To the contrary, with the accurate ADI value there is no safety zone after reaching the J exposure point or level. This means that the safety zone in the case of overestimated ADI value is nothing but an exaggerated safety that will never protect people and the environment from the pesticide harm.

By looking at this figure, one can easily extract two intimately related points:

A. The higher the magnitude of ADI overestimation, the bigger the chance of missing the assessment of a significant portion of the actual risk;

B. The bigger the difference between the inaccurate and accurate ADI values, the bigger the area of safety misconception or deceiving safety with reference to the inaccurate (overestimated) ADI value.

Obviously, a result like the above erodes confidence in regulatory-promulgated ADI values, at least in the case of glyphosate-based formulations. With this conception in mind, it appears that levels of these formulations, for which the active principle is claimed to be safe, may in fact pose serious risk to humans over the long term. It is, therefore, believed that people are misled by the current safety measures (ADI values) of pesticide active ingredients when these measures are applied to interpret and assess the risk of exposure to end-use products or formulations. Even if the safety thresholds or measures adopted by regulatory authorities for glyphosate were accurate, the overuse of this herbicide in the past two decades and after the introduction of Roundup Ready (RR) crops may have driven its exposure to levels far above these measures; thereby making the on-paper or hypothetical certainty of no harm foggy or uncertain. Despite all the promulgated propaganda about glyphosate safety a positive and highly significant correlation between annual glyphosate use in the USA and the spread of hypertension, stroke, diabetes prevalence, diabetes incidence, obesity, lipoprotein metabolism disorder, Alzheimer's, senile dementia, Parkinson's, multiple sclerosis, autism, inflammatory bowel disease, intestinal infections, end stage renal disease, acute kidney failure, cancers of the thyroid, the liver, the bladder, the pancreas, the kidney and myeloid leukemia was recently documented [51].

Adverse Effects of Pesticides, Epigenetic Responsibility and a Quest for Justice

Unfortunately, epigenetic responsibility has not been specifically defined. For the sake of this review epigenetic responsibility is defined as: "The lone or collective accountability of individuals, groups, companies, government authorities, etc. for any decisions, choices, actions that cause epigenetic harms(s) to themselves, others or descendants without

entailing changes in their DNA sequences." Epigenetic responsibility, in our opinion, is a specific category of moral responsibility, wherein individuals from future generation may be affected without being directly exposed to tortuous decisions, choices, or actions. "The term moral responsibility refers to the duty that individuals and groups have to act in accordance with the moral principles that are important to their social communities and to humanity at large" [52]. Before going into details with the legal dimension of epigenetics, it may be appropriate to give an overview on the biological/toxicological dimension of epigenetics and its possible transgenerational inheritance. This type of inheritance is not a Mendelian type, and sometimes called 'soft inheritance'. The term soft inheritance was coined by Mayr [53], referring to the inheritance of variations that are not the result of genetic effects. One of the suitable definitions of epigenetics that has been articulated more than half a century after the term epigenetics was coined by Waddington in 1942 [54]is quoted as: "Epigenetics is study of changes in gene function that mitotically and/or meiotically heritable and that do not entail change in DNA sequence" [55].

An overview of epigenetics

Epigenetic toxicity has become one of the features of endocrine disruption; and some pesticides share these features. Since the main theme of this review is epigenetic responsibility for the adverse effects of pesticides that may impact future generations of exposed people, the author has dedicated this subsection to the origin, essence and function of epigenetic regulation and the impact of its perturbation on human-health. The work of developmental biologist Conrad Hal Waddington in the early forties [54] and that of David Ledbetter Nanney in the early and late fifties [56] has bridged the historic gap between two supposedly inseparable fields, i.e., Developmental Biology and Genetics by means of what was, and still is, called epigenetics or epigenome [57,58]. Epigenetics explains why a conservative/constant genotype is giving rise to several phenotypes even among identical-DNA-twins [59]. Even though the two epigenetic pioneers (Waddington and Nanney) independently coined the term epigenetic or epigenetics, they apparently used it in two different perspectives [54,56]. Waddington prophetically surmised epigenetics as a means for studying and understanding the 'causal mechanisms' by which genes of the genotype interact with the environment and bring about development and phenotypic plasticity. Although Waddington's perspective was shifted towards developmental biology with a lack of explicit focus on the inheritance of any particular phenotype(s), we consider it to be a revolutionary landmark in a time where DNA-transcription/translation/expression was not in vogue. Nanney, on the other hands, was the one who emphasized that the expression patterns or states of genes could persist through cell division in what is now called 'cellular heredity or cellular inheritance', i.e., cell with the same genotype may not only manifest different phenotypes, but phenotypic differences may also persist indefinitely during cellular division in essentially the same environment. These two perspectives had significant impact on the direction of this field till date. However, Nanney should be highly credited for igniting a 'paradigm shift' from the 'Orthodox Heredity' of Gregor Johann Mendel towards what is now close to be a credible fact: "not everything that is apparently inherited is necessarily laminated in the genome." It is even acceptable and safe now to say that our genome should not be treated as an ironclad code of our life; to the contrary, epigenetic malleability allows us to sometimes depart from this code, regardless of whether or not this departure is for the sake of our health and life.

