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Risk Management of Genetically Modified Organism Product: Experience from Indonesia, Malaysia, and Thailand

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ABSTRACT

Genetically modified organisms (GMOs) have become a subject of significant debate and monitoring due to their potential implications for human health, environmental impact, and socioeconomic considerations. As a result, risk management strategies and regulatory frameworks have been developed to assess and mitigate the potential risks associated with GMOs. This review focuses on examining the current landscape of risk management approaches and regulations pertaining to GMOs. The review analyzes the key components of risk management, including risk assessment, risk communication and bioethics. It explores the role of regulatory authorities in establishing guidelines for the evaluation and approval of GMOs, ensuring their safety for human consumption and minimizing potential environmental risks. The study also investigates the involvement of international organizations in harmonizing regulations and facilitating global trade of GMO products.

Keywords: bioethics, biotechnology, Genetically Modified Organisms, regulation, risk management

INTRODUCTION

Agriculture is one of main sectors that has a big impact on public welfare in a country, because large food production is a key to reach food security. Nevertheless, there are several issues that prevent food production from remaining stable and one of them is pest infestation. Based on previous study, global economic losses caused by pest infestations can reach up to 220 billion dollars every year (PPID IPB, 2022). This enormous amount could be increased if there is no solution in the near future.

The field of biotechnology has generated a solution to inhibit an increase in economic losses caused by pest infestation. By genetic engineering, crops can build up their own defense against pests (Talakayala *et al.,* 2020). It can also inhibit the production of some compounds such as ethylene (Schaller, 2017). Ethylene is a naturally occurring plant hormone that regulates various physiological processes in plants, including fruit ripening, leaf aging, and abscission (the shedding of leaves, flowers, or fruits) (Liu *et al.,* 2015). Ethylene produced in gaseous form can accelerate the ripening of fruits or vegetables. Therefore, by inhibiting its production, it can extend product shelf life after being harvested (Schaller, 2017).

Products circulating in the United States are generally found in two types, namely *Bt* crops and HT crops. *Bt* crops are crops that have been genetically modified by adding genes through the bacterium *Bacillus thuringiensis* (*Bt*) which produces insecticidal proteins. This protein is toxic to some insects (specifically), such as corn borers, cotton bollworms, and tobacco budworms (Abbas, 2018). *Bt* crops can help farmers reduce the use of chemical insecticides which can harm the environment and human health. Meanwhile, HT crops are crops that are genetically engineered to be tolerant to certain herbicides. This makes it easy for farmers to kill all kinds of weeds without having to worry about damaging the crop (USDA, 2022).

With various advantages that was mentioned above, land development for planting GMO crops has increased to 194.4 million ha since 1996 which was only 1.7 million ha (ISAAA, 2019). In addition, in recent years, various developing countries have planted more GMO crops than industrialized countries with a total planting area of 56% of the global total with the commodities planted as follows (Fig. 1) (ISAAA, 2019).

To further demonstrate the growing significance of GMOs, the adoption of GMOs in the United States shows an increase since 1996 (Fig. 2) (USDA, 2022).

The increase in adoption is closely related to the superiority of GMO products compared to conventional products. Although genetic engineering seems to be a bright solution for agriculture problem, in its application, this method reaps controversy from the public. GMO, as the product of biotechnology, has generally been unwelcome (Arcieri, 2016). This is because people still doubt the safety of these products for human health and the environment.

Therefore, assessments and regulations are required for GMO products before they are released to the market. The assessment and regulation that applied must be able to assess product safety both in terms of health and the environment. This can prevent any adverse effects that come after being consumed and prevent negative impacts on the ecosystem. It can also be an effective way of gaining the trust of the public.

Genetically Modified Organism

Genetically Modified Organism (GMO) is an organism whose genetic properties have been altered for various purposes. In short, GMO is a genetic engineering product. GMO can be derived from microorganisms, animals or plants. One of the method to making them is by using recombinant DNA technology to enable specific functions, such as enhanced productivity or disease & pest resistance.

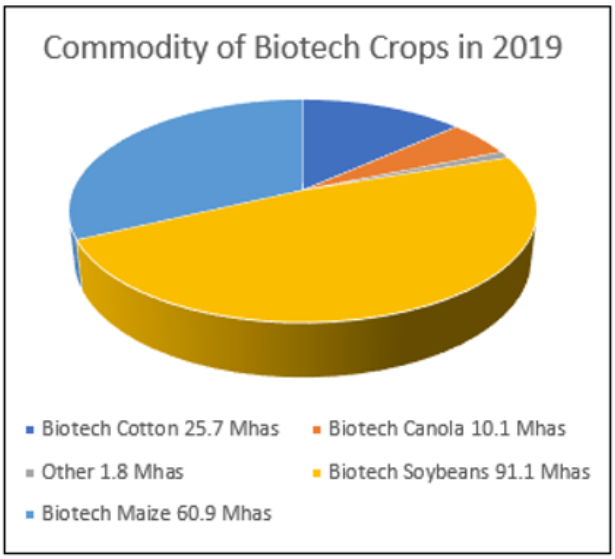

Figure 1 Commodity of Biotech Crops in 2019
Source: ISAAA, (2019)

