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Pesticide residue analysis in Hungary between 1967 and 2015*

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1. Summary

Around the same time of the development of modern large scale plant protection, exemplary even on an international level, it became necessary to check pesticide residue concentrations in treated crops, soils and surface waters. OÉTI methods were continuously improved by the young, well-trained and enthusiastic staff of the testing laboratories equipped with state-of-the-art instruments, and procedures satisfying the needs of wide-ranging analytical tasks were developed, as a result of which a four-volume integrated method collection was already published in 1976, and from 1978 analytical results were already processed and evaluated with the help of computers.

By regular training courses and by prescribing strict quality assurance requirements, we ensured that the results of the 20 testing laboratories were comparable. For the staff of a network, having such a methodological background and this high level professional knowledge, it was not a problem to obtain accreditation, in accordance with international requirements, according to the Good Laboratory Practice (GLP) and standard ISO 17025, and then to participate outstandingly in international conferences and proficiency testing schemes after joining the European Union.

However, the economic state of the country did not allow for a large number of testing laboratories to be maintained. Concentration of the analyses and operating a smaller number of laboratories but with larger staffs were also justified by the optimal utilization of high performance, expensive instruments.

Reduction in the number of laboratories started at the beginning of the 90's, and currently there are 4 laboratories with 37 employees, performing the pesticide residue content inspection of nearly six to seven thousand samples of foods and feeds of animal or plant origin, and also a limited number of analyses investigating environmental pollutions.

Analytical requirements are continuously becoming stricter. Today, a pesticide residue testing laboratory is expected to analyze samples for the residues of 400-500 different pesticides and their toxic metabolites, within days. These expectations can only be met by using state-of-the-art instruments and, in this respect, we are seriously lagging behind. Following the instrument purchases and training courses held in 2008 within the framework of the EU transition facility programme, substantial purchases and organized training courses were very limited or non-existent. Replacement of the instruments that are 9 to 16 years old being at the very end of their expected life span, and regular training of the staff that, fortunately, consists mainly of young people, thus ensuring continuity, are necessary without delay for laboratories to be able to perform the control inspections essential for the realization of food safety objectives, satisfying EU requirements.

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2. The need for pesticide residue analysis and development of the testing network

In the 50s, damages due to the potato beetle, the fall webworm, the blossom feeder scarab and sugar beet pests had become commonplace all over Hungary, against which mandatory protection was ordered, using primarily persistent DDT and other chlorinated hydrocarbon pesticides. In 1954-55, county plant protection stations were established in every county, with extremely modest infrastructural backgrounds. In 1958, graduate training of plant protection special engineers was launched at the Gödöllő University of Agriculture. Systematic and complex development of plant protection is associated with the name of dr. Bálint Nagy, who considered Hungarian plant protection as a major element of the whole agricultural sector, affecting certain elements of the living and non-living environment, as well as society as a whole **[1]**.

Integral elements of this comprehensive approach were the ban on organic chlorinated hydrocarbons (DDT, aldrin, dieldrin, HCH) that accumulate in the environment and human and animal tissues, instituted in Hungary in 1968, a world first, as well as mercury and arsenic removal programs. It became necessary to check regularly the residues of the ever-increasing amounts of the much more toxic organophosphorus, carbamate and other types of insecticidal, fungicidal and herbicidal agents replacing chlorinated hydrocarbons in treated crops, soils and surface waters. To this end, the Pesticide residue analytical group to section was established in 1967 as part of the MÉM Central Plant Protection and Quarantine Laboratory (MÉM KNKL) at the Budaörs site of the aerial plant protection unit operating within the framework of the Pest County Plant Protection Station.

Of the wide range of tasks of the Pesticide residue analytical group (NACs), the most important ones were as follows:

- taking over of the previous analytical experience and methods of the National Institute for Food and Nutrition Science (OÉTI) **[2]**, development of new analytical methods;
- determination of the optimal operating parameters of the new instruments;
- organization of the county pesticide residue analytical laboratory network, its professional management, compilation of annual work programs;
- establishing a system of pesticide residue analyses, related to pesticide pre-authorization efficacy studies, evaluation of the test results;
- development of methods for verifying the effectiveness of protective equipment (gloves, filters, clothing) used during the application of pesticides, performing the analyses;
- methodological assistance to the development of the Hungarian pesticide industry.

