IN FOCUS

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Food safety assessment of the mycotoxin and pesticide residue contamination of our foods, Part 1. Pesticide residues

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1. SUMMARY

In the first part of our paper, the regulation of pesticide residues in foods and feeds is presented, as well as the requirements regarding their analytical examination, and the experiences of current domestic practice are analyzed. Based on the analytical results of NÉBIH between 2014 and 2018, the pesticide residue content of the foodstuffs on the market is analyzed and the exposure of Hungarian consumers is estimated in order to facilitate the rational and regular use of pesticides by means of a scientific evaluation of the situation; recommendations are also made.

Based on extensive studies and international information it can be stated that pesticide residues in our foods, including glyphosate residues, do not pose a food safety or public health risk to consumers.

1.1. Abbreviations used in this paper:

ADI: Acceptable Daily Intake

ALARA: As Low As Reasonably Achievable

AMPA: main metabolite of the active ingredient glyphosate

ARfD: Acute Reference Dose

Bw (tt): Bodyweight [kg];

CAC: Codex Alimentarius Commission

CCPR: Codex Committee on Pesticide Residues

EC: European Commission

EDI: Estimated Daily Intake

EFSA: European Food Safety Authority

ÉLB: FCS – Food Safety Database and Information System (Hungarian system);

EPC: European Parliament and Council

ESTI: Estimated Short Term Intake

EU: European Union

DNA: deoxyribonucleic acid

FAO: Food and Agriculture Organization of the United Nations

GAP: Good Agricultural Practice

GLP: Good Laboratory Practice

HPLC: High Pressure (Performance) Liquid Chromatography

MS/MS: Tandem Mass Spectrometry

IARC: International Agency for Research on Cancer

ISO: International Organization for Standardization

JECFA: FAO/WHO Joint Expert Committee on Food Additives and Contaminants

JMPR: FAO/WHO Joint Meeting on Pesticide Residues

LD_{50}: lethal dose given all at once, which causes the death of 50% (one half) of a group of test animals

LC_{50}: lethal concentration that kills 50% of the test animals during the observation period (used in environmental studies)

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LOAEL: Lowest Observed Adverse Effect Level [ppm in feed expressed also in mg a.i/kgbw per day]

LOQ: Limit of Quantification

MRL: Maximum Residue Limit [mg/kg]

NOAEL No Observed Adverse Level [ppm in feed expressed also in mg a.i/kgbw per day]

NOEL: No Observed Effect Level

OECD: Organisation for Economic Cooperation and Development

P: primary samples

RIVM: National Institute for Public Health and the Environment, the Netherlands

QC: Quality Control

UNEP: United Nation Environment Programme

SFC: European Commission Scientific Committee on Food

STMR: Supervised Trial Median Residue

USA: United States of America

US FDA: US Food and Drug Administration

2. Introduction

The European Food Safety Authority (EFSA) regularly measures the opinion of the population of European Union member states on various food safety risk factors. The 2019 survey **[1]** reported the results broken down into 15 main groups. **Table 1** shows the perception of the four food safety issues the Hungarian public is most interested in, in terms of the percentage of member state populations.

The National Population Roundtable (NKK) has called on relevant organizations and recommended the development of a strategic action plan at the government level to reduce the health and fertility effects of chemicals and toxins of agricultural origin in foods that are consumed daily. The call identified, as major sources of pollution, everyday foods containing mycotoxins and glyphosate residues (cereal based products, beer, soy-containing products, fish, meat and dairy products). The adverse health effects of the above-mentioned substances have been substantiated by reference to several scientific articles.

In our publication, the international and Hungarian regulations on the use of pesticides are summarized. The control system for pesticide residues in foods marketed is presented, as well as the test results. Based on the results, consumer exposure to pesticide residues is analyzed and evaluated and measures are proposed for the rational use of pesticides.

2.1. Regulation of the placing of pesticides on the market and control of their rational use

Intensive large-scale agricultural production today is unthinkable without the use of pesticides, because of the high losses in yield caused by various pests (insects, mites, fungi, weeds, rodents). So-called organic products and foods produced by organic farming can only satisfy the food needs of a fraction of the growing population of Earth. In order to achieve the proper biological effect, it is necessary that the applied pesticides remain on the surface of, or enter the treated crop. As a result, in many cases, the presence of a certain amount of pesticide residue in the harvested crop is inevitable. For a given pesticide, the primary factors affecting the distribution and average concentration of the pesticide residues are the type of crop treated, environmental conditions, the method of application, weather conditions of the growing period and the time elapsed between the treatment and the harvest **[2, 3]**.