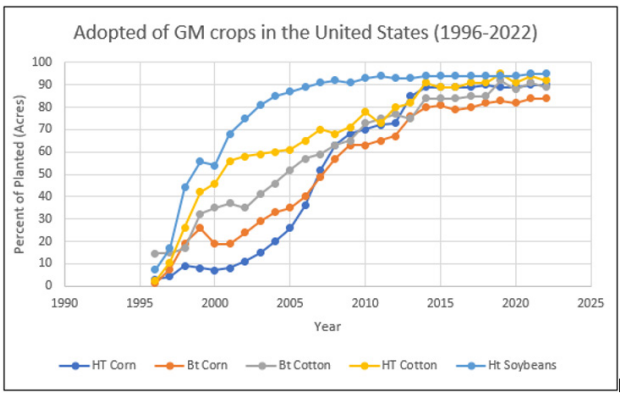

Figure 2 Adoption of GM crops HT (herbicide-tolerant) and *Bt* (*Bacillus thuringiensis*) in the United States
Source: USDA, (2022)

GMO transgenic is produced from a combination of a host, vector and genetic material. The process itself involves insertion of DNA Recombinant to the host. Recombinant DNA usually consists of genes of interest, terminator, promoter and marker genes. All these parts are introduced into plants usually by two methods: biolistic transformation and agrobacterium tumefaciens-mediated transformation (Chaurasia *et al.,* 2020).

Biolistic transformation allows for direct introduction of DNA or RNA into cells. In a brief explanation, DNA or RNA construct is coated onto gold or tungsten particles. The gene gun then releases the particles with high-pressure helium gas and directly penetrate the cell wall (Batles *et al.,* 2017). The second method, Agrobacterium tumefaciens-mediated transformation involves the help of bacteria to deliver genes of interest into a host plant. After entering the plant nucleus, rDNA is capable of integrating into the genome system and inherit desired traits in the next breeding (Hwang *et al.,* 2017). Besides that, there are also various other methods of making GMOs.

In addition, GMOs can also be made using genome editing techniques. In its definition, genome editing is a method or technology that allows scientists to change the structure of a DNA. This technology allows adding, removing, or changing a genome in a specific location. One of the well-known technologies for genome editing is CRISPR-Cas9 technology. CRISPR-Cas9 itself is a bacterial defensive mechanism against various viral infections. This protective mechanism generally consists of the Cas9 protein as a DNA cutter and Guide RNA as a guide for the location of the cut. CRISPR-Cas9 works by cutting off a part of a sequence from a genome (in this case the sequence derived from a virus) and inactivating it so that viral particles cannot be produced. CRISPR-Cas9 was then developed into a genome editing method by changing the guide RNA from Cas9 so that it attaches to the desired sequence. The CRISPR-Cas9 method has a good level of accuracy, effective and relatively affordable. By doing this genome editing, the GMO produced can have various desired traits such as lowering ethylene production (in fruits) to inhibit fruit ripening, eliminating hereditary defects or diseases in plants, animals or humans, increasing product resistance from pest and disease, and many more (Medline Plus, 2022).

Potential Risk of GMO

When GMO insulin was first introduced as the first GMO product in the medical field in 1982, people saw genetic engineering as an accelerator in the advancement of medical technology (FDA, 2023). It is because genetic engineering method is seen

as a new solution that can solve various diseases that have been a common cause of patient death, such as cancer, tumors, etc. (Teferra, 2021). However, when GM foods were first introduced in 1990s, people began to debate about the safety and ethics of the manufacture and consumption of these products. The use of GMOs in daily products is still a hot debate to this day (FDA, 2023).

In the manufacture of GMO products themselves, there are various risks that can cause harm. These risks are generally classified into 4 categories, which is human & animal health, socioeconomic and environment. In human and animal health, the GMOs that are produced have the potential to be toxic and can cause allergies. Some plants deliberately inserted a gene that can produce toxic compounds. It is intended so GMO plants can produce their own defense system against pests. Therefore, it is necessary to determine how much toxic compound is produced by a GMO so that it does not cause any adverse effect on humans or animals that will consume it. In addition, the insertion of a new gene in an individual can create a new protein which is one of the causes of allergic effects. Some allergic effects can cause severe symptoms or even end in death. Therefore, there is a need for testing that can capture the allergic effects of GMOs in a potentially allergic subset of the human population (EFSA, 2011).

In the environment, poisons that are deliberately formed through genetic engineering in crops can also cause death to useful non-target organisms, such as butterflies or bees. This can disrupt the ecosystem balance of the natural surroundings and reduce natural biodiversity. In addition, there is also the possibility of unintentional breeding between GM crops and domestic crops in the nature. This breeding can transfer transgenes that exist in GM crops to wild plant, resulting genetic contamination in nature which can cause various disasters such as the growth of super weed plants (herbicide tolerant weed). In addition, plants that are tolerant to pests will trigger the creation of super pests, or pests that are tolerant to pesticides (ISAAA, 2018).