Between 1968 and 1974, Pesticide residue testing laboratories were established and equipped with modern glass column gas chromatographs **(Figure 1)**, thin layer chromatographs, UV spectrophotometers and other equipment necessary for the analyses. By orders of the Plant Protection Department Director, well-trained, enthusiastic chemists or people with degrees in chemistry/biology/physics were hired by the laboratories. The number of employees at each laboratory varied between 3 and 5 people.

Based on the annual work plan compiled by the NACs and approved by the Plant Protection Department of MÉM laboratories operated in the following areas:

- determination of the pesticide residue content of products of plant origin;
- testing of sols and surface waters for pesticide residues;
- performing pre-authorization and technology development pesticide experiments;
- performing regular control (what is called today quality management)) measurements to verify the reliability of the analyses;
- development and adaptation of test methods;
- carrying out special analyses by the orders of the Plant Protection Department;
- assistance in investigating local problems.

3. Laying the foundation for world-class professional work

3.1. Coordinated method development

From the establishment of the first laboratories, we considered it an important aspect to involve all county employees in the development and implementation of the method development program. As opposed to the practice of other Hungarian institutions, method development was not the sole responsibility of the central laboratory. In this respect, there was no difference between the employees of the NACs and of the county laboratories. To develop a method suitable for the determination of a certain class of compounds, or to find the optimal operating conditions of certain instruments and their area of applicability, working groups were established, in which all of our colleagues participated according to their capabilities, but wholeheartedly and enthusiastically.

3.2. Regular theoretical and practical training courses

Experience in method development and analysis was exchanged at annual trainings and workshops during the year, where carrying out of the methods developed and instrument optimization were also demonstrated. The length of annual training courses was two weeks in the beginning, later it was five days and, by the end of the 90s, it was only 2 or 3 days. Members of the staff of the network were asked to prepare for the trainings with theoretical lectures and practical demonstrations. This made it possible that, in spite of a lack of English skills, compared to today's levels, our colleagues could get acquainted with the theoretical basis of gas and thin layer chromatography, UV-VIS spectrophotometry and polarography, conditions for their proper use, the teaching of which was highly deficient at the universities, and they could use the instruments available to them not only routinely, but consciously. In addition to the professional advantages, trainings played an important role in establishing good work relations and a friendly atmosphere, making it possible to develop a united network of laboratories helping each other, and not competing with each other.

3.3. Setting high quality requirements and monitoring compliance with them

The work of the laboratories, performing the analyses correctly and proper documentation of the results were checked by NACs on-site 2-3 times a year. In 1974, we introduced the so-called test sample analyses, in which laboratories received samples containing 8-12 different pesticide residues four times a year, and they had to identify the active ingredients and determine their concentrations.

3.4. Utilizing international relationships and experience

When selecting and developing analytical methods, the experience gained in the Work Group on Methods of Analysis and Sampling of the Codex Committee on Pesticide Residues (CCPR) was utilized. Professional relationships established while participating in the Codex work, in the IUPAC Committee on Pesticide Chemistry and the FAO WHO expert committee on pesticide residues played an important role later in the area of international cooperations. Utilizing the bilateral scientific cooperation opportunities announced in the first half of the 90s, our colleagues spent nearly 50 months' time at leading English, Dutch, German, Austrian and American institutes, and employees of partner institutions were also hosted in our laboratories.

3.5. Management support

Coordinated development work and the holding of training courses was fully supported by the Plant Protection Department, indicated by their participation for shorter or longer periods. This is evidenced by the fact that the deputy head of the department, dr. Ferenc Hargitai was present for the full two weeks of the first training course. Appreciating the level of professional work, the management of the Plant Protection Department, the MÉM KNKL, and later the MÉM Plant Protection Center supported the regular organization of domestic and international training courses, participation in the work of international bodies and in international cooperations, and also publication of the results at international professional conferences and workshops.