A significant proportion of pesticides is a chemical that is hazardous to various living organisms. Their use is therefore preceded by a variety of biological efficacy, as well as human and environmental toxicology tests, and their authorization is subject to strict conditions in order to ensure that pesticide residues do not adversely affect consumer health or the environment **[4, 5, 6, 7]**. In all cases, tests before the authorization are performed at GLP-qualified testing laboratories, using state-of-the-art methods approved by the member states of the European Union and/or recommended by OECD specialized working groups **[8]**. Following the authorization of pesticides, the continuous development of analytical and test methods and the significant increase in their sensitivity lead to new experimental and research results. The results obtained are reviewed at regular intervals at EU and national levels and within the framework of the Codex Alimentarius periodic review program, and the authorization already granted is modified, if necessary, taking into account the risk-benefit ratio.

For decades, Hungary has been at the international forefront of controlling the rational and professional use of pesticides. It should be sufficient to mention the establishment of the county plant protection stations (1954-1955), the launching of postgraduate training in plant protection, the ban on persistent chlorinated hydrocarbons first in the world in 1968, the mercury and arsenic reduction program, and the national pesticide residue analytical network established to ensure proper control (1968-1974) **[9]**. It is worth noting that the Stockholm Convention on Persistent Organic Pollutants on discontinuing the manufacture of persistent pesticides and restricting their use to specific purposes (such as vector control) **[10]** was only adopted by a majority of UN member states in 2002. During this period, the agricultural use of chlorinated hydrocarbons, triazines and certain phenoxyacetic acid derivatives was banned in many countries. In the framework of the ongoing review program in the European Union, the withdrawal or severe restriction of the use of several active substances (e.g., neonicotinoids, organophosphoric esters) was adopted by the member states.

The toxicity of pesticides is most often characterized by the LD_{50}, LC_{50}, NOAEL, LOAEL, ADI and ARfD values **[11]**. The toxicity of pesticide active substances on the market varies widely. For example, the ADI values for active substances evaluated by the JMPR in 2018 varied from 0.001 to 4 mg/kgbw. However, the lowest ARfD was 0.003 mg/kgbw and for many compounds it was not necessary to determine an ARfD value, because they did not show acute toxicity in non-target organisms **[12]**. These toxicological reference values parctically cover all pesticide active substances authorized in the European Union **[13]** and evaluated within the framework of the Codex Alimentarius **[14]**.

Expected pesticide residue levels under the recommended application conditions are estimated by the experts of the national authorization authorities and the JMPR, based on the available biological efficacy studies and experimental results, and the acceptable maximum residue limit (MRL) is determined. The MRL is a legal category, but not a food safety reference value. Use under the proposed crop protection technology is only authorized if the combined concentration of all toxicologically relevant pesticide residues in the harvested produce does not exceed the ADI or ARfD value for average and large portion (97.5 percentile) of the daily consumption. It should be emphasized that, in the case of many pesticides, the composition of the pesticide residues and metabolites to be taken into account when checking the MRL or calculating consumer exposure is different. The value of the latter is obviously always higher, as they contain a larger number of components **[15]**. Up unitl 2018, 311 pesticide active substances had been evaluated by the JMPR **[16]**. The proposal of the scientific body for pesticide residue definition and maximum residue levels is evaluated in several stages by CCPR member countries, and then submitted to the Codex Alimentarius High Commission for adoption **[17]**. The Codex database contains Codex MRL, ADI and ARfD values **[14]**. The pesticide residue limit values currently in force in the European Union **[18]**, including Hungary, and toxicological reference values are available on the Commission's website.

Rational use of pesticides in accordance with regulations is checked by testing a large number of samples worldwide **[19, 20, 21]**. For example, within the framework of the European Union's coordinated monitoring program, which defines the range and number of samples to be tested by member state, more than 84,000 samples were analyzed by the laboratories in 2016 and 2017. 95-98% of the samples contained pesticide residues below the permitted MRLs, and a significant portion of them did not contain any detectable pesticide residue at all **[22, 23]**.

