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"Glyphosate: effects on the health of users and consumers, and potential consequences with regard to its approval as a pesticidal active substance"

Question 1

What is the substantive basis for the different opinions which exist on the question of whether glyphosate is likely to be carcinogenic? How should these differences be viewed and what course of action will now be taken in this regard? What role does the fact that exposure varies depending on directions for use play in assessing the risks? What routes of exposure which could lead to an increased risk of cancer are relevant for Germany, with the directions for use currently in application?

a) Cancer development is a very complex event which consists of three different steps: *initiation*, *promotion* and *progression* (Pitot, 1993).

* *Initiation* is a step which develops after a mutation or other genotoxicity (*e.g.* chromosomal damage) event which damages genetic material. In theory, *initiation* may occur after exposure of one single molecule. Therefore genotoxic compounds DON`T present safe limits of exposure.

* *Promotion* is a step which involves several different events which leads to cell proliferation of cell mutated during initiation. Chemical agents which are classified as promoters usually follow a linear dose response curve and possess theoretical limits of safety.

* *Progression* is a step where more mutations occur associated to cell proliferation leading to invasiveness and metastasis.

Glyphosate elicits carcinogenicity through different mechanisms and steps. The most serious information is that glyphosate promotes both *initiation* and *promotion*, increasing probability of eliciting cancer diseases.

It is also important to have in mind that a chemical agent may elicit some types of cancer but not others. That is why decision makers should take into consideration all scientific database with limits and a critical view. A merely "quantitative" analysis of scientific literature may lead to “less protective” measures because glyphosate has not been not associated to the causation of several (or all) types of cancer but on the other hand it is strongly associated to the causation of non-Hodgkin lymphoma and other types of cancer.

Epidemiological studies performed with populations exposed to pesticides are scarce due to several reasons, such as ethical aspects, high costs and enough time to elicit long latency diseases such as cancer. Besides that epidemiological studies investigating association of pesticides with diseases, almost always researchers face situations where study populations are exposed to a mixture of pesticides. That is another reason why few epidemiological studies were found manifesting cancer after glyphosate usage exclusively.

Altogether scientific literature regarding both human and animal evidence reinforces that glyphosate may cause cancer to human populations exposed to glyphosate.

Some different opinions may have rised because only studies performed by industry were considered, such as the one performed according to international guidelines which are very limited to predict the broad spectrum of toxic effects that glyphosate may elicit in human populations.

b) Those differences should be viewed under the precautionary principle which should be applied according to european regulation concerning the placing of plant protection products on market (EC 1107/2009 p.2). Besides cancer development, glyphosate elicits other effects such as developmental toxicity, endocrine disruption and immunotoxicity which are cause of concern according to european regulation.

On the other hand, even though different sectors disagree about IARC assessment, taking into consideration precautionary principle, glyphosate ought to be banned from Europe and other countries in order to protect human life (EC 1107/2009) not only because its potential to cause cancer but all his spectrum of toxicity.

c) Agriculture use of glyphosate may expose workers, bystanders and food consumers. The two first groups present higher risk of eliciting both acute and chronic diseases because are exposed (through oral, inalatory and dermal routes) to a higher dose than food consumers. It is important to emphasize that bystanders may include vulnerable population such as pregnants, lactating and children. Food consumers is a populational group exposed to chronic diseases such as reproductive damage, endocrine disruption and cancer. Cancer and endocrine disruption are of especial concern due to its properties of being elicited after very low doses of exposure which may be present in food or water.

It is also important to state that active substances of pesticides are seldom used alone. It is very frequent that in agriculture food producers apply different types of pesticides which may interact and increase damage, or even show effects that were not found when tested alone for licensing process.

Another point of concern is that imported food from countries where glyphosate is used in large amounts especially encouraged by genetic modified organisms resistant to this herbicide, may present higher levels of glyphosate.

All those facts should impact in risk assessments. Acceptable daily intake (ADI) which is defined as the estimate daily amount (mg/kg body weight) of a chemical which can be ingested without appreciable risks to health, present some limitations such as not considering exposure to the mixture of pesticides which may interact and increase risk of adverse effects; and doesn´t consider all sources of exposures of a pesticide especially glyphosate which has a great probability of being found in industrialized food made of corn and soybean which are also the basis of animal food. On the other hand it is important to mention that other sources of exposure such as through inhalation or dermal exposure may impact on toxicity and therefore susceptibility of a chemical carryed on food.

d) All routes of exposure are reason of concern for risk of cancer and the agriculture workers, rural bystanders and food consumers are susceptible groups. Therefore inhalation, dermal and oral routes may be a source of cancer, especially in people which may be exposed simultaneously to these three routes. Taking into consideration the number of people exposed, food consumers and consequently the oral route, should be more relevant to decision makers.

