

A graphic celebrating 10 years of PhytoLab. The number '10' is rendered in a large, white, digital-style font. Below it, the words 'YEARS OF' are written in a smaller, white, digital-style font. At the bottom, the word 'PhytoLab' is enclosed in a white rounded rectangle with a thin border. The entire graphic is centered over a background of a white flower with green leaves.

## Professional dependability

10 years developing, analysing and  
registering herbal products

# 10 years of PhytoLab – 10 years of competence in the laboratory for your security



When we at Martin Bauer decided to establish a laboratory company 10 years ago, it was our reaction to the economic changes that were taking place at the beginning of the 1990s. That was the time when the customs barriers were lifted and multinational concerns were developing strategies which made optimum use of the new-found liberties and privileges. A comprehensive, internationally oriented competence centre for herbal products and preparations was founded to meet the increasingly stringent requirements of the pharmaceutical industry in terms of development, analysis and registration – PhytoLab was born.

In our capacity as the founding team of PhytoLab, we had the tremendous advantage of not having to start from scratch: This is because Martin Bauer already had a Quality Control/Science division employing 43 people – most of whom still influence the company's capabilities today. They provided a sound foundation that enabled us to offer services to companies outside the Martin Bauer Group as well.

The main pillars of our business have not undergone any fundamental changes over the years: they still include contaminant analysis and quality control of herbal starting materials and preparations to the same extent as project management and marketing authorisation dossiers, as well as advice and expert's reports on plant-based products. Some things have changed, however; first and foremost the increasingly stringent requirements to be met on all sides.

This is the main reason why we at PhytoLab have made security the focal point of our thoughts and actions. We have been able to improve product safety continuously over the past few years, for instance, by extending the number of substances under surveillance within the framework of pesticide, heavy metal and mycotoxin analysis. Apart from this, we have also established new experimental and analytical methods to examine other contaminants, such as acrylamide, nonylphenol and PAHs.

Considerable financial investments were needed in order to acquire the laboratory instruments and facilities required for all of this. Our equipment pool gradually grew to such an extent that – in spite of using the laboratory formerly belonging to Addipharma in Hamburg – a new building had to be erected in Vestenbergsgruth. This means that we shall have another 1200 m<sup>2</sup> laboratory area available to us in 2004. Incidentally, our service spectrum has also been augmented over the years. One example that is becoming increasingly crucial is the verification of plant-based pharmaceuticals' efficacy and safety. The importance of foresighted risk management is demonstrated by the most recent turbulences surrounding such tried-and-trusted phytopharmaceuticals as kava-kava or St. John's wort. We can also offer a variety of services to our customers in international markets within the framework of the global nature network, a valuable benefit for many companies in the light of the pending eastward expansion of the European Union.

PhytoLab has become a strategic partner with a widely diversified range of services and international orientation. This development would certainly not have been possible without the loyalty of our customers and I would like to take this opportunity to promise you that we will continue to do everything in our power to comply with all of your requirements and wishes in the future. I am looking forward to another 10 years of our shared success.

Best regards

Dr. Lothar Kabelitz  
Managing Director



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# Experience

# Reliability

## Security is in our nature

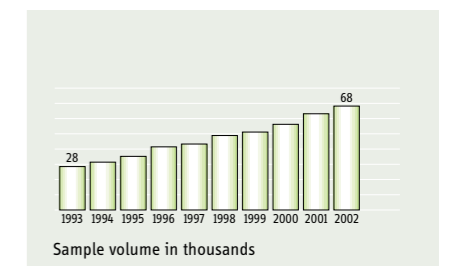
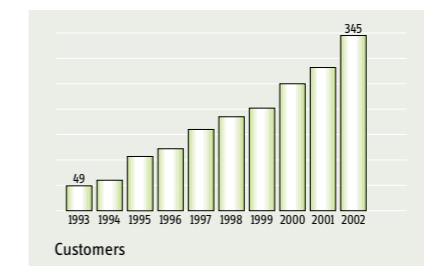
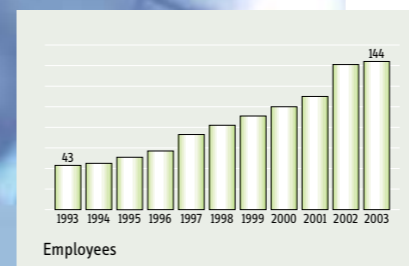
We have been your full-service laboratory, developing, analysing and registering your plant-based products, for 10 years now. Right from the very beginning, all of our activities have been focussed around one central aspect: maximum possible security for our customers' foodstuffs, medicinal products and cosmetics. A criterion that you will also be able to apply to our work in the years to come. After all, security and dependability are the most important things that we can offer you.