The coordinated monitoring program is complemented by the analysis of roughly another 100,000 samples each year within the national competence of the member states, with similar results. Despite these known facts, approximately 30-50% of the population of European countries considers the potential presence of pesticide residues in foods to be harmful (***Table 1***).

The Codex sampling procedure **[24]** developed for the control of pesticide residues adopted all over the world, including the European Union **[25]**, precisely regulates the the minimum number of primary units and mass of composite sample, in a composite sample, depending on the size and nature of the product sampled. Because there may be up to a 100-fold difference in the pesticide residue content of different fruits and vegetables **[2]**, and the MRL refers to the average pesticide residue concentration of the laboratory sample, correct analytical results can only be obtained if the whole amount of the laboratory sample or, in the case of large products (for example, melon, pumpkin, cabbage), a representative portion is processed, and an appropriate part is extracted. Critical elements and quality assurance of the sampling and the determination process have been discussed in separate publications **[26, 27]**.

2.2. Checking the conformity of produce on the market

Legal maximum residue limits (MRL) refer to the average concentration of the sample taken in accordance with the standard from a lot on the market. If, taking into account the measurement uncertainty, the average concentration measured in the sample does not exceed the MRL, the product may be marketed. However, a valid conclusion regarding the average contamination of a lot cannot be drawn on the basis of a single sample. For example, if the measured pesticide residue or mycotoxin contamination is equal to the legal limit, then large proportion of the sampled lot may contain them at higher concentration due to their heterogeneous distribution and the uncertainty of the analytical measurements. Farkas et al. **[28]** found that if during pre-marketing self-control the pesticide residue content of a composite sample taken in accordance with the standard from medium, small and large products does not exceed 30% and 25% of the MRL, respectively, then, in case of repeated sampling, the marketed product will have a 95% probability of complying with MRL.

2.2.1. Quality assurance of pesticide residue analysis in foods

In Hungary, official control of the pesticide residue concentration of agricultural crops, foodstuffs and feedstuffs on the market is carried out by the national reference laboratory and three regional authority analytical laboratories of the National Food Chain Safety Office (NÉBIH); within the framework of targeted sampling programs, pesticide residues are also investigated in soils and surface waters in certain cases.

The laboratories are accredited according to standard MSZ EN ISO/IEC 17025:2018 (hereinafter ISO 17025), and the laboratory in Szolnok is also certified in the GLP quality system. Requirements for obtaining reliable results and the methods for statistical evaluation of quality assurance results are discussed in a separate paper **[26, 27]**.

The laboratories performing official control are required to participate in European proficiency tests, in which, depending on the sample type, they are required to determine qualitatively and quantitatively approximately 20 of the 90 to 230 predetermined pesticide residues that are actually present in the sample. The organizers evaluate the results using robust statistical methods **[29]**, and determine the expected value (μ) and the characteristic standard deviation of the measurements (σ). The reported concentration (x_i) is used to calculate the standard normal variate of the given component:

$$z_i = \frac{x_{i-\mu_i}}{\sigma} \qquad (1)$$

In the next step, the average Z value is calculated by averaging the squares of the Z values obtained for each component:

$$AZ^2 = \frac{\sum_{i=1}^{n} z^2}{n} \qquad (2)$$

If the AZ value is <2, the result is good, 2≤AZ≤3 is acceptable, while AZ>3 is unacceptable and the laboratory is not awarded an 'A' classification. Based on the evaluation method it is clear that laboratories with a score of Z<1 are „rewarded", while those with a score of Z>2 are „penalized".

All four laboratories of NÉBIH regularly achieve excellent results in the 6 to 8 annual proficiency tests; examples are shown in **Figures 1-3**. The laboratory that achieves the best average result in two consecutive years is awarded the Arné Arnold prize, named after a Swedish analyst who passed away at a young age. The laboratories in Miskolc and Velence have been first of the 110 to 170 participating European laboratories four times on three topics in recent years.

2.2.2. Processing the test results, risk-based planning of sampling

Since 1978, the large number of pesticide residue test results are evaluated by computerized processing. The program has expanded over the years in proportion to the performance increase of computers. The ÉLB program currently used allows us to store, download using given filters and statistically evaluate all information related to sampling and the sampled products, the analytical parameters and performance characteristics.