The Waddingtonian and Nanneyan perspectives have been loosely unified by a common interest of understanding how any constant genotype produces different phenotypes [60]. This unification can 'simply' be explained by stating that the process of making different phenotypes from the same ancestral genotype cannot happen in regular or irregular development in the absence of a DNA-expression modulator(s); in this case it is the epigenome. Since genes alone do not determine phenotypic plasticity or explain the post-adaptive phenomenon associated with certain phenotypes of the same DNA sequence, mechanisms have to exist at the molecular level in order to mediate gene-environment interactions. As soon as some of these mechanisms were discovered, the term epigenetics came to be applied to them as well. A number of mechanistic tools have been implicated in epigenetic regulation of gene expression including DNA methylation; histone acetylation and methylation, chromatin remodeling (structural, topological, conformational or packaging modification); and un-translated (micro or non-coding) RNAs [61-62]. The best known of these mechanisms is methylation, where a methyl group binds to cytosine on a stretch of DNA, and renders it less active or silent. Interestingly, the epigenetic marking of the human genome by DNA methylation is heritable (from one cell to the other during cell division), and also stable or persistent through recorded cellular epigenetic memory that may subsequently be transmitted to future generations [63]. The epigenetic mechanisms themselves are very common in nature, e.g., in developmental biology, metamorphism and polyphenism. Quite aside from environmental influences, these mechanisms govern gene expression in all kinds of ways, including turning: a stem cell into a liver or kidney cell; a bee larva into a bee worker or queen; solidarity into migratory locust - all without entailing change in DNA sequences.

Figure 2 (below) is the author's model to conceptually integrate his simple perspective with:

1. The hypothesis that the epigenome interfaces environmental cues or environmental information and genomic DNA blueprint to establish transcriptomic profiles and functional identities of individual cell types [64];
2. The Holliday's proposal that epigenetic effects or defects in germ line cells could be inherited in offspring [65].