From a socioeconomic perspective, the sale of GMO production in the market will lead to dependence of farmers on companies that create GMO seeds while controlling prices and seed supply. This happens because GMOs are not something that is easily made in general by various groups. The price gap between conventional seeds and GMO seeds can create inequality among farmers as poorer smallholders will be left behind by their competitors. In addition, there is a possibility that the introduction of GMOs will result in economic losses. This possibility arises from the consideration of consumer perceptions as a determining factor for the success of GMO products in the market. If consumer perceptions of GMO products are poor, there will not be many consumers who want to buy GMO products. As a result, the income earned is not enough to cover the production costs of the product and results in economic losses (LaHorgue, 2019).

Benefits of GMO

Apart from the various risks that exist, GMO products also come with various advantages and opportunities. By carrying out proper risk management, GMOs that pass the assessment can become goods that are superior to conventional products. In United States, several GMO products have been on the market for a long time, such as maize, soybean, cotton, potatoes, etc. (FDA, 2022). All of these products have passed various assessments in accordance with the established standards. This makes GMO products have the same quality, nutrition and safety as conventional products (Bawa & Anilakumar, 2013). Some GMOs are even made to increase the nutritional value of the product (FDA, 2022). Although there are no studies yet that say clearly that GMOs can have a negative effect on body health. Recent studies have shown that consuming GMO products can increase the number of tumors in mice. Even so, the study was later retracted due to unreliable data (Hefferon, 2015).

It is known that number of farmers in India who have committed suicide are around 15,000 with a peak in 2004, the year *Bt* cotton was first commercialized in India. In 2007, there was a significant reduction in farmer suicides by up to 25%. This data proves that the introduction of *Bt* cotton to India has solved many problems in agriculture while promoting the mental health of farmers (Smyth, 2020).

Genetically modified organisms (GMOs) have been instrumental in addressing specific issues, such as reducing pest and disease infestations on plants. GMO crops have commonly been developed with three prevalent traits: resistance to pest infestations, tolerance to herbicides, and resistance to harmful microorganisms (FDA, 2023). These traits significantly affect the development of a farmer's farm, starting from reducing costs for using pesticides and using herbicides which are much easier because there is no need to worry about damaging crops. The use of herbicides is also not necessary after carrying out soil tilling which can maintain the health of the soil and the worker's energy.

Some GMOs are also specifically designed to increase profits for consumers. For instances, production of GMO soybeans that can improve the health of oil and apples which do not experience a browning reaction when cut. The development of GMOs can also reduce the possibility of food loss can also increase people's access to food and make prices affordable.

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GMO Classification

In general, according to Health and Safety Department University of Edinburg (2022), GMO can be classified as Class 1 to Class 4 based on the risk the GMO poses to human health and environment (Table 1).

This classification plays a crucial role in determining the strategies for containing the product in question, taking into account several key criteria. Firstly, the evaluation considers the product's ability to cause harm or damage. This includes assessing the potential risks associated with its usage or exposure. Secondly, the severity of the harm or damage that could result from the product is taken into consideration. This helps in understanding the magnitude of the potential consequences. Additionally, the assessment includes an examination of the risk of spreading harm or damage to the population, gauging the likelihood of transmission or adverse effects on individuals. Furthermore, the potential harm to the environment or the possibility of economic loss is evaluated, considering the broader impacts beyond human health. Lastly, the availability of vaccines and effective treatments is factored in, as this can influence containment strategies and mitigation efforts. By considering these diverse criteria, an appropriate containment approach can be developed based on the specific characteristics and risks associated with the product.

In determining the risk level of a GMO product, several assessment considerations are needed which include risks to human health and their impact on the environment. In class determination, it is generally carried out to evaluate the high potential for a disaster from GMOs and the magnitude of the consequences. This relationship can be represented in the following formula.

$$Risk = Likelihood\ X\ Consequences$$

The results of the calculations can produce risks that are effectively zero, low, medium/low, medium, or high (Health and Safety Department University of Edinburgh, 2020). The results of the calculations are then adjusted to the level of risk in the following matrix (Table 2).

Table 1 GMO Classification

Class	Containment	Description
1	Level 1	Unlikely to give adverse effects to human or environment.
2	Level 2	May cause human disease or danger to employees, but it is not possible to spread to the community. This class is also not possible to cause significant environmental damage.
3	Level 3	May cause severe human disease and has serious threat to employees. This class is also possible to spread to the community but there is usually effective prophylaxis or treatment available. This class is possible to cause significant environmental damage or economic loss.
4	Level 4	May cause severe human disease and has serious threat to employees. This class can also spread to the community with no effective prophylaxis or treatment available. This class is possible to cause significant environmental damage or economic loss

Table 2 Risk Assessment Matrix

Consequences of Hazard	Likelihood of Hazard			
	High	Medium	Low	Negligible
Severe	High	High	Medium	Effectively Zero
Modest	High	Mediun	Medium/Low	Effectively Zero
Minor	Medium/Low	Low	Low	Effectively Zero
Negligible	Effectively Zero	Effectively Zero	Effectively Zero	Effectively Zero