Throughout the years, we received special attention and support from department heads dr. Bálint Nagy, dr. Ferenc Hargitai, István Fésűs and dr. István Eke, and from directors dr. Imre Kovács and János Szabó. Without the support of the management and ensuring proper technical and human resources, the professionalism and enthusiasm of our colleagues would not have been enough to produce outstanding results on an international level. The excellent professional work was also recognized by senior management: three of our colleagues, entering their retirement years, were awarded the Hungarian Silver Cross of Merit in 2012 and 2013.

As a result of the combined effect of the five factors described above, county laboratories formed a well-organized, coherent unit, pesticide residue analytical results were equivalent, regardless of the laboratory, and with employees helping each other and willing to put major extra effort into their work for meaningful goals, internationally significant and recognized results could be achieved.

4. Results of coordinated, high quality professional work

4.1. Publication of an coherent analytical method book

As a result of systematic method development, within the plant protection organization we were the first to publish in 1976 a four-volume method book titled "Analytical methods of pesticide residues", containing methods checked in several laboratories and the theoretical basis of the analyses **[3] (Figure 2)**, which served as the foundation for the analyses of the next decade. The following colleagues were involved in the preparation of the book: Á. Ambrus, Z. Árpád, Sz. Bálint, E. Dudar, I. Csatlós, A. Fülöp, F. Hargitai, J. Lantos, Á. Pápa, L. Sárvári and L. Szabó.

4.2. Publication of the results at international conferences and in scientific journals

As a recognition of high level professional work, the management of the Plant Protection Department made it possible for several employees of the network to participate in and present lectures at all IUPAC congresses starting from the IUPAC 3rd International Congress of Pesticide Chemistry in Helsinki in 1974 (with the exception of the one held in Australia in 2010). Funds to cover travel expenses were obtained from budget support, as well as from the gradually increasing revenue from international projects and expert activities.

Our general method suitable for the simultaneous determination of several pesticide residues, which formed the basis for the analyses, was presented as three posters at the 4th IUPAC Congress, and then it was published in three papers in the most prestigious scientific journal **[4], [5], [6].**

The column extraction method, generating great international attention, was also introduced at an IUPAC Congress (Ottawa 1986). There have been more than 200 independent references to the paper describing this **[7]**. The level of the posters presented is indicated by the fact that they were awarded first place positions among hundreds of posters twice, at the 10th and 13th congresses in Basel (Dr. Lajos Kadenczki and Gabriella Suszter) and in San Francisco (Zsuzsa Farkas, Kata Kerekes, Zsuzsanna Horváth, Gabriella Köteles-Suszter, Árpád Ambrus) **(Figures 3 and 4)**.

4.3. Self-education

Although the primary task of the network was "routine" determination of pesticide residues, in addition to the carrying out the usual pesticide residue analytical tasks and related method development, intensive research work was also performed, increasing the reliability and correctness of the test results and facilitating the evaluation of the results and the assessment of the environmental impact of pesticides, mainly through the extra effort of participating colleagues. Targeted research work was also helped by the definition of method development tasks and by participating in international cooperations. 185 professional articles have been published in national and international journals by the network staff and 118 lectures were held on registered national and international forums. The list of relevant publications and lectures presented at international forums is contained in an electronic annex to this paper, available at the website of the Journal of Food Investigations: **http://eviko.hu/en-us/Downloads**

As a "byproduct" of this development work, Árpád Ambrus was awarded a candidatorial degree in the chemical sciences **[8]**, while Miklósné Ferenczi **[9]**, István Füzesi **[10]**, Lajos Kadenczki **[11]**, Gabriella Károly **[12]**, Istvánné Korsós **[13]**, Ágoston Pápa **[14]** Etelka Solymos-Majzik **[15]**, Mária Susán **[16]** and Györgyné Visi **[17]** prepared and successfully defended their doctoral theses.