The risk-based sampling plan for pesticide residue tests is prepared using a three-stage model (**Figure 4**) by a working group of experts from different disciplines. To determine analytical priority, the model uses data from existing authorization dossiers (pesticide residue distribution, ARfD, ADI) for new products, and also previous analytical results of individual pesticide residue-sample combinations for products already used in agricultural practice **[30, 31]**. For this purpose, a separate query format was created (**Table 2**), in the background of which the program automatically calculates the main weighting factors and basic data.

Depending on the calculated factor, the model offers three options for the pesticide residue analysis of the given crop:

1. No pesticide residue test is required;
2. Regular monitoring is required;
3. Targeted sampling and analysis is recommended.

Laboratories determine the total pesticide residues present in a product or food included in the test program by a *multi-residue* method (co-testing of several active substances). The number of samples to be tested is optimized by taking into account the calculated weighting factors and the available laboratory capacity. The number of primary samples taken for testing and their minimum weight of sample are subject to the provisions of FVM decree 66/2010 **[32]**.

The number of random samples required to detect the selected percentile (βp) of pesticide residue values with a certain probability (βt) is calculated from the binomial distribution **[24]**:

$$\beta_t = 1 - \beta_p^n \quad n = \frac{\lg(1-\beta_t)}{\lg\beta_p} \qquad (3)$$

Assuming that the amount of pesticide residues in the marketed lots is ≤MRL in 98% of the cases, then at least 149 lots must be sampled at random in order to find pesticide residues exceeding the limit value in at least one sample with a probability of 95%. The reverse of this statement is also true, that is, if none of the 149 randomly selected batches contains pesticide residues exceeding the limit value, then it can be stated with a probability of 95% that more than 98% of the batches contains less pesticide residue than the limit value.

Ideally, the number of samples to be tested according to the calculated weighting factors (F) is shown in **Table 3**. The sample numbers given in the table are also suitable for estimating the probability of correctness of conclusions drawn from the monitoring results.

The number of samples depends on the available sampling and laboratory capacity and the financial means. If one of the sources is insufficient, then the critical crop-pesticide combination takes prece-

dence, so that the number of samples of other crops is reduced proportionally to the factor.

For targeted analysis, it is advisable to take two independent samples each from ≥8 randomly selected areas with known pesticide treatment. According to the research of Farkas **[33]** et al. **[34]**, analysis of samples taken from more than twenty areas (**Figure 5**) practically does not affect the reliability of the obtained results.

2.2.3. Methods for estimating consumer exposure

The extent to which the population is exposed by toxic substances in foods estimated daily intake (EDI) is determined using a deterministic or probabilistic method. Probabilistic estimations are routinely used only in the USA so far, the European Union is in the process of finalizing this procedure, taking into account the experience of a number of publications published in the meantime **[35]**.

The average daily exposure of consumers is calculated using a deterministic method, i.e., by taking into account the average mass of each foodstuff consumed on a given day (F_i g/kgbw) and the median pesticide residue values measured in the composite samples (M_{ex} mg/kg). The calculation takes into account the supervised trial median residue (STMR) value obtained from the pre-authorization pesticide experiments **[15]**. The simplified calculation is shown in ***Equation 4***.

$$EDI = \sum (R'_{exi} \times F_i) \text{ vagy } \sum (STMR'_i \times F_i) \qquad (4)$$

The value of R_{exi}, which is the pesticide residue concentration determined for the risk assessment of the raw product **[36]**, is determined by the JMPR, EFSA and the national authorization bodies on the basis of pesticide experiments and toxicological studies. Monitoring tests are carried out to verify compliance with the permitted limit values. In cases where the pesticide residue definition used for risk assessment differs from that defined for monitoring tests, the monitoring results first have to be modified on the basis of the available experimental results, according to the concentration ratio of the two pesticide residue definitions **[30]**. The R'_{exi} also includes the pesticide residue value modified by the processing factor (Pf_i):

$$R'_{exi} = R_{exi} + Pf_i \times R_{exi} \qquad (5)$$

Processing factors are expressed as the quotient of the pesticide residue (test compound) in the processed product (C_f) and the starting raw material (C_0): $Pf = C_f/C_0$. Experimental data for Pf values can be found in JMPR assessments, EFSAT Scientific Opinions and in the publication of BfR **[37]**.