GMO Risk Assessment

GMO Risk assessment is an effort to assess the risks posed by GMO products. Conducting a risk assessment is required for any commercial activity involving the use of GMOs. Risk assessment is commonly used in assessing potential risks to humans, animals, plants, or other aspects related to the environment. The assessment must be carried out by a person who is competent in his field. The work itself is categorized into several sections such as assessments on hosts, vectors, genetic materials, GMOs, types of activities, containment levels, classes, and others. The purpose of conducting this assessment is none other than to minimize adverse effects that may arise due to GMO products. This assessment also aims to select a suitable, sufficient and proportionate control method (Health and Safety Department of the University of Edinburgh, 2022).

In its method, the GMO assessment must be able to cover various important points such as composition, nutrition and comparison with conventional products, toxicity, allergenicity, molecular characteristics (such as stability of the inserted gene), potential of harming important microorganism, effect on non-target organisms, unintended effect on target organisms (such as resistance development), effects on biogeochemical processes (such as in the nitrogen cycle) (EFSA, 2019).

Points that have been mentioned above are useful in assessing the quality of the risk assessment itself. In carrying out a risk assessment, the initial step that is usually taken is to understand the overall molecular characteristics of the GM plant. Followed by an analytical comparison of the differences between the GM plant and the original. In more detail, understanding these molecular characteristics involves a comparative analysis of composition, phenotypic, and agronymic. This comparison is made to ensure that the molecular characteristics of the GM plant do not fall far beyond the range of natural variation. The results of this comparative analysis then build a risk assessment procedure for a GMO product (EFSA, 2011).

Some GMOs were created to produce toxins independently to create mechanisms of protection from pests. However, these toxic compound can potentially be produced in excessive amounts. Therefore, a toxicological study is needed to ensure that the toxic content produced is correct (Giraldo *et al.*, 2019). Toxicological studies of GMO should be performed with method described by Organisation for Economic Co-operation and Development (OECD) and in accordance with the quality assurance principles laid

by Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances. Some guidelines that can be used in testing the toxicity of chemical compounds in GMO risk assessment are as follows (Table 3) (EFSA, 2011).

Any adaptation of the protocol or use of any method different from the main protocol must be clearly explained and justified. In addition, GMO product toxicity testing must be carried out in a facility that can perform well. It's required to ensure that the test results that appear are high quality data. Toxicity potential is not only tested on GMO products, but also on the expression of new genes in them. The outcome of the toxicity test should indicate the availability of information regarding the adverse effects of expression of new proteins and other novel constituents created by genetic modification in particular along with specific dose levels.

Allergenicity assessment also must be conducted to see if there is any adverse reaction from consuming GMO food. This is because food allergy is a public health problem that is common and very important. Unlike, toxic reactions, allergies are deviations from the body's immune response to a compound which causes the individual to experience serious symptoms or even death. One type of allergy that has severe reactions and can create life-threatening conditions is IgE-mediated food allergy. Therefore, it is necessary to conduct specific studies that focus on the emergence of this allergic reaction due to consuming GMO products. Usually, the types of chemical components that often cause food allergies are proteins. Compounds resulting from protein breakdown can create allergic reactions, including new protein breakdown products (Herman *et al.,* 2022; EFSA, 2011).

Allergenicity is a symptom commonly experienced by a portion of the human population. The causes of allergies can vary from genetic, geographic or environmental factors. Therefore, in testing, it is necessary to interact between food and several individuals who have an allergic background. In addition, it is also necessary to ensure that the source of the transgene given to GMO products is not an allergen. If the new gene in a GMO plant is proven allergenic, testers should test for potential changes in allergenicity in all foods derived from that GM crop. This is recommended because there is a possibility that genetic modifications may induce unintended effects.

Nutritional assessment needs to be done in producing GMO products. This test is useful for demonstrating that there are no nutritional disadvantages in GMO products compared to conventional products. These tests include the effect of the presence of new protein expression on changes in nutritional value, changes in the levels of endogenous constituents in GM plants and their product derivatives, and potential changes in the total diet for consumers. If testing of the nutritional content of GMO products is not in accordance with conventional products, further assessment is required (EFSA, 2011).

Table 3 OECD guidelines for testing of chemicals

OECD Number	Title
402	Acute Dermal Toxicity
406	Skin Sensitisation
407	Repeated Dose 28-day Oral Toxicity Study in Rodents
408	Repeated Dose 90-Day Oral Toxicity Study in Rodents
410	Repeated Dose Dermal Toxicity: 21/28-Day
415	One-Generation Reproduction Toxicity
416	Two-Generation Reproduction Toxicity Study
417	Toxicokinetics
421	Reproduction/Developmental Toxicity Screening Test
471	Bacterial reverse mutation test
473	In-vitro mammalian chromosome aberration test
474	Mammalian erythrocyte micronucleus test
475	Mammalian bone marrow chromosome aberration test
476	In-vitro mammalian cell gene mutation test
479	In-vitro sister chromatid exchange (SCE) assay in mammalian cells
482	DNA damage and repair, unscheduled DNA synthesis in mammalian cells in vitro
487	Draft guideline on: In-vitro mammalian cell micronucleus test