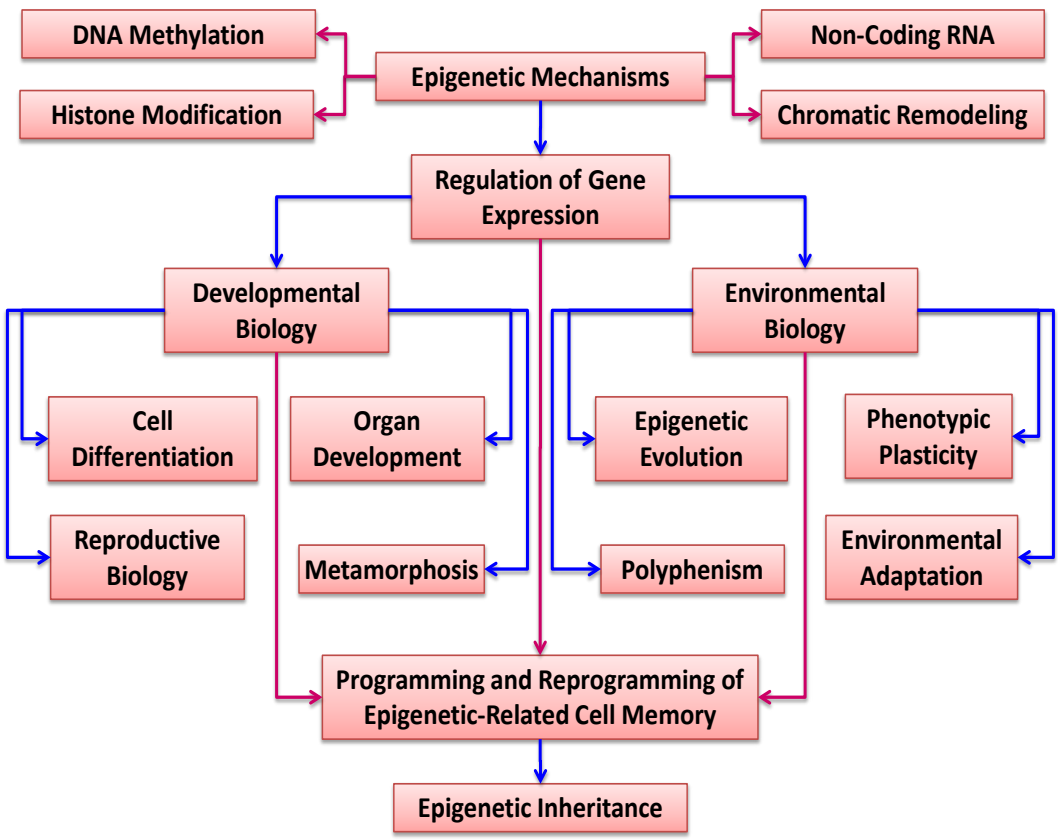

Figure 2: A model shows the role epigenetics plays in gene expression and function either under conditions of a normal development (left side) or under the influence of some environmental cues (right side). Epigenome is shown to interface environmental cues and the genome. Pesticides enter this model from the environmental biology side and may then lead to epigenetic inheritance.

The above model creates a "Waddington-Nanney-Holliday" recombinant perspective, and also shows that the environmental stimuli or cues play a critical role in phenotypic plasticity through the epigenomic or epigenetic malleability. It is therefore the epigenome's responsibility to respond to environmental cues and regulate the capability of an organism to adapt and evolve into different phenotypes [61]. Pesticide chemicals are well-known contaminants of the environment and are not excluded from affecting our epigenome. Most of the time such effects are harmful to the health of exposed people and/or their offspring and future generations.

Many environmental cues have been found to affect the epigenome including diet, smoking, child care, and environmental pollutants, especially those with endocrine disrupting capabilities [66]. Figure 2 implies that we are not bound to our genes; in fact environmental chemicals, especially endocrine-disrupting chemicals including pesticides, could inflict human-health and the environment with severe epigenetically - not just genetically - mediated adversities. Even worse is that these adversities could be epigenetically transmitted to progenies that are not 'previously' exposed to these chemicals; a phenomenon called 'Epigenetic or soft Inheritance'. Hormones are genuinely considered to be the signals that promote specific cell-memorized actions, especially when they exert their effects in the fetal stage and sustain these effects by influencing or dictating the functions of endocrine and physiological systems in later stages or later generation(s). Although it was coined and conceptualized in the forties, only in the last few years, epigenetics has seized scientists' imagination and the public attention [67-69]. Astonishing book titles and magazine articles on epigenetics have been everywhere

in the past decade. As examples, magazine like New Scientist published an article entitled: "How to change your genes by changing your lifestyle" [70] and a book entitled: "The Epigenetic Revolution" [71] has become a bestseller. In addition, the popular press regularly entertains epigenetic research, including a recent study purporting to show that severe psychological trauma can be passed down through one's genes [72, 73]. Overall, it would be easy for anyone nowadays to form the impression that the genetic destiny of future generations is not entirely in the DNA sequence; it is mainly in the regulatory machinery of gene expression and function. DNA expression is highly malleable; thus Darwin and Mendel have been steadily discredited in the wake of epigenetic inheritance [68].

The epigenetic machinery is there specifically for biological functions, among them is empowering the organism with a potential adaptation to environmental changes and chemical stressors. Some of these stressors disrupt other systems and play havoc with the epigenetic machinery in ways that induces serious human diseases like cancer [50]. Even more dangerous is that these epigenetic-mediated diseases can overpass the exposed generation to future unexposed generations. The literature is now full of evidence indicating that this is the case, especially with endocrine-disrupting chemicals including some pesticides [50 and references there in]. For example, when pregnant mice were fed Bisphenol A, a toxic ingredient of plastics, the resulting adverse effects appeared not only in their offspring but also in the following generation [74]. These effects include obesity, diabetes, an increased frequency of cancer, and yellow fur instead of brown. In another much quoted study, scientists claimed that mice bred from fathers who had been trained to become afraid of a particular smell also showed avoidance of the same smell - although it is hard to understand how such a specific outcome could be achieved through known molecular mechanisms [75]. It is the author's belief that the epigenetic machinery is highly responsive to any external or internal input so long as this input is timely and spatially matching the sensitivity window of this machinery. Therefore, all pesticides are expected to have some epigenetic effects, whether harmful or not and whether transgenerational or not.

Pesticide epigenetic harm is missing a legal responsibility

The use of pesticides became widespread during the last century, and the incidence of non-Hodgkin's lymphomas (NHL) also increased during the same time [76]. Some pesticides have demonstrated potential for tumor initiation and/or promotion in experimental animals [77]. According to the US-EPA, almost all pesticides marketed in the USA have not been shown to be genotoxic [78]. Due to increase in its global incidence, cancer cannot be explained only in the light of genotoxic effects; to the contrary, epigenetics likely plays a much significant role [50]. Similar to other xenobiotics, exposure to pesticides may lead to modification in gene expression without entailing change in DNA sequence. Alteration of DNA methylation patterns has been increasingly found in different types of tumors [79, 80], and endocrine disruption may have been involved [81]. Far from being conclusive, many published studies suggest that epigenetic modifications may be one of the mechanisms by which pesticides can have noxious epigenetic effects on human-health and the environment [50 and references therein].