The amount of toxic substances that are sometimes ingested with large amounts of food (estimated short-term intake, ESTI) is taken into account with the 97.5 percentile of the food consumed over 24 hours. Given that if a person consumes much more of a certain food than the average, then he or she is not expected to eat much other food, therefore, short-term (acute) exposure is calculated separately for each food and the highest of the values obtained is taken into account and compared to the ARfD value.

ESTI [mg/kgbw] is calculated by the following formula:

$$ESTI = \frac{U_e \times HR \times v + (LP - U_e) \times HR}{ttkg} \qquad (6)$$

In the formula, U_e is the wieght of the produce/food consumed [kg], HR is the maximum pesticide residue concentration observed in the pesticide experiments or monitoring studies [mg/kg]; ν is the so-called dimensionless variabilty factor, which is the quotient of the 97.5 percentile concentration of the pesticide residue measured in the individual produce and the average pesticide residue content of the lot, which is represented by the average pesticide residue content of the composite sample taken from it; LP is the 97.5 percentile of the amount of the given food consumed over 24 hours per kilogram of bodyweight [kg].

To determine EDI and ESTI deterministically, an Excel-based calculation model based on WHO international consumption data was developed by experts from the Dutch RIVM institute. To calculate EDI, countries with nearly the same consumption habits are divided into 17 groups by the model, while to calculate ESTI, LP and body weight data provided by Codex member countries are used **[38]**. These models are used by the JMPR to calculate the consumer risk of the evaluated pesticides. Experts in the European Union use an Excel-based program (Primo 3.1) containing consumption data for the 27 member states, and this program can calculate both EDI and ESTI **[39]**. Under current regulations, a pesticide is only authorized within the European Union if the amount of pesticide residues in foods under the proposed conditions of use does not pose a risk to the population of any country.

Equation 6 gives a specific estimate for consumer exposure, covering 97.5% of consumers of a given food, but it does not provide information on the distribution of the exposure. Therefore, to estimate exposure to different chemical contaminants and pesticide residues more accurately, probabilistic methods should be used. The advantage of this procedure is that it enables the estimation of the distribution of the exposure of a particular consumer group, taking into account the differences between the consumptions of different individuals and between the daily consumptions of the same individual, as well as the measured concentrations of the contaminants.

The probabilistic method for determining the exposure of Hungarian consumers was developed by Zentai et al. **[40, 41]**. The principle of the model is shown in ***Figure 6***.

When calculating acute exposure, it should be taken into account that the pesticide residue content of individual crops from the same growing area varies widely, sometimes even by a factor of 100 **[3]**. There is also a significant difference in the individual weight of the crops. This means that fruits and vegetables of different size and pesticide residue content can be consumed on the same day, and this can be taken into account in the probabilistic calculation of exposure **[42]**.

Comparing the calculated EDI and ESTI values to the ADI and ARfD values, the consumer risk of pesticide residues under the particular conditions of use can be estimated.

The uncertainties of the calculated EDI and ESTI **[36, 43, 44]**, as well as the variability factor distribution **[45]** and pesticide residue distribution **[46]** of individual crops were reported in separate publications.

3. Analytical results and their evaluation

3.1. Pesticide residue analytical tests

The most commonly used method in the laboratories of NÉBIH is the appropriate version of the so-called QuEChERS **[47, 48, 49]**, which has been validated for more than 650 pesticide residues/metabolites so far **[50]**. The performance of the LC-MS/MS and GC-MS/MS instruments used for the analysis of the sample extracts allows, depending on the sample, the detection of nearly 600 active substances and metabolites, with a few exceptions at concentration levels ranging from 0.001 to 0.01 mg/kg. The broad range of the compounds sought ensures that all detectable amounts of pesticide residues that may be present in the samples are determined.

Between 2014 and 2018, the laboratories of NÉBIH carried out the analysis of approximately 2,348,347 pesticide residues in 9,883 samples of 266 types of crops/products[1]. Almost 1.5 million analyses of pesticide residues and metabolites were performed for 636 different pesticide residues and metabolites in 5,275 food samples of Hungarian origin. Pesticide residues exceeding the MRLs were found in 62 samples (1.17%). There was no detectable pesticide residue in 50.9% of the pesticide residue-sample combinations tested. As an example, the pesticide residue distributions in all foods, as well as in some fruit and vegetable samples are presented in ***Table 4***. The pesticide residues sought in 662 Hungarian and imported apple samples by 201.923 analyses and the number of tests are summarized in ***Table 5***. The pesticide residue distribution was similar in all other food samples.