Question 2

How do you view the approval of active substances and plant protection products at European Union (EU) level and at national level? Should the existing legal requirement obliging companies applying for approval to make available and finance the necessary scientific studies be changed? And, if so, who should cover the costs? How many scientific studies on the possible carcinogenicity of glyphosate were assessed and did the studies apply to the active substance or to the plant protection product?

a) Since 2009 when restriction to endocrine disruptors, neurotoxic and immunotoxic agents was adopted, it is expected that less toxic compound, especially those very harmful effects are licensed. It is important that regulators take into consideration all scientific database and not only studies performed or sponsored by industry.

b) Government should sponsor independent studies to be performed by recognized reputation in some fields of knowledge such as mechanisms of carcinogenesis, endocrine disruption, ecotoxicity field and so on. Those studies should be made in order to investigate whether pesticides may be harmful in conditions of use in real life.

c) Scientific literature points that not only glyphosate active substance but also glyphosate-based formulations may cause cancer, endocrine disruption, nephron and developmental toxicity and ecotoxicity which are unacceptable.

Question 3

What alternative plant protection products are available to the agricultural sector to replace glyphosate and what environmental and health impacts would increased use of these products have? What would be the impacts on resistance management

if glyphosate were no longer used? What would be the impacts on conservation tillage of replacing glyphosate?

a) Viable, stable agricultural production systems (resilience capacity), agriculturally productive incorporate all local biodiversity in its reproduction strategy with good agricultural practices. In these systems the plants are never considered "weeds". In these systems chemical interventions are not required, but just some punctual management.
b) In more conventional technological systems mechanical procedures and electrical shock are used to control undesirable plant with very low environmental and health impacts. For transgenic crops highly dependent of glyphosate replacement of this herbicide is already a fact in the medium term because of its technological obsolescence. Nevertheless alternatives based on chemical may have similar or even higher impacts to environmental and human health.
c) Studies also indicate that the best strategy to save the crops and food production consists of providing rotational crop management techniques, biological control and traditional genetic improvement. Adoption of those techniques are less harmful to environmental health.

Question 4

What indications of other health hazards posed by glyphosate are you aware of, apart from the probable carcinogenic effects? Which institutions, particularly at international level, are investigating these indications of possible health hazards and what current international research projects assessing the possible health hazards posed by the active substance are you aware of?

a) Glyphosate is associated to several health disorders such as endocrine disruption, developmental and reproductive toxicity, nephrotoxicity and effects on immune functions. Those effects are found in different animal experimental models (amphibians, fishes, rodents etc) which corroborate to epidemiological findings due to similar mechanisms.

b) Several independent research groups in Europe, Asia, Latin America and North America in last few years published studies enlightening about health and environmental negative impacts of glyphosate.

On the other hand industrial groups have sponsored researches in order to renew glyphosate registration. Those data published disagree negative effects due to exposure to glyphosate declaring their products are safe to both human and wild life.

Question 5

A significant proportion of studies used by the Federal Institute for Risk Assessment (BfR) are financed or initiated by the chemical industry. What is your opinion of such studies and how do you view their findings?

a) Tests performed by industry in order to product licensing are performed according to international guidelines and following Good Laboratory Practice (GLP). Although this paradigm guarantee recording of data, it doesn´t assure that an assay is performed in order to cover all possibilities that a chemical possess to harm human health. In other words, those guidelines describe all steps the companies must follow but may be limited or even unable to detect some effects such as endocrine and immunotoxic effects, especially those elicited at very low doses.

Besides that some categories of toxic effects don´t have enough sensitive or specific methodology covered by USEPA or OECD guidelines.

Therefore independently peer-reviewed replicable non-GLP studies should have the same weight as GLP studies in risk assessments performed by regulatory agencies. As well as regulatory agencies should make his decisions independent of economic biases and interests of industries in order to make decisions that protect public interests, human and wild life.

Question 6

To what extent should the monograph produced by the International Agency for Research on Cancer (IARC) influence the re-authorisation of glyphosate at EU level in your view and to what extent should the precautionary principle be applied regarding authorisation of glyphosate, against the background of studies concluding that glyphosate is “probably carcinogenic”?

a) IARC monograph considered independent studies including those published more recently. IARC classification of glyphosate as “probable carcinogen” should be enough

to ban glyphosate from Europe and other countries. However other studies also justify glyphosate prohibition once show that this herbicide has the potential to cause effects such as endocrine disruption, developmental toxicity and immunotoxicity.

Even if some sectors mainly industrial don`t agree with those conclusions, those different opinions should be viewed under the precautionary principle and lead to the prohibition of glyphosate until companies prove the contrary.

Question 7

What impacts on the health of users, local residents and consumers in your opinion indicate that glyphosate ought not to be used in agriculture?

a) Glyphosate is associated to several health disorders such as endocrine disruption, developmental and reproductive toxicity, nephrotoxicity and effects on immune functions. Those effects are found in different cell culture and animal experimental models (amphibians, fishes, rodents etc) taking altogether those studies not only corroborate each other findings, but also diseases detected in epidemiological studies.