To the best of the author's knowledge, no pesticide has been the court case specifically for an epigenetic responsibility. Therefore, diethylstilbestrol (DES), an endocrine modulator drug, will be used to shed some light on the future epigenetic responsibility of pesticides. DES was chosen as a case model in this review for a number of reasons. First, it is probably the first chemical to be blamed in a court of justice for its epigenetic effects. Second, DES and many pesticides have several toxicological features in common. Third, both DES and glyphosate have been so widely used despite the predominance of conflicting evidence over their sustainable efficacy and safety. Fourth, there has been struggles between the producer companies of DES and regulatory authorities to maintain its legal use, a case that is extremely similar with some pesticides, especially glyphosate. Fifth, glyphosate which has been used in this review as a case study for the inaccurate determination of safety measures is also known as an endocrine-disrupting chemical with epigenetic effects. Sixth, DES is used in the context of this review to point out the disturbing possibility of repeating its worst case scenario with glyphosate-based herbicides. It may serve the objectives of this review to give a brief overview of DES before discussing its epigenetically-related legal issues.

The leading case of DES epigenetic responsibility

DES is one of the most powerful case studies in the history of endocrine-disrupting chemicals which shows how government authorities sometimes face opposing public and political pressures while making their regulatory decisions of drugs and pesticides. The DES case will be discussed in this review to indicate what can go wrong with public health if the safety measures are not carefully determined and/or if the precautionary principles are not strictly followed. Although DES was prescribed for use in all pregnancies to ensure healthy babies, there was no science to support its safe use in normal pregnancy. DES was first synthesized in 1938 by British biochemist Sir Edward Charles Dodds to possibly use it for an easy and inexpensive treatment of menopause symptoms [82]. Less than two decades after its synthesis, DES was used like vitamin pills, not only for humans but also for poultry and livestock. This compound was approved in 1947 by the FDA for a diabetic

treatment in pregnant women, and for the enhancement of growth in poultry and cattle [83]. Following its approval, drug companies widely advertised promoted its use in 'healthy pregnancies' to reduce the risk of miscarriage. Not only DES was used widely for long time to treat miscarriage, breast and prostate cancer, menstrual disorders, acne and many other health problems, also it was quickly introduced into veterinary practice to treat infertility and mastitis in livestock, and to improve feed efficiency and weight gain in poultry and cattle. By 1955, > 90% of the livestock was DES-treated in the USA; thus it was not surprising that the substance was found in almost every aspect of American life [84]. This has been exactly the case with glyphosate presence in the environment of countries cultivating RR crops and using glyphosate much frequently at higher rates [12,37]. Although DES was used against breast and prostate cancer, it was found that when applied during prenatal development, it causes significant increase non-cancer reproductive abnormalities in male and female offspring and a cluster of vaginal cancers in female offspring [84]. In utero exposure to DES induces persistent epigenetic changes in the developing uterus and also increases the risk of breast cancer in adult women [85]. Investigators found similar results in experimental animals, e.g., sexual dysfunction, infertility and cancer with extended effects on offspring and descending generations (DES grandchildren) [82]. Like glyphosate, DES posed problems for regulatory authorities as they were accused of not responding properly and promptly to scientific findings and safety concerns while surrendering to political pressures from chemical industries. As it was reported, DES came before the FDA three different times, and despite the administration's safety concern, it backed away from making decisions and/or taking actions due to strong political pressure from the pharmaceutical and agricultural communities [84]. The author of this manuscript does not fault government authorities for ill-regulating DES and glyphosate. To the contrary, he points out how lessons from history can be used to make better policy and ensure that skillful manipulation of scientific uncertainties does not stop regulatory authorities from making critical decisions in due time to assure that put public health is always above business health. At this point, it can be fairly said that DES and glyphosate exhibit similar pattern for the lack of proper regulatory actions taken, respectively by the FDA and EPA in the face of major health concerns. It is believed that the lesson of DES and its epigenetic effects have not been learnt in the case of other endocrine-disrupting chemicals including glyphosate and its co-formulants.