99,117 analyses of 321 baby food samples were carried out in the following distribution: cereal-based baby food (1,392); fruit-based baby food (21,946); fruit dessert (baby food: 301); fruit juice, vegetable juice, nectar (baby drink: 19,008), fish-based baby food (343); meat-based baby food (1,890); biscuit, zwieback, cake for children (670); tomato potato-based baby food (299); carrot-based baby drink (293); tea, herbal tea (baby drink: 1,672), milk-based foods for children (1,976); milk-based infant formula (14,114); mixed baby food (22,623); water (332); vegetable-based baby food (11,969); turkey with vegetables and rice baby food (289). None of the samples contained detectable amounts of pesticide residues.

In the period under review, residues of pesticides not authorized in Hungary or in the given product were found in samples taken from 160 products of Hungarian origin. Analytical results are summarized in ***Table 6***.

Foods of non-Hungarian origin came from 83 different countries. A total of 1,399,761 analyses have been performed on 183 products. Pesticide residues exceeding the limit value or not authorized in the European Union were found in 0.43% and 5.3% of the samples, respectively. In 47% of the samples there was no detectable pesticide residue.

Daily intakes of pesticide residue in excess of the permitted limit values and maximum pesticide residues resulting from the use of unauthorized pesticides were calculated on the basis of consumption data registered in the 2009 cosumer survery **[51]**. The 97.5 percentile of the daily consumption expressed in kg/kgbw ($F_{0,975}$), for medium sized crops (e.g., apples, potatoes, table grapes, peppers, tomatoes, cucumbers), was calculated with the variability factor (n) of 3 and the highest observed pesticide residue (R_{max}).

$$EDI_{max} = F_{0,975} \times R_{max} \times (3) \qquad (7)$$

The ARfD value was exceeded by the measured pesticide residues in 0.04% of the samples. The highest values were observed for the pesticide residues dimethoate and omethoate: in samples of cucumber (2.9 ARfD), lettuce (2.8 ArfD) and radish (2.9 ARfD). Given that the average pesticide residue of the sample was used when calculating the daily intake and the variability factot referred to the total amount consumed, the exposure calculated in this way is slightly higher than the actual one, which increases the reliability of the estimation.

[1] Besides the laboratories of NÉBIH, pesticide residue analyses are also carried out, on behalf of producers and distributors, typically on samples provided by the customer, by the laboratories of SGS Hungária Kft. and WESSLING Hungary Kft., among others, but their results were not available to us.

Hungarian results indicate (***Table 6***) that there is not sufficient plant protection products available in small-scale cultivated plants (grown in small areas) that would ensure adequate plant protection. In order to carry out the pesticide residue analyses necessary to expand the scope of the Hungarian use of active substances authorized in the European Union, the cooperation of pesticide distributors, producer associations, the Hungarian Chamber of Agriculture and the authorization body is necessary. It also seems appropriate to prepare and publish information material on the effective crop protection of crops affected by plant protection technology deficiencies using currently authorized and marketed pesticides and other plant protection methods (e.g., biological, agrotechnical).

Considering that, in more than 99% of the cases, the more than 600 pesticide residues sought by highly sensitive analyses in nearly ten thousand samples covering a wide range of crops could not be detected, and that only 0.04% of the samples contained pesticide residues exceeding the ArfD value indicating acute consumer risk, it can be safely concluded that the pesticide residues present in our foods do not pose a risk to public health.

3.1.1. Evaluation of glyphosate residues

Since most often contradictory opinions are published regarding the adverse side effects of glyphosate, following a brief summary of the current view on glyphosate, a detailed evaluation of analytical results is presented.

Glyphosate-containing Roundup is the total herbicide used in the largest amount in the world (almost 200 million tonnes per year), used primarily for growing genetically modified sorghum, sugar beet, cotton, corn, lentils and soy. It is also used for the desiccation of non-GM crops before harvest, as well as the weed control of non-agricultural areas. It may endanger specifically the health of persons (agricultural workers, gardeners) who may come into direct contact with it. In California, in 2018, there have been several court rulings in favor of patients with Hodgkin's lymphoma associated with glyphosate **[52]**.