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Risk Assessment Procedure

Risk assessments need to be conducted with adequate procedure. The procedure itself consists of hazard identification, dose-response assessment, exposure characterization, and risk conclusion. In the first step, it is necessary to identify the various types of risks or hazards that may occur due to GMO products. Afterwards, dose-response study needs to be conducted to determine the critical level above which the risk that has been found becomes a threat. Based on previous studies, the next step is to identify the different routes through which the hazard can pose a threat. The last step is to understand perceived risk and recommend necessary action (Carzoli *et al.,* 2018).

As an example, *Bt* maize is one of the GMO products that has been declared safe. This product has gone through all the assessments that have been mentioned above. One of the major concerns about the release of *Bt* maize is how it will affect consumer's health, whether it is human or animal. A series of assessments carried out to check if Cry protein (toxic compounds that produce in *Bt* maize) can give an adverse effect to the consumer (Carzoli *et al.,* 2018).

Step 1: Hazard identification

Hazard identification begins with looking for evidence or signs of poisoning that occurred after the product was consumed. This identification is usually done using animals as models that represent the human body. Based on this test, no signs of poisoning were found after consuming *Bt* Maize.

Step 2: Dose-response assessment

The resulting data of this assessment is quantitative and is usually assessed before negative effects due to poison occur. This value is commonly called the No Observed Adverse Effect Level (NOAEL) which is expressed in units of milligrams of the compound per kilogram of body weight per day (mg/kg/day). The formula commonly used in determining NOAEL is as follows:

$$Exposure\ Dose\ (ED) = \sum \frac{Residu\ Concentration\ x\ Food\ Comsumtion}{Body\ Weight}$$

To estimate the risk to humans, toxicological results to animals must be multiplied 10-fold into the NOAEL value as a form of avoiding uncertainty from potential differences due to species and sensitivities of some sub-populations. Based on NOAEL values obtained from toxicological animal models, the potential risk can be calculated in the human population consuming products containing *Bt* Cry protein.

Step 3: Exposure characterization

Exposure characterization. In animal studies conducted on various models, no toxicity was observed from any class of Cry proteins, even at the highest dose used in acute oral feeding experiments. The US Environmental Protection Agency acknowledges oral toxicity studies involving animals, which included doses exceeding 5000 mg of Cry protein per kilogram of body weight. By considering 5000 mg of Cry protein per kilogram of body weight as a hypothetical No-Observed-Adverse-Effect Level (NOAEL) and applying a 1000-fold uncertainty factor to account for variations among species and sensitive populations, the reference dose for humans is calculated to be 5 mg of Cry protein per kilogram of body weight. Assuming a Cry protein concentration of one part per million in maize grains and an average human body weight of 70 kg, it would require consuming 350 kg of maize per day to reach the dosage of 5 mg of Cry protein per kilogram of body weight. Considering the unlikelihood of consuming such a large quantity of *Bt* maize, the hazard identification studies suggest that the exposure to Cry proteins from the consumption of *Bt* maize by humans or animals does not pose a risk. Furthermore, research on other known toxic proteins indicates that they are usually harmful at low doses. Therefore, increasing the amount of potential Cry protein consumed is unlikely to result in any adverse effects not previously observed in the described studies.

Step 4: Risk conclusion

Risk conclusion. Based on the previous studies, it was found that the consumption of Cry proteins didn't have any adverse effects, leading to the conclusion that chronic studies were unnecessary. The proteins are digested in the stomach, which makes acute exposure the primary concern. Furthermore, *Bacillus thuringiensis* (*Bt*) has been used as an insecticide for many years without any reported negative effects on human health. This collective evidence supports the notion that there is no significant risk associated with the consumption of Cry proteins from *Bt* crops for humans or animals.

Risk Communication of GMO

According to (WHO 2017), risk communication is a real-time exchange of information, advice or opinions between an expert and an individual or community who is faced with danger whether in health, economy or social. The purpose of implementing risk communication is to enable effective distribution of information to someone who has the potential to have a risk or hazard in order to make the right decisions to reduce the effects of the threat. Risk communication has proven to be an important tool that can be used in an emergency situation. In the field of biotechnology, risk communication is the main key in controlling risk assessment and management of the development, importation, and use of GM crops. In the assessment process, risk communication plays a role in ensuring the scope and limits of GMO risk are clearly defined.

Risk communication also includes explaining to stakeholders how the regulatory system works, how regulatory decisions are made and the meaning of each decision. In distributing information, there is a risk of perception that can disrupt the flow of information. For example, many people will be confused when it is explained that one of the risks of using a GM crop is that it will turn into a new invasive species. This kind of misunderstanding can lead to the decisions taken by the recipients of the information will be less effective or even wrong. Therefore, various ways are needed to increase the effectiveness of risk communication.