Pesticide epigenetic responsibility in the wake of DES litigations

As a start of this subject, it is important to sate that the definitions of genetic and epigenetics have not been legally explored by courts [86]. There are few instances where epigenetics has been investigated indirectly using the 'Tort Law'. "The term tort is the French equivalent of the English word wrong. The word tort is also derived from the Latin word tortum, which means twisted or crooked or wrong, in contrast to the word rectum, which means straight (rectitude uses that Latin root). Thus conduct that is twisted or crooked and not straight is a tort. This term was introduced into the English law by the Norman jurists [87]. According to the Legal Dictionary, the Tort law refers to a set of legal articles that provides some remedies and/or compensation to individuals who have been harmed by the unreasonable acts of others [88]. This law is based on the thematic concept that people are 'liable' for the consequences of their intentional or accidental actions that harm others. Unfortunately, under this law the long lag time before epigenetic effects might become obvious creates a challenge for those who are harmed and desire to seek legal rights. In particular, the common legal principles such as the 'Statute of Limitations' and the 'Discovery Rule' present a huge challenge for injured people seeking court orders for remedy or compensation. Sometimes it is uncertain when statutory limits should expire, and for how many decades is it reasonable to hold a company and/or regulatory authority fairly liable. This challenge is amplified when the harm appears in pesticide-unexposed descendants farther away from exposed parents or ancestors. Since epigenotoxic effects are transgenerational in nature, the issue of dilution also comes into play. It is the long latency period between exposure and response that makes it sometimes extremely difficult to accurately identify the pesticide responsible for the epigenetic harm and assign the remedy or compensation for the epigenetic outcomes. As pointed out before, one of the first examples of epigenetic harms has been addressed by the US legal system occurred in the United States when mothers and daughters exposed to DES began suing manufacturers for reproductive problems and cancers in the exposed daughters [89]. In 1990, a DES son filed a lawsuit against a US drug company alleging that his in utero exposure to DES elicited cancer to his daughter [90]. In both the USA and Canada, the principle of 'discoverability' can introduce a loophole to strict statutory limits [86]. Statutory limits and 'Repose' present substantial constraints that prevent the system from appropriately dealing with epigenetic liability cases. Legally, the period for litigating claims is limited, and in most cases it runs out before any of the epigenetic harms manifest themselves [91]. It can be hard to reconstruct who manufactured, marketed, used or dispensed a pesticide, and given the complex and combinatorial nature of epigenetic imprints, it is also hard to demonstrate direct and unadulterated cause and effect. The litigation surrounding DES is an illustrative model of the complexities associated with legal epigenetic responsibility. It is important to note at this point that glyphosate and DES share two

important features; they both have endocrine-disrupting potential, and they both seem to play havoc with our epigenetic machinery. The DES cases have proven an interesting testing ground as second generation claims have been permitted in some jurisdictions and under specific circumstances [86]. Accordingly, descending generations from glyphosate-mediated epigenetic harm can be treated likewise.

Epigenetic harms can have a transgenerational impact, and the harms are sometimes unknown and only displayed after one or more generations. For instance, it took years before the side effects of DES became known. Many of the women who took the drug are now deceased; yet the side effects are only just now being encountered in their children grandchildren, and only time will tell if the adverse effects extend themselves to further generations. The imposition of strict time limits could eliminate future generations from filing claims. On the other hand, the absence of limitations could render the economic environment too insecure to support vibrant business and product development. In many jurisdictions, there is a 'Discovery Rule' indicating that the time limit does not start until the epigenetic harm is discovered. For example the Ontario Limitations Act of 2002 provides for a two year period following discovery for litigation to be pursued [86]. Some jurisdictions also have a 'Statute of Repose' which limits the discovery rule to prevent litigation decades after the drug use [92]. This statute prevents victims and claimants from exposing the defendant to the threat of indefinite liability. Besides, in the instance of epigenetic effects, this statute sometimes runs out even before the epigenetic injury or harm has been noticed or identified; thus making it impossible to assign the blame to anyone [91]. Under the current legislation, it seems that the chance of pursuing an epigenetically-related claim against a pesticide company or regulatory authority is almost impossible. Some states have introduced changes to their legislation with regards to statute of limitations to make second and third generation claims acceptable and more sustainable in courts [93]. Generally, although the subject of epigenetic responsibility is so complicated and the cases are so confusing to court authorities, the public has the right to claim responsibility assignment and receive compensating court orders.