Glyphosate is the most widely used pesticide active ingredient in Hungary as well. Its annual turnover in the period between 2013 and 2018 ranged from 890 to 1650 tonnes/year, representing 25-40% of the total herbicide turnover and 12-17% of the pesticide turnover **[53]**.

Glyphosate has been evaluated several times by the JMPR. During the 2005 periodic review **[54]**, experimental results showed that after a treatment with 1.4-1.5 kg a.i./ha rate 7 to 14 days prior to harvest, maximum glyphosate residues of 5-17 mg/kg were present in the treated produce (barley, peas, wheat, corn, sunflower, soy, rye, oats). The concentration of the major metabolite, AMPA (aminomethylphosfonic acid) was typically below the limit of detection (0.05 mg/kg). According to the calculation of the JMPR that used regional consumption data, taking into account the above pesticide residue levels, the estimated daily intake less than 1% of the ADI (1 mg/kgbw).

In October 2019, the EFSA updated its assessment of pesticide residues based on EU glyphosate usage regulations and European Union MRL **[55]**. The checking of MRL in plant products was recommended on the basis of glyphosate residue analysis, while consumer exposure assessment and the analysis of foods of animal origin was recommended by taking into account the combined amount of glyphosate and its major metabolites (AMPA, N-acetylglyphosate and N-acetyl-AMPA). Following treatment of 0.72-2.16 kg a.i./ha 7 to 14 days prior to harvest, in treated and harvested crops (barley, peas, wheat, corn, sunflower, soy, rye, oats) a maximum of 2-21 mg/kg glyphosate residues were found. Glyphosate residues were not expected in secondary crops in areas treated according to the use recommendations. The amount of the major metabolite (AMPA) was predominantly below the limit of detection (0.05 mg/kg). According to the calculation of the EFSA, which used the consumption data of EU member states, taking into account the above pesticide residue levels, the estimated daily glyphosate intake was ≤4% of the ADI (in the European Union ADI=0.5 mg/kgbw). The highest ESTI resulted from the consumption of dried beans, which was 80.4% of the acute reference dose (0.5 mg/kgbw).

Glyphosate has been classified by the WHO and IARC as „probably carcinogenic" **[56]**. However, but based the available information the European Chemicals Agency (ECHA) concluded that there is no reason to classify glyphosate as a carcinogen **[57]**. In the USA, the EPA has maintained its view that use according to the regulations does not endanger consumer health. According to the EFSA, glyphosate has no endocrine disrupting properties **[58]**. Based on the professional opinion of the ECHA and the EFSA, in 2017 the European Commission extended the EU approval status of glyphosate for five years **[59]**. During this time, but no later than the 2022 expiration, a full reevaluation of the dossier should be carried out. Given the complexity of the problem, in an extraordinary step, four countries (France, the Netherlands, Hungary, Sweden) were charged by the commission to reevaluate glyphosate-related material starting in early 2020 **[60]**. The evaluating member states are committed to ensuring the full transparency of the process.

Currently there are numerous glyphosate-containing products authorized for use in Hungary, primarily on arable lands, in horticulture and forestry, and for total weed control before sowing or planting and after harvest. It is also used extensively as a desiccant in corn, sunflower, soy and rapeseed crops, and as a herbicide before the harvest of wheat and barley.

Given that glyphosate is not a selective herbicide, but a total one, the crop to be protected from weeds cannot come in contact with the active substance, apart from its use before the harvest, because of its harmful effects. Accordingly, with the exception of its possible drifting or getting pesticide residues on the fruit in orchards during ground weed control, no residues are expected in other crops or in secondary crops.

The laboratories of NÉBIH analyzed 560 samples of 105 types of products (including 50 foods) for glyphosate residues between 2014 and 2018 (***Table 7***). Measurable amounts of pesticide residue were found in three wheat grain (R<MRL/2), a wine grape, a raspberry and a lettuce sample (0.05 mg/kg). The remaining samples contained no detectable pesticide residues (<0.05 mg/kg).

Measurable amounts of the pesticide residue are not transferred from feedstuffs that contain glyphosate (including the metabolites) to milk or fat (with the exception of sheep). Maximum expected values in liver and kidney are in the 0.4-0.9 mg/kg and 3-10 mg/kg range, respectively **[55]**.