### Quality across the line

Any company wishing to launch products onto the food or pharmaceutical markets needs to be absolutely certain that the herbal components are pure and of a high quality standard, and requires detailed information about their effects. You can rely on PhytoLab completely in this respect. This is because we conduct tests on official reference samples of herbal drugs and foodstuffs in our capacity as an independent laboratory company, accredited in accordance with Directive 93/99/EEC. In addition to this, PhytoLab has been acknowledged as a testing laboratory in accordance with § 14 paragraph 4 of the German Drug Law (AMG). Customers also regard our membership of the nature network – the global alliance of strong brand names and resources for everything related to plants – as being a guarantee of quality. This means, for example, that we can acquire the most diverse raw materials of the desired quality and constitution directly through our partner company Martin Bauer for the development of new products. An excellent basis for maximum product safety and just one example of the many synergetic effects within the nature network.

### Continuously reliable

Continuity is essential to dependability. That is why we have taken up the course of preserving and protecting traditions. A philosophy that we live out with success: our staff enjoy working for PhytoLab. This is the only way of ensuring that know-how expands and provides the only basis for a cooperation based on trust with our customers – another important aspect of security. The Management of PhytoLab has also remained unchanged since the laboratory company was founded ten years ago.



The high esteem in which we hold on-going relationships is expressed in the sustained positive development of our business. We enjoy the trust and confidence of more than 345 customers and are happy to draw attention to the continued growth in our sales figures. 68,000 samples examined in 2002 alone not only reflect the general growth in the market for herbal products, this figure also documents the reliable and convincing quality of our work. And it doesn't stop there. Increasing internationalisation, new markets in Eastern Europe and in the USA open up a multitude of new opportunities for PhytoLab customers and we can help you to use these to best advantage. We take time for you and your ideas.

### Competence and know-how

Our pleasure in innovations and our courage to explore new avenues both thrive on our consistent, dependable corporate culture. We are therefore able to take up new trends quickly and implement them constructively for our customer, one example being the demand for herbal dietary supplements. Or the increasingly frequent requests for verification of specific preparations' efficacy, and we have established our Pharma Service department to deal with these. Our sound background knowledge of the pharmaceutical market has put us in a position in which we can give our customers valuable impetus for the development of their products and advise them with the backing of specialist medical competence for the planning, implementation and evaluation of studies on efficacy and safety.

We owe a great deal of the credit for our success to the experienced and competent members of our staff. They include more than 25 scientists who, apart from working for us, are also actively involved in various associations and expert committees, publish scientific papers and are often asked to give lectures at international phytopharmaceutical conferences. It goes without saying that all of our employees have an in-house library at their disposal, which is kept up-to-date with scientific advances, as well as direct access to professional on-line databases. Incidentally, so do our customers.

We also benefit from the synergetic effects within the nature network as far as "know-how" is concerned. This alliance offers us a means of establishing and maintaining contacts with authorities and scientists all over the world and ensures that we are familiar with the regulations that apply in your potential markets. This means that we can guarantee complete security – on international level as well – for all of your current and future projects.

### Technological leadership too

High-quality equipment and facilities are required for sophisticated services in the laboratory sector, of course, as well as qualified personnel. Our laboratories are therefore equipped with top-quality, state-of-the-art instruments and machines – meeting the technical prerequisites for maximum safety and security.

We attach maximum importance to having innovative machines and instruments. ICP-MS technology, for instance, enables us to analyse up to 40 different metals simultaneously in a single measuring run and saves both time and money. Our video documentation systems supply you with graphic evaluations of thin layer chromatographic analyses and microscopic examinations. This means that, apart from analysing your substances, we also generate exact images of the results. Our HPLC-MS/MS allows us to examine the molecular structures of the compounds which we separate chromatographically, giving us security when identifying active substances and contaminant loads. Another technical highlight: our liquid-liquid partition chromatography unit in Hamburg. It enables us to manufacture reference substances of the purest quality for you at an affordable price.



HPLC-MS/MS inlet

# Innovation

# Knowledge

# Service

# Trust

## Modular full-service concept

PhytoLab customers have been appreciating the range of our service spectrum for many years now. Our activities are primarily focussed on:

- Development
- Analysis of active substances and contaminants
- Development and validation of methods
- Stability testing
- Reference substances, also according to customers' requirements
- Efficacy and safety
- Regulatory affairs

At PhytoLab you receive all services from a single source. In addition to this, you enjoy the benefits of holistic project management. If you wish, we can take care of the complete project, including stability testing, analytical expertise and the text on the packaging.

We prepare modular quotations for services from our extensive spectrum and process them quickly and reliably. You can then choose the modules that you need because, after all, it is your specific wishes and requirements that count. Or to put it another way: we won't let you go as long as you still have a problem that hasn't been solved. And that's another fact.

## Partnership for your future

We attach great importance to trust and partnership. You will therefore be accompanied by the same contact person throughout the duration of your cooperation with PhytoLab. This prevents information being lost and we will be able to help you find solutions tailored to your own individual requirements quickly and reliably.