The tort law and pesticide epigenetic responsibility

It is the norm of life that one should be held accountable for his/her decisions and actions. Unfortunately some people may lack the knowledge required to make intelligent and healthy decisions and choices, or may lack the socioeconomic means to live better lifestyle and remedy their situation [94]. Moreover, the disadvantageous epigenetic side effects might be so profound or insidious that the cost of correction is unaffordable for the individuals or their families. While no laws currently exist regarding the assignment of responsibility for the causation of epigenetic insults, some believe that the tort system could be modified to address these issues [86,94]. In general and as defined before, the tort law is enforced by the government to ensure the public health safety [91]. Thus the tort law could be used to address some pesticide-mediated epigenetic harms. However, the legitimate requirements of the current law may pose several problems for the victims of epigenetic insults, especially if the harmed people are generationally distant from their exposed ancestors. In particular, there are two legal concerns when applying the tort law to pesticide-related epigenetic cases; one is related to defining 'liability' and the other is related to establishing the 'causation' chain.

The liability concern: It is mainly due to the ambiguous nature of both epigenetics and collective responsibility in the case of chemical products in general [95], and pesticides in particular. Following the basics of tort responsibility compiled by Hedlund [94], liability can be assigned to individuals (factory laborer, pesticide applicator, farm-worker, consumer, bystander), to a pesticide company or plant owner, to a group of companies producing the same pesticide(s), to a government employer/employee, to a pesticide regulatory authority or to a group of authorities working towards a common purpose and are responsible for occupational or environmental exposure and related hazard. The liability can sometimes be extended to reach the state or federal government. Since there can be a long latent period between exposure and effects, the makeup of individuals within a company producing an offensive pesticide can completely change by the time the plaintiff makes a claim. Therefore, it has been legitimately argued that it is unfair to throw blame on current individuals for harms caused by the past action of their predecessors [91]. Joint venture liability suits have also been filed for DES related cases. In these suits, all the companies who manufactured or sold DES are held jointly responsible and proportionately liable for the damages incurred irrespective of which manufacturer's doses were prescribed to a specific patient [96]. In the Netherlands, collective settlements have been reached using a joint venture prosecution. A fund for victims was set up, however, it took 20 years to reach an agreement and the compensation has proven to be too little as the settlement has to be spread among multiplying claimants [97]. Likewise, pesticide companies can be charged for joint-venture liability if they produce the same pesticide(s) with - for example - harmful impurities exceeding the limits specified by the Food and Agriculture Organization and the World Health Organization [98]. How is responsibility or blame assigned 'quantitatively' when more than one individual or group is involved in the same harm(s)? Although there are ways in which percentage blames can be assigned, the constantly changing and inherently complex nature of the epigenome likely means that the

precise assignment of proportional responsibility will be difficult if not impossible to determine. The complex combinatorial interplay of epigenetic influences also makes it difficult to assign a specific cause to an effect.

The causation concern: It is all about proving and documenting the causation. The accuracy in assigning legal responsibility to an individual(s) or a group(s) requires a causal chain - that the actions of the individual or collective directly caused the adverse outcome of interest. In most of the tort laws, the victim is required to prove that the harm was a direct result of the defendant's actions by more than 50% probability [99]. This becomes difficult when the causal stimulus and the revealed effects are separated by years or generations, as it is often the case with transgenerational epigenetic effects. Since individuals are generally exposed to thousands of different chemicals including pesticides, either simultaneously or consecutively, and to the same chemical(s) from several different sources, it can be difficult to prove that exposure to a single pesticide has resulted in negative epigenetic effects; thereby making it difficult to establish one sole culprit. Within the huge diversity and multiple formulations of generic pesticides, it may be difficult or even impossible for a plaintiff or claimant to identify with proof that a particular pesticide has caused specific or claimed epigenetic harms(s). On the other hand, the generation of causation information and documents would be beyond the abilities of most plaintiffs [91], especially in poor countries wherein pesticides are used heavily and sometimes irresponsibly. When making a second or third generation claim, which would be the case with pesticide-epigenetic harms, it is difficult to have all the required information on hand to track the record, and sometimes a record might no longer even exist. Let alone, the use of illegal or counterfeited pesticides and the widespread of orphan pesticides in many countries around the world. In a final retrospect, given the latency of epigenetic effects and the lack of knowledge on the exact effects of substances on the human epigenome, it is unclear whether unforeseeable negative effects could be punished by tort law [100]. Meanwhile, it is highly recommended that an epigenetic tort law must be drafted to deal with pesticide unforeseeable adverse effects to human-health and the environment. Experts from fields such as law and justice, toxicology, public health, environmental biology, developmental biology, etc. must be involved in extensive discussion to draft such a law.