Considering that genetically modified plants (GMO) are not allowed to be grown in Hungary, and that during 324 analyses of 50 foods measurable amounts of pesticide residues were only found in a total of six cases, to the best of our knowledge, the Hungarian use of glyphosate is unlikely to cause a public health or food safety risk.

Nevertheless, we would like to emphasize that we do not have sufficient data to reliably estimate the amount of pesticide residues in treated crops following application before the harvest (desiccation, weed control), since the analysis of 47 randomly taken wheat samples only indicates with a 60% probability that 89% of the marketed produce complies with the limit value (***Table 3***).

To confirm the results of the large number of pesticide experiments published in the EFSA evaluation **[55]** with pesticide residue values expected in normal Hungarian practice, targeted analysis of glyphosate residues in wheat (including its processes products such as whole grain wheat flour, wheat flour, bran), barley, corn and oats following treatment before the harvest is recommended. Sunflower and corn oil analyses are not necessary because processing experiments have shown that the polar molecules of pesticide residues are transferred to the oils to a negligible extent.

We also recommend a more accurate assessment of the exposure of the Hungarian population, as well as the screening for the possible appearance of glyphosate and its major metabolite (AMPA) in the blood and urine of people who are professionally exposed to glyphosate **[61, 62]**.

4. Summary, recommendations

Today, pesticides are indispensable for providing Earth's population with food of sufficient quality and quantity. Their authorization for use is preceded by extensive testing based on EU and OECD test guidelines. A given compound is only authorized by the relevant bodies if, on the basis of the scientific results available at that time, its use does not endanger the health of consumers or damage the environment. Licenses are reviewed at regular intervals in the light of new knowledge and experience, revoked if justified, or the application of the substance is restricted.

In Hungary, the pesticide residue content of the foodstuffs marketed is checked by the laboratories of NÉBIH in a large number of samples taken on the basis of a risk-based sampling plan, using state-of-the-art test methods and the highest reliability in Europe. For reliable results, professional sampling performed in accordance with the relevant regulations is essential.

Considering that in almost 50% of the cases the more than 600 pesticide residues sought in nearly ten thousand samples covering a wide variety of crops could not be detected using highly sensitive analyses, and that only 0.04% of the samples contained pesticide residues in amounts exceeding the ArfD value indicating acute consumer risk, we can safely say that the pesticide residues present in our foods do not pose a risk to the health of the population.

In order to reduce the use of *„black technologies"*, i.e., the use of pesticides in crops not included in their licensing document, it is necessary to expand the use of active substances authorized in the European Union in Hungary. In this context, a closer cooperation is needed between pesticide distributors, producer associations, the chamber of agriculture and the licensing authority to carry out pesticide residue analyses.

It also seems justified to prepare and publish information material on the correct use of currently authorized pesticides and various, such as biological or other agrotechnical technologies, with special emphasis on crops affected by plant protection technological deficiencies.

There are contradictory opinions about the adverse side effects of glyphosate. For this reason, after briefly summarizing the current view of glyphosate, analytical results were evaluated separately. 560 samples of 105 types of products were analyzed for glyphosate residues by the laboratories of NÉBIH. Measurable residues were found in three wheat grain (R<MRL/2), a wine grape, a raspberry and a lettuce sample at the detection limit of the method (LOQ=0.05 mg/kg). There were no detectable residues in the other samples (<0.05 mg/kg).

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Considering the genetically modified plants (GMOs) cannot be cultivated in Hungary, and that there were a total of six cases among the samples analyzed that contained measurable amounts of glyphosate residues, according to our current knowledge, the domestic use of glyphosate is unlikely to pose a risk to public health or food safety.

To confirm the results of the large number of pesticide experiments published in the 2019 EFSA evaluation with pesticide residue values expected in normal practice, targeted analysis of glyphosate residues in wheat (including its processes products such as whole grain wheat flour and bran), barley, corn and oats following treatment before the harvest is recommended. Sunflower and corn oil analyses are not necessary because processing experiments have shown that the polar molecules of pesticide residues are transferred to the oils to a negligible extent.

We also recommend a more accurate assessment of the exposure of the Hungarian population using screening methods, with special emphasis on the possible appearance of glyphosate and its major metabolite (AMPA) in the blood and urine of people who are professionally exposed to glyphosate

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