4.4. Successful solving of specific professional tasks

It became clear that manual processing of the 50,000 to 80,000 analytical results obtained each year could only be done by spending disproportionate amounts of time on it, and even then, only partially. Therefore, the algorithm for computerized evaluation of the analytical results was developed in 1978, being the first within the plant protection organization, and its practical realization was achieved with the involvement of an external expert. Development of the program and processing of the results were done under rather unfavorable conditions on the central IBM 360 computer of MÉM, with machine time regularly provided between 2 and 4 am. The basic query format of the processing was also adopted by our Dutch colleagues. It was also used, complemented by several queries of other aspects, in our currently used computerized processing program developed within the framework of the EU transition facility programme (2009). The increase in data volume can be illustrated by mentioning the fact that nearly 620,000 analytical results were process and evaluated in the year 2014.

At the beginning of method development, to support the sampling process developed for Codex pesticide residue analyses **[18]**, the pesticide residue distributions in individual crops (apple, tomato) and in incremental samples taken using a hand auger were investigated **[19]**, as well as the errors of the sampling procedures used in pesticide experiments **[20]**. Taking incremental samples from randomly selected location was no easy task **(Figure 5)**, but it was performed by our colleagues with great enthusiasm and precision, because they knew that useful results could only be obtained by carrying out the analytical study plan accurately. The procedure recommended for the determination of acute pesticide residue exposure was developed by the FAO/WHO expert meeting in 1995 **[21]**, taking into consideration the analytical results obtained in 1977 for the pesticide residue distribution of incremental samples **[19]**.

As a result of the faulty financial takeover practice, large amounts of nitrogen were used by producers when growing sugarbeet, resulting in beet sugar contents of 7-8% in some cases, overloading processing plants and decreasing percentage sugar yields significantly. It was our task in the initial phase of an agrochemical program based on targeted fertilization to develop a method for the determination of the nitrogen content of beet and soil, and to explore the relationship between them by analyzing samples taken from different locations. Urgent analyses, regularly lasting late into the night, were performed at the Komárom county Plant Protection Station by a team complemented by colleagues from Csongrád and Hajdú counties. Our results contributed to the development of the rational fertilization advisory system, thanks to which, and to the modified collection system, the sugar content of beet increased to 17-20% within a few years. Based on management decisions, the range of tasks of the laboratories was not extended with the planned nutritional analyses.

The rapid deterioration of the water quality of Lake Balaton was blamed on intensive agricultural production and livestock farming, even in certain scientific circles. Within the framework of an FAO project performed together with the Water Management Research Institute (VITUKI), a complex analytical program was designed at the beginning of the 80's, mainly involving the Somogy, Veszprém, Zala and BAZ county stations. In the project, among other things, pesticide residue, NO_3^-, phosphorus and organic carbon contaminations and several water quality parameters of streams and rivers flowing into the Balaton were analyzed for a year. The contamination of shallow groundwaters of surrounding settlements in direct contact with Balaton were also investigated, as well as the relationship between agricultural production performed in the catchment areas of the Rakaca and Tetves creeks, as model areas, pesticide mobility and water quality. Our results clearly demonstrated that it was the untreated wastewater due to the greatly increased people spending their vacations at the surrounding settlements with no sanitation systems that was responsible for the deterioration of the water quality of Lake Balaton. Results were sufficient to convince members of the Balaton Subcommittee established under the auspices of the Hungarian Academy of Sciences (MTA), and in the proposal submitted to the Government they advocated the building of sanitation systems at the settlements surrounding Lake Balaton and proper treatment of wastewater as solutions. The result is well-known: today, the water quality of Lake Balaton is good again for vacationers and the local population to enjoy.