Those findings show that glyphosate may cause harmful effects to human life in doses plausible to current use. Not only workers and local residents (bystanders), but also food and water consumers are susceptible to those toxic effects because some of them are elicited in low doses.

Question 8

In your view, what impacts on the environment and on agriculture of the active substance glyphosate on the one hand and herbicide-resistant genetically modified plants on the other indicate that glyphosate ought not to be used as an active substance in agriculture?

Some statements about transgenic agriculture:

1. It is not democratic: the transgenic agriculture does not allow coexistence with other models of agriculture due to its high capacity of gene dispersion (*e.g.* corn), contaminating conventional production systems, making it unviable the harmonious coexistence with other systems production unviable, such as agroecological and organic.
2. Technological and economic dependence: the vast majority of genetic modified (GM) seeds used in the world is associated with the use of herbicide-conditioning. Therefore

herbicide-resistant GM seeds has no impact on reduction of pesticides or even financial costs resulting in increased technological and economic dependence of farmers to industries and increased governmental subsidies.

3. Environmental damage: formulated products have shown several impacts on wildlife, soil, air and water contamination. Besides transgenic seeds promote gene contamination, reduction of biodiversity, soil contamination, water and air.

Question 9

What consequences would a ban on the use of glyphosatehave on the agricultural sector in the EU and in countries which export agricultural commodities to the EU?

Glyphosate is strongly associated to transgenic seeds commodities, especially soybeans and corn, articulated in a commercial strategy of the chemical industry, creating a selling package formed by seeds and pesticides. Glyphosate sale is not correlated to improved productivity of the agricultural sector. On the contrary, analysis point out that technologies which used glyphosate intensively showed low productivity gains and also the gradual increase in farm production costs due to the increase of the volume demanded explained by increased resistance of plants considered “weeds”. Thus, new glyphosate replacement technologies are already underway in a kind of "commercial ban" with immediate impact of 30% of all planted area of transgenic RR. Thus the ban on glyphosate for agriculture will only have significant impact for some commodities that have not yet migrated to new production systems, but that are already planning such migration in two or three years. So governmental ban can be a technological and commercial opportunity for the sector in short and medium term, through the orderly and adequate monitoring, beneficiating farmers and health of the population.

Question 10

What differences are you aware of regarding the regulations,procedures and criteria applied in assessments by the IARC,Joint Meeting on Pesticide Residues (JMPR), Institute for RiskAssessment (BfR), European Food Safety Authority (EFSA)and, if applicable, the United States EnvironmentalProtection Agency (EPA)? Which regulations may lead to scientific studies not being taken into account and how are the different conclusions reached by these institutions

regarding the carcinogenicity of the active substance glyphosate to be viewed against this background? (If you represent one of the institutions listed above, please indicate this to the *left* of the descriptions of the various regulations, procedures and criteria.)

a) Some of the regulations mentioned were performed years ago, before some of the studies referenced by IARC were published. Some regulations bodies also focus its rosk assessments procedures on studies accomplished following GLP which possess serious limitations to predict toxic effects in real conditions of use, as mentioned before in Question 5.

b) JMPR assessment of glyphosate was performed in 2011, considering new data was generated since then, JMPR is planning a new assessment of glyphosate.

Some regulations may take into consideration only studies performed according to GLP. By not considering peer reviewed non-GLP studies pointed some important findings which may have been originated from detailed investigations which is possible only by independent research groups.

Question 11

How do you assess the current availability of data regarding the exposure of various groups in the population to glyphosate (with particular reference to professional and non-professional users, residents/bystanders/land users,consumers and children/infants)? In particular, how precisely can the level of (acute and background) exposure be assessed in your view and what (if any) recommendations do you have to improve the availability of data on glyphosate?

a) Acute and chronic exposure to glyphosate and other pesticides may be difficult to prove in order to its kinetics, in other words, the short time it is retained in human body. Most of glyphosate is eliminated in urine on the first 24 hours. Unfortunately fast elimination does not mean that glyphosate (or any other chemical substance) are safe, because during its way in the body it damage molecules, cells and tissues and may disrupt signaling cascades and other normal functions which cause serious and irreversible adverse effects.

b) Precision in assessment of exposure is very difficult to achieve, because it would demand mapping market and use, monitor water, soil, vegetable, fruits, grains, industrialized and imported food. Nevertheless this action may be very expensive and very low concentrations may not be measured although it may cause some health effects such as genetic damage and endocrine disruption.

Question 12

What consequences would adoption of the IARC classification as "probably carcinogenic to humans" have on the possible new authorisation of glyphosate as an active substance? (c.f.:http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20150601p. 152 onwards, Annex 1, 3.6: Carcinogenicity)

Classification of glyphosate as probable carcinogen would indicate its prohibition in Europe, at least taking into consideration the precautionary principle.

Besides, other relevant diseases which may be caused after glyphosate exposure, such as endocrine disruption, developmental toxicity and immunotoxicity, would justify its prohibition.