Based on the article that was published by (ICGEB 2018), the first step to make an adequate risk management is developing a risk communication strategy. Risk communication can begin by explaining how the regulatory program works, what obligations the applicant has for the government, how data will be collected and how decisions can be made. Regulators must publish all regulations, policy statements, and guidance documents to support the administration of regulatory programs. Furthermore, regulators can plan risk communication campaigns based on the most likely regulatory scenario so that risk communication can be implemented efficiently.

The next step is to identify the stakeholder. Stakeholder can be divided into various sub-populations and have different interests. Some stakeholders sometimes have a narrow focus. For example, some stakeholder only care about the impact of implementing GM crops regulations on trade. There are also some stakeholders who have a broad interest but don't understand the technology behind the development of biotechnology. Therefore, regulators must be able to devise a risk communication plan that can cover various classes of audiences and develop appropriate messages for each stakeholder group.

After the message for each audience is well made, the regulator must be able to determine an effective way to spread the message. Dissemination of the message must be done in a creative way to increase its effectiveness. Several ways can be done with the help of information technology such as the internet which includes the dissemination of messages through social media, websites, etc. By carrying out these steps, it is hoped that the message created can be conveyed effectively.

GMO Analytic Standardization Based on ISO

International Organization for Standardization (ISO) has standardized several analytical methods for detecting GMOs and their derivative products. The standard is regulated in standard number ISO 6498:2012, ISO 21569 concerning Qualitative nucleic acid-based methods, ISO 21570 concerning Quantitative Nucleic acid-based methods, ISO 21571 regarding Nucleic acid extraction, and ISO 21572 concerning protein based methods. Specifically, information regarding protein detection methods can be seen in standardization ISO number 21572.

As an example, there is standardization in screening for GMO in cotton and textiles which is regulated in standard number ISO/IWA 32:2019. In general, this standard was created to provide laboratory guidance worldwide in assessing cotton, cotton fiber, genetically modified cotton plants, etc. in a standardized manner. This document is intended for non-GM and textiles production lines but can be applied to any production line that wants to check the presence of GM cotton.

ASEAN Guidelines Regarding GMO

Based on the results of the 44th AMAF meeting conducted by (ASEAN, 2022), regulated guidelines were obtained for conducting proficiency testing (PT), analysis, validation, & verification on genetically modified organisms (GMO). As one of procedure that has been regulated by ASEAN, PT is used as a tool or method in demonstrating the competence and capability of a laboratory in carrying out specific test analysis. PT is also commonly used in validating and demonstrating laboratory measurement processes by comparing test results from one laboratory to another. In other words, PT is an essential element in knowing laboratory quality. The guidelines and regulations provided by ASEAN are based on the criteria stated in ISO/IEC 17043:2010.

In the ASEAN guidelines, proficiency testing for GMOs requires several technical requirements which include personnel, facilities, environment and equipment, methods of analysis, reporting of results and documentation. At the personnel stage, there are the following requirements:

1. Laboratories shall appoint one of their permanent employees.
2. The designated personnel must be qualified and competent in carrying out the process of proficiency test samples.
3. Laboratory management must include a plan in handling PT scheme and communicate it to personnel about their responsibilities and roles in PT sample.
4. Personnel must have good knowledge and skills related to the PT sample.
5. Laboratory management can delegate authority to appointed personnel to choose a good PT scheme.
6. The appointed personnel must be able to plan and carry out a good sample test using the right test methods and instruments.
7. Appointed personnel must have the capability to express opinions and interpret results.

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8. The designated personnel must be able to evaluate the results obtained and be able to perform statistical analysis on the data that has been obtained.

In terms of facilities, environment, and equipment are as follows:

1. Participants must be able to ensure that the laboratory used is adequate in handling and analyzing GMO PT samples.
2. Participants can ensure that the laboratory environment such as temperature, humidity, and cleanliness of the work area does not adversely affect the PT sample analysis process.
3. Participants can ensure segregation of the work area to minimize cross contamination.
4. PT samples must be stored separately from various materials and reagents to prevent cross contamination.
5. Analysis of the sample pt should be carried out in the correct order and workflow in order to ensure the accuracy of the test.
6. Access and use of the work area must be monitored and strictly regulated regarding staff allowed access to minimize sources of contamination in the PT sample during analysis
7. PT samples must be able to be analyzed separately from other samples to prevent cross-contamination.
8. Participants must be able to ensure that the reagents used are not expired, the equipment used has been properly maintained, and calibration is carried out on a scheduled basis.

In the analysis of methods and procedures, there are the following requirements:

1. The participant must use a chosen test method, calibration or measurement procedure, which must be consistent with the routine procedure.
2. Participants must be able to ensure that the results obtained after the PT sample analysis are valid and reliable.

In reporting the results, the results from the PT must be able to be submitted to the PT provider within the allotted time based on the format or instructions that have been given. Results can be a copy of the number or weight-for-weight (% w/w) percentage or as a statement e.g. “Detected” or “Not Detected” depending on the format provided by the PT provider. After submitting the results, the PT provider will evaluate the final results of the report to all participants. The performance of the participants in the PT must be able to be evaluated as “Satisfactory” or “Not Satisfactory” depending on the evaluation results of the PT. Participants should be able to review the final evaluation report and ask for suggestions for better results.