As a recognition of the high level professional work performed in the pesticide residue analytical network, we were given the task to hold the first FAO/WHO regional pesticide residue analytical training course. Although we had plenty of practice in compiling and presenting professional training courses in Hungarian, a training to be organized for European analysts presented a great challenge. Of the Hungarian experts, András Fülöp, Ferencné Hargitai, dr. Lajos Kadencki, dr. János Lantos, Györgyné Visi and dr. Katalin Soós of OÉTI were invited by dr. Árpád Ambrus, organizer of the training, to present the lectures and instruct laboratory exercises. Mr. Paul Baker (UK), dr. Roy Greenhalgh (Canada) and dr. Peter Greve (Netherlands) participated as foreign lecturers in the training of 15 Bulgarian, Greek, Yugoslavian, Polish, Maltese and Portugese analysts at the Heves county Plant Protection Station in 1983. The material of the lectures and the exercises was published as a book by the WHO **[22]**. During the two-week training, close professional relationships and friendships were formed, lasting to this very day. This very successful event was followed by other 20-25-strong international training courses, held at the BAZ county (1996, 1998 and 2015) and Fejér county (2001) laboratories and in Budapest (2012). Over the years, we had the chance to have employees of several Hungarian institutions, as well as fellows of the FAO or the International Atomic Energy Agency (IAEA) get acquainted with the basics of pesticide residue analysis and good laboratory practice.

With the above-mentioned coherent testing regimen, professional knowledge and quality assurance program in our possession, it was not a problem to introduce working arrangements conforming to OECD's Good Laboratory Practice (GLP) guidelines. As the first phase of the preparation, in accordance with well-established practice, standard operating procedures were prepared together with a team selected from employees of the county laboratories, and in the second phase, these had to be updated in the laboratories and introduced into the daily work routine. Within a year after the approval of the preparatory program, international accreditation of the laboratories selected for obtaining GLP certification was performed in 1992. The committee consisted of dr. David Moore, former chairman of OECD's GLP Panel and head of the British GLP Compliance Monitoring Authority, dr. Peter Greve, chairman of the CCPR Analytical Working Committee and dr. Gézáné Perjés, inspector of the GLP supervision unit of the National Institute of Pharmacy (OGYI). The accreditation, performed with the participation of renowned international experts, was necessary, because the Hungarian GLP accreditation system was not yet internationally recognized at the time. Based on the very positive experience gained during the accreditation, on the recommendation of dr. David Moore, Hungary was invited to participate in OECD's GLP panel, a year before Hungary became member of the OECD.

5. International tests

Following Hungary's accession to the EU, participation of laboratories performing authority inspection tasks (OFL) and the national reference laboratories (NRL) in proficiency testing schemes became mandatory. These proficiency tests present a major professional challenge, because 15-22 pesticide residues and sometimes their metabolites have to be identified and quantified in different samples, several times a year.

Evaluation criteria are very strict. Without going into detail, their main theoretical principles are described below. If the pesticide residues in the sample are determined accurately by the laboratories, then measurement results will show a normal distribution. 68% of the results are expected to be in the μ (average) ± s (standard deviation) range, 95% in the $\mu \pm 1.96s$ (roughly 2) range, and 99.7% in the $\mu \pm 3s$ range. According to the usual practice, results are considered to be good, if they fall in the $\mu \pm 2s$ range. In the case of proficiency tests, much stricter criteria apply. From the reported results, the average value (μ) and the standard deviation (σ) are calculated using robust statistical methods, and the z-value calculated from these [$z_i=(x_i-\mu)/\sigma$] forms the basis for evaluation, according to the following formula.

Laboratories that identify correctly approximately 90% of the pesticide residues in the sample, and do not report pesticide residues that are not present in the sample (false positive detection) are classified as category 'A'. Laboratories not satisfying the requirements of category 'A' are considered unsatisfactory and are classified as category 'B'.

Within category 'A', laboratories with an AZ^2 number ≤ 2 receive a rating of good, those falling in the $2 < AZ^2 < 3$ range receive a rating of adequate, and those with an AZ^2 value ≥ 3, a rating of inadequate.

It is clear that results with $Z \leq 1$ are rewarded, because Z^2 is then reduced, while $Z > 1$ results are penalized. For example, if the z-value calculated from the analytical result of one pesticide residue is 1.5 (a good result in normal practice), the calculated AZ^2 value in the PT (proficiency test) will be 2.25, and the result will be only "adequate". Considering that, in some cases, more than 160 laboratories participate in the analysis of a certain test sample, the overall scores of the Hungarian laboratories, summarized in **Table 1**, can be considered excellent.