Models for assigning pesticide epigenetic responsibility

Up until today, legal and regulatory frameworks have been concerned with assigning responsibility to blame causally responsible stakeholders, when unfavorable outcomes are clearly identified. This model is called a 'Retrospective Responsibility' [94,101]. As explained before, when this model is applied to pesticide-related epigenetic harms, identifying those to blame will prove to be a challenging task. However, for a number of reasons, the author believes that when pesticides are properly used according to their labels and government-set instructions any epigenetic harm must be the 'sole' responsibility of the regulatory authority. This implies a shift in the responsibility from the individual to the society and the government, which will ultimately bear much of the cost associated with ill health and lowered productivity. The other model of responsibility is called 'Prospective Responsibility'. This model takes into account structural conditions, and to some extent frees the disadvantaged from total responsibility [94]. The prospective model acknowledges that even if individuals are complicit in damaging their own interests, this creates costs to society in terms of health and productivity, not merely insofar as the individual is concerned, but also for innocent, successive generations who ought not to be punished. It is difficult to determine the boundaries of responsibility between the individual and society, so it is economically and procedurally simpler to facilitate better health via societal support than by assigning individual blame. The prospective responsibility is certainly critical but only complementary to the retrospective responsibility especially for pesticide-related epigenetic harms. When inaccurate regulatory policies are the reasons behind those harms, the retrospective type of epigenetic responsibility is not enough; thus policy change must be taken into consideration and be given a high priority. This applies to the inaccurate regulatory policy of measuring the safety measures (e.g., ADI values) of pesticide active ingredients when in fact pesticides are applied in formulation blends of unknown or even higher hazard than their active ingredients.

Since there are many legal concerns and challenges with regard to assigning liability on those who impose pesticide-related epigenetic harms to human-health and the environment, it is suggested here to levy a 'pesticide epigenetic tax' to compensate epigenetically-disadvantaged people, their offspring and descendants. As described in a model proposed by Yehia A. Ibrahim [102] for the 'Extended Pesticide Producer and User Responsibility' (EPPUR), this tax would increase the production cost of pesticides, increase their market price, decrease their sale and prevent their overuse. Liability in the form of epigenetic taxation must not impede progress in pesticide industry. One way to reach this objective is to give companies an incentive to ensure epigenetic safety by inversely tying the taxation rates to their investment in research and prevention. This would benefit companies by decreasing the taxes levied, as well as the potential liability costs of their product.

Conclusion

To understand the negative impacts of pesticides, one should refer back to four important pieces of information.

First, pesticides are chemically and toxicologically designed to kill pests by interfering with key processes in their biological systems. Second, because some of these processes are also present in non-target species, selective toxicity of pesticides is not always pro the safety human-health and the environment. Third, not only pesticides are chemical stressors, they are also intentionally placed into the environment in huge quantities [103]. Fourth, there is a common belief that less than 1.0% of applied pesticides reaches their target pests and the rest (more than 99.0%) moves into the environment and adversely affect its overall ecology, public health and beneficial biota. By integrating these pieces of information, one can fairly state that the risk of pesticides to human-health and the environment is inevitable, and pesticide regulatory policies and strategies are set to minimize, rather than prevent, this risk. The first and most important strategy for risk management is pesticide registration, i.e., pesticides are only manufactured, marketed, handled, exported, imported, stored, disposed, etc., according to some legal rules, principles, policies and processes set by government authorities. A chemical company desires to register one of its products must provide these authorities with a dossier containing rigorous data on pest-efficacy, mammalian- and eco-toxicology, and environmental persistence. Pesticide regulatory authorities carefully review the dossier and when they found that the pesticide is unlikely to pose any appreciable risk to human-health and the environment, a registration eligibility decision is made and a label is approved. It is critical that pesticide stakeholders abide with the government regulation; in particular, pesticide users are morally responsible for applying registered pesticides only and strictly according to product specifications and label instructions.

At this juncture, when a registered pesticide is used and causes unexpected harm to human-health and the environment, there is a hierarchy of at least five reasons.