After that, documentation was carried out on the basis of the results of the PT sample analysis which had been well recorded. This includes associated worksheets, operators, instrument print out of results, final evaluation reports from pt providers and various related documents such as test methods, work instructions, and laboratory standard operating procedures (SOPs).

GMO Regulations in Indonesia

In Indonesia, the supervision and control of genetically engineered agricultural crop varieties is regulated by the Indonesia Ministry of Agriculture in regulation No. 50 Year 2020. This regulation stands on the basis of considering that genetically engineered plant products

apart from having advantages, also have risks to human health, animals, and environment. To minimize this risk, it is necessary to have supervision and control. Under supervision, GMO plants are carried out through routine monitoring and reporting of cases by permit owners. This monitoring was carried out in the third year since agricultural GMO crops have been circulating in the territory of the Republic of Indonesia. Monitoring is carried out for 3 consecutive years to determine the impact on livestock health and the environment.

Routine monitoring is carried out through farmer questionnaire surveys, analysis of scientific papers and analysis of agricultural environmental data. The survey was carried out by an independent survey institution or university using a questionnaire according to Format-1 as listed in the attachment which is an integral part of Ministerial Regulation No. 50 Year 2020. The survey was carried out using the multi-stage cluster sampling method with a sample taken of at least:

1. 3 regencies/cities if agricultural GMO crops are grown in one province.
2. 3 regencies/cities in 2 provinces if agricultural GMO crops are grown in two provinces.
3. 3 provinces if agricultural GMO crops are grown in 3 or more provinces.

Meanwhile, the scientific work that has previously been alluded to is explaining the impact of agricultural GMO crops on the health of livestock and the environment. Impacts can be in the form of negative impacts and/or positive impacts on the circulation of agricultural GMO plants on the health of livestock and the environment.

Analysis of agricultural environmental data in the planting area is carried out by an independent survey agency funded by the permit owner. Environmental data were obtained from supervisors from various supervisory networks including plant pest and disease inspectors, veterinary medicine, seed inspectors, pesticide supervisors, livestock feed supervisors, and irrigation water quality supervisors.

The implementation of routine monitoring is submitted to the Minister in writing through the head of the agency in the form of a routine monitoring report. The report is conducted once in 12 months by attaching an analysis of farmer questionnaires, scientific papers on the impact of agricultural GMO crops on the health of livestock and the environment, and analysis of data in the area of planting agricultural GMO crops.

Monitoring reports are submitted in Format-2 as listed in the Ministry of Agriculture Regulation No 50 Year 2020. Report inspection is carried out within a maximum period of 14 days from receipt by the Head of the Agency. If the inspection results are declared incomplete, the routine monitoring report is returned to the permit owner by the head of the agency.


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The assessment is carried out by the head of the agency who is assisted by the agricultural GMO plant supervisory team before being reported to the Minister with the consideration that the agricultural GMO plants in circulation do not have a detrimental impact on the health of livestock and the environment or vice versa.

Case reports are submitted within a maximum period of 10 days after the negative impact is known. Case reports are prepared in Format-3 as stated in the Ministry of Agriculture Regulation No 50 Year 2020. The report review will be carried out by the Head of the Agency and the Agricultural GMO Plant Supervision Team.

Apart from that, there are various other rules related to GMO requirements before being released to the market. These requirements are regulated in the Regulation of the Government of the Republic of Indonesia Number 21 Year 2005 concerning the biosafety of genetic products. The requirements listed include, description and purpose of use, detected genetic changes and phenotypes, clear identity regarding GMO taxonomy, physiology and reproduction, organisms used as gene sources, engineering methods used and procedures,

molecular characteristics of GMOs, gene expression transformed into GMO, method of extermination in case of irregularities.

GMO Regulations in Thailand

The Minister of Public Health of Thailand regulates the circulation of GMO products through notification (No. 431) B.E. 2565 (2022) regarding the regulation of foods containing genetically modified organisms (GMOs). The notification stipulates that control measures are necessary to protect the health of consumers. This supervision includes the requirement that GMOs that are produced, imported or sold must pass a biological food safety assessment which will then be reviewed by the Food and Drug Administration of Thailand.

The notification prohibits all manufacture, import, or trading of GMO products except under 2 specific conditions. The two conditions are that GMOs have been approved by the Thai FDA or have passed the required assessment. GMOs that have been legalized will be included in Annex 1 (positive list). Annex 6 (temporary approval list) lists GMO products that have not been approved, but can still be produced, imported and sold while the assessment is still being carried out. This temporary permit is valid for 5 years but can also be revoked at any time if the product fails to be assessed. Developers must submit documents or evidence specified in Annex II for GM Plants, Annex III for GM Microorganisms or Annex IV for GM animals to the National Center for Genetic Engineering and Biotechnology (USDA, 2023).