The performances of participating European laboratories and of Hungarian pesticide residue analytical laboratories are illustrated in **Figures 6-13**. The figures clearly show that even the performance of category ‚A' laboratories varies widely. Hungarian pesticide residue analytical laboratories are continuously among the best, and have achieved the best results on several occasions, finishing ahead of much better equipped, "big-name" laboratories.

During the proficiency tests, several laboratories showed consistently outstanding performance over the years in different categories. In connection with this, to commemorate a prematurely deceased excellent Swedish analyst, the Arne Andersson award was founded, the purpose of which is to lift these authority laboratories from anonymity and reward them. During evaluation, results of the last three years are considered in each category. The award was first given in 2013 in four categories, and in the cereal category the Arne Anderson award was given to our Borsod-Abaúj-Zemplén county laboratory for the best performance **(Figure 13).** The Velence Pesticide Analytical Laboratory finished first among 185 participating laboratories.

6. Present and future

Personal relationships among the employees of the laboratories are very good, sometimes friendships have developed. Colleagues were happy to participate in the joint realization of common goals. Gradual closing of the laboratories did not influence the relationship between former colleagues, nearly sixty of whom were happy to participate in a meeting with excellent atmosphere, organized in Fácánkert on the occasion of the retirement of two of their colleagues **(Figure 14)**, which was also attended by dr. Bálint Nagy, dr. Ferenc Hargitai and dr. István Eke, former heads of the Plant Protection Department.

After several reorganizations, of the 20 laboratories established in the early 1970s, only 4 still operate with a staff of 37 people, 20 of whom have university degrees. Since 2011, the laboratories have continued their work as organizational units of the National Food Chain Safety Office (NÉBIH), and their scope has expanded significantly to pesticide residue analysis in foods of animal origin, feeds, wine and, within the framework of environmental analyses, in bee carcasses. The significant decrease in the number of laboratories was partly justified by professional considerations. Current high-performance instruments requiring specific professional knowledge cannot be used efficiently in laboratories of 4-5 people. High procurement and operating costs can only be recouped under optimal utilization conditions. For supervising the realization of food safety and environmental objectives and for carrying out the necessary technology development analyses in plant protection, the current laboratory capacity is sufficient, if only barely **(Figure 15)**. However, its further reduction would significantly endanger the security of basic service, and also the realization of the above government goals.

Maintaining the current analytical quality and performance is negatively affected by several factors.

Coordination of the work of the laboratories is performed by a single person, in addition to her other tasks, as an employee of the Directorate of Plant Protection, Soil Conservation and Agri-environment of the National Food Chain Safety Office (NÉBIH).

The cooperation between laboratories that worked very well and which had been very successful is now practically ceased to exist, resulting in significant extra work, because the same tasks have to be performed in each laboratory, instead of only one.

Instruments purchased in 2007 from the EU transition facility programme are nearing the end of their lives. Obtaining parts is becoming harder and harder because of the closing of manufacturers, and the business policies of the companies taking over the product portfolio. According to international standards, a manufacturer has to ensure the availability of parts for the instruments manufactured by him for 10 years. **9-17 years old** instruments that are still operational, due to very careful handling and thorough maintenance, can become irreparable at any time, making it impossible to perform the analyses on the work schedule. Analytical conditions have been improved by the 3 LC-MS/MS instruments installed in 2013-14, but provisions should be made for the continuous replacement of other instruments that cannot be safely maintained any more.

Since the training course that was organized in 2008-2009 within the framework of the EU Transitional Funding Project with the involvement of internationally renowned experts, that covered all branches of the field – the presentations of which were also published as a two-volume book **[23]** – there has been no professional training course providing new knowledge. For the optimal use of high performance instruments and to get to know the advantages of complex analytical methods (for example, the QuEChERS procedure that can be used in a number of specific variants) it would be necessary to learn about the latest scientific developments and their practical applications. It is very unfortunate that the management of NÉBIH did not take the extraordinary chance to invite the two prominent internationally renowned experts, Michelangelo Anastassiades and Lutz Alder, who were giving lectures in 2015 at an international training course held in Miskolc, for a one-day training for the Hungarian chemists as well.

If we want to maintain the current analytical quality and international prestige, urgent solutions to conquer the above problems have to be found.

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