1. The pesticide company could have provided regulatory authorities with inaccurate information regarding the hazard of the pesticide.
2. Regulatory authorities may have instructed the pesticide company with the wrong or incomplete protocol and guidelines for generating the hazard data. This reason reflects on two serious regulatory policies. The first policy requires the company to provide hazard data on the 'pesticide active ingredient alone' with the wrong assumption that its formulation additives are all inert. This policy results in overestimating safety measures and underestimating actual risk. The outcome would simply be uncalculated adverse effects on human-health and the environment. This review provides glyphosate and its end-use formulations as a crystal clear case study that proves irrefutably the erroneousness of this policy. Another reflection is that regulatory authorities do not carefully choose the endpoint(s) for the pesticide-caused adverse outcomes. These two reflections are clearly indicated in the light of the recent adjustment of the regulatory-held ADI values (0.3-1.75 mg a.i./kg bw/day) to become only 2.5 ng a.i./kg bw/day, i.e., 4-5 orders of magnitude less [13]. The endocrine-disruption and its consecutive epigenetic effects are clear examples of the most serious; yet not properly addressed or considered, endpoints and related outcomes. The effects on these endpoints can be elicited at exposure levels far below the regulatory certified acceptable daily intake. Furthermore, when exposure occurs during critical developmental stage(s), these effects can be transmitted to offspring of exposed parents and even to their future unexposed generations following the Lamarckism theory of acquired traits [104]. The use of epigenetics in human and environmental risk assessment and management should be among the first applications in new regulatory policies. This will add multigenerational dimension to pesticide-related health effects.
3. The human safety measures extrapolated from laboratory tests on experimental animals could collapse under field-use scenarios of pesticide application. If the fidelity of man-like models from among placental mammals, even the presumed closest human relative (e.g., the old-world macaques primate), could be valid for traditional toxins, it is definitely a 'fallacy or myth' for endocrine disruptors and epigenotoxic agents. The conclusion of high fidelity fallacy was prophetically reached more than 50 years ago by Russell and Burch [105]. Today, this conclusion is more important than ever before from both the toxicological and humane perspectives. The huge differences of sensitivity among different animal species and also among different individuals of the same species, makes the extrapolation from experimental animals to humans dangerously ambiguous. The author of this review shares the conclusion reached by Wei et al [106] and extends it for pesticide-related epigenetic perturbations to suggest that in vitro human cell testing, methylated reporter and other epigenetic marker assays could be better than, or complementary to, experimental animals. This will take us close to Bill Russell and Rex Burch's principles of humane experimental technique [105,107]. Russell and Burch's pivotal publication [105] recognized that the future risk-assessment testing would lie in the use of human cell cultures.
4. The history of pesticides tells us that there is always an iceberg for human and environmental toxicity of these pesticides. The advancement in toxicology can disclose some deep levels of this

iceberg. Therefore, regulatory authorities must review registered pesticides and adjust their safety measures based on new safety-related discoveries.

5. The last but not least reason for experiencing unexpected adverse human-health and environmental effects is the use of pesticides 'above' and 'beyond' the regulatory-certified label of well-studied and carefully registered pesticides.

Individuals who are epigenetically disadvantaged should have the right to present their cases within a legal system and get the compensation they deserve. The uncertainties and challenges that have arisen in the DES cases of epigenetic litigation imply that:

a) The current laws are not fully adequate to handle the pesticide epigenetic effects; and

b) An explicit inclusion of epigenetics into the current laws or creating a specific pesticide-epigenetic-tort-law becomes a necessity.

This law will not only provide justice to citizens by ensuring that those who are liable are held accountable, it will indeed prevent future harms from occurring.

Given the reasons or causes (1. to 5.) mentioned in the previous paragraph, one can hypothetically draw a panorama of the moral and/or legal responsibility for the adverse effects of pesticides. Epigenetic responsibility is commonly understood in a retrospective (backward) manner, i.e., identifying causally responsible actors to blame for a bad outcome(s). This type of responsibility can definitely be applied to a number of the above reasons or causes. When epigenetic harm occurred because of forced ignorance or belated toxicology knowledge, this harm can be best handled in a prospective (forward) responsibility manner, i.e., adjusting the safety measures and re-regulating the pesticide of interest based on the new understanding. This type of responsibility would partly free disadvantaged individuals from responsibility, and identify actors with power and capacity (e.g., regulatory authorities) to do something about their structural policies. Pre-market and license testing should be required to address the epigenetic side effects of each substance, as well as to predict changes in the metabolic mechanisms whereby xenobiotics themselves could be modulated by varied epigenomes [108]. It is impractical to make human cross-generational studies a part of the approval process. This could render the development of pesticides a lengthy and impossibly expensive process. Clearly cell and animal models will have to be developed to prognosticate potential pit falls, while simultaneously, longitudinal studies on human cell lines and in vitro tests should be required even after pesticides enter the market and is applied in the field. Not only that testing is necessary, but also there is a need for a regulatory policy regarding how and where the testing is done. Considering that epigenetic modifications are species specific, it is important to choose the right model organism for testing and if extrapolating to include humans, to do so cautiously [93]. As such, the results should not be taken as the final word, but rather, they should be seen as a guide, and further investigation should follow to determine possible long term effects. Not only a pesticide hazard should be identified with classical toxicological and reproductive endpoints; it should also track the effects of this pesticide for at least three generations to reveal, characterize and predict further transgenerational harms. Because regulatory and/or use precautions might fail or collapse at certain points, national and international authorities should have some epigenetic tort laws to compensate those who do not benefit directly from the use of pesticides; to the contrary they pay external costs for the epigenetic harm imposed on them, their descendants, their property and their environment by these pesticides.

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