The PhytoLab idea of partnership also includes thinking and acting with foresight. Based on a spirit of partnership, you can be sure that the strategic advice that we give you today already allows for specifications and regulations that will not be relevant to you until some time in the future. As you can see, your safety and security make up the baseline for every detail at PhytoLab. This is because we want both of us to be successful.

# PhytoLab – certainly the right choice.

For us, being a pioneering company is both an obligation and an incentive. We have just one target in mind as far as development, analysis and registration are concerned: the future success of your products and of your company. We therefore believe that creativity must also be coupled with responsible far-sightedness. It is our experience that makes the technical equipment perform in the way that our customers trust.

## Development

We are living in a time of upheaval. Everything is being called into question and the dividing lines between the ever-increasing generic names of health products are becoming blurred: drugs, traditional drugs, medicinal products, supplementary balanced diets, dietary supplements, functional foods. The markets are opening up and are thirsty for new ideas. Orientation is becoming increasingly difficult. In this situation, both imagination and common sense are required for the development of new products.

PhytoLab is at your disposal here in its capacity as an experienced and reliable partner. Our philosophy has always advocated customised solutions. We are therefore used to joining forces with our customers to produce tailor-made, well thought-out product concepts. Technology, Analysis, Medicine and Registration work hand in hand for this. We can offer you complete project management, from the concept via product development, right through to registration – aiming to offer the right plant in the right form of administration with the right claim based on sound documentation – to ensure the reliable marketability of your product.

## Analysis

Identity, purity, content and technological parameters determine the term “quality” to an equal extent for plant-based drugs and foodstuffs. Quality cannot be “analysed into” a product, but the analyst must be a master of his profession in order to be capable of testing quality reliably and accurately. And to be initially capable of describing and defining properties that are important with respect to the benefits of a product in a sensible manner. Apart from outstanding instruments and equipment, the analyst also requires extensive experience and an in-depth knowledge of potential problem areas. From the origin and constitution of a drug, via processing, extraction and manufacture of the finished product, right through to the primary packaging. The desired

quality can only be assured on a long-term basis when all of the factors that are relevant within the framework of testing raw materials and finished products or stability tests are taken into consideration. Identity or sensory tests, content quantitation of specific markers and ingredients affecting efficacy, microbiological purity, testing for pesticide residue or mycotoxins by means of GC-MS or HPLC-MS/MS – with more than 68,000 samples of herbal starting materials and products tested every year, PhytoLab has the equipment and experience required for reliable and professional assessment of the quality of plant-based products.

## Development and validation of methods

There's no substitute for the know-how of experienced personnel, particular when it comes to the development of methods, whereby PhytoLab uses modern software as a tool to make the method optimisation process even more efficient. Method development must always go hand in hand with validation. Apart from the frequently over-estimated reproducibility factor, such aspects as the method's robustness to slight changes or the stability of sample and standard solutions also play a very important role. We therefore regard method validation as being a great deal more than simply running through the minimum requirements of ICH Guidelines. For us, it refers to a continuous in-depth examination of the requirements to be met by the individual product, in the form of a close cooperation between the Regulatory Affairs

department and Laboratories, preceding and accompanying practical implementation. Valid methods are not only needed for verification purposes but are also required to define specifications. We are active members of various committees, such as the Pharmaceutical Biology Committee of the German Pharmacopoeial Commission, and as such contribute towards ensuring the practical feasibility of specifications and methods. At international level, as well, within the framework of the joint working group established between the AOAC (American Association of Analytical Chemists), the FDA (Food and Drug Administration) and the NIH (National Institute of Health) in the USA, whose work is incorporated into the monographs of the USP-NF. You can find a list of the methods published by PhytoLab at

## Stability tests

Hardly any other area of quality documentation has been subjected to such increasingly stringent requirements in recent years as stability testing. The organisation, performance and evaluation of stability tests for phytopharmaceutical products has become a highly complex field and requires intensive coordination between Regulatory Affairs and Stability Control with respect to content and organisation. Virtually all important aspects of quality documentation play a role in this context, beginning with the testing of starting materials for the stability batches.

The robustness of analytical methods to slight fluctuations in material quality and equipment parameters, as well as the analyst's particular way of working, has become an extremely important factor in terms of stability testing. The reference standards used in stability tests may also be subject to changes while testing over a longer period. The range of the reference substance available at the beginning of a stability test may not extend over the entire test period, for example, or the reference substance itself may undergo qualitative changes during the period of use. Reference standards therefore constitute an important factor, which we already take into consideration as early as the planning stage for your stability studies.

[www.phytolab.com](http://www.phytolab.com)

## Reference substances

Nowadays, the qualitative description and testing of herbal drugs is fundamentally based on the “marker substance” concept. Nevertheless, the trend towards singling out and praising bio-active secondary substances is giving rise to the need for analysis of specific constituents in other plant-based health products as well and, with it, an increasing demand for herbal reference standards. PhytoLab has also been manufacturing and supplying reference substances since the Addipharma laboratory in Hamburg was integrated in 2001. However, in our capacity as a service provider, we do not simply regard the