In its assessment, GMO products must meet the following criteria:

1. Does not pose a health risk compared to conventional methods.
2. The GMO product has the same nutritional value and required properties as conventional product.
3. Meet the food quality and standards set by the Ministry of Public Health Thailand
4. Meet various applicable qualities and other standards required in the assessment results and some supporting documents or evidence.

Packaged products containing GM ingredients greater than or equal to 5% by weight with detectable GMOs and recombinant protein resulting from biotechnology must have a label indicating that the product contains GMOs. The same applies to products that contain less than 5% GMOs of plant or animal origin. This labeling is regulated by the Minister of Public Health Thailand through notification No. 432 Re: Labeling of GM Foods. If the importer is unable to provide specific information regarding the raw materials in the product (USDA, 2022).

GMO Regulations in Malaysia

Regulations in the distribution and assessment of GMO products in Malaysia are regulated by the Ministry of Natural Resource and Environment of Malaysia under the Biosafety Act 2007. Legalization of GMO products in Malaysia requires one of the following conditions:

1. Accepted by the National Biosafety Board
2. Notified by the National Biosafety Board

Approval means that all import activities or processes involving GMO products require a permit from the National Biosafety Board. Licensing can take the form of a certificate of acceptance. Any process involving GMOs may be commercialized only after the certificate has been issued.

Notification means that all participants who export or import goods involving GMOs require a notification from the National Biosafety Board. The NBB will then provide a notification statement letter to the participant who submitted the notification. Any process involving GMOs may be commercialized only after the declaration has been issued.

Trafficking of illegal GMOs will result in violation of the law with a maximum fine of RM 250,000 and/or imprisonment for a maximum of 5 years (individual). Meanwhile, companies will be fined a maximum of RM 500,000.

In the distribution of GMO products in Malaysia, regulations were made based on food regulations regulated in the Malaysian Food Act 1983 which forced every GMO product to have a label. This regulation is useful for informing consumers about GM foods and the substances contained in them. GMO content itself should be at less than 3% of the food composition. Labeling GMO products makes it easier to trace GM products at every stage of marketing, making it easier to control (Sanmugam *et al.,* 2021).

Bioethics Regarding GMO

The rapid development of biotechnology generate various new innovations. As time goes by, more and more "unnatural" entities have appeared in biotechnology. The topic of genetic engineering always triggers an interesting topic of conversation, but it is also a deep concern (Arcieri, 2016). The problem of genetic products is not always related to the safety of its consumption, but it's not uncommon to be involved in religious debates which judge that changing an organism's genetic system is an immoral act that should not be done by humans (CABI, 2001). With all of these controversy, traditional bioethics cannot cover all these areas. Therefore, bioengineering ethics was established to regulate ethics in engineering biological resources.

The regulations previously mentioned were created because of bioethical reforms. This aims to prevent indiscriminate planting of genes that can lead to unwanted results. The inclusion of GMOs into bioethics is nothing but to keep the process of genetic modification of living things in a humane and responsible way.

Existing GMO regulations are useful for ensuring that there are no adverse effects on the health or safety of humans, animals and the environment. On environmental factors, modified genes present in GMOs may be released into the wild causing various ecosystem problems such as species invasion, decreased biodiversity, or the growth of wild plants that have too strong pest resistance. While in human and animal health factors, allergenicity and toxicity produced by modified genes, especially in antibiotic resistance can lead to unintended catasthrophy. Based on these various considerations, GMO products usually take 10 years and cost millions of dollars just to reach consumers (Uzochukwu *et al.,* 2022).

Bioethics does not only cover GMOs, but also one of the methods for making them, like genome editing. Genome editing technology itself has been the subject of debate for more than 50 years. The debate includes the topic of bioethical boundaries and regulatory practices of genome editing. Even though it has been running for a very long time, the results of the debate still have not found a satisfactory result (Mandrioli, 2022).

CONCLUSION

While genetic engineering is developing rapidly in this era, there are various consequences and risks that come with it. GMO products are like a double-edged sword, providing new breakthroughs in solving problems from various sectors such as agriculture, food or medical. However, without proper risk management, regulations and bioethics, these innovations can become a threat to humans, animals and even the environment. Therefore, various international organizations have established standardization and strict assessment procedures for all activities related to GMOs. This standardization is then adopted in every country in the world with various modifications to suit the social and cultural environment in each country.

The risk management that is carried out needs to emphasize the safety of GMO products for the environment, nature, and human and animal health. Various lengthy tests need to be carried out to ensure safety, starting from the level of toxicity produced, allergenicity, to the effects of new traits developed on living creatures in natural ecosystems such as bees or butterflies. It should also be noted that decisions in implementing regulations can also be influenced by various subjective factors such as political interests, the state, miscommunication etc. So we need the right way of communication through the design of risk communication.

It should also be underlined that the development of genetic engineering must be based on humanity principles and global needs which include humans and all parts of nature and not running on the subjective goals of certain groups. Therefore, all GMO-related activities must not go beyond the limits set by bioethics. With these things, the risks and threats from developing GMOs can be minimized and kept under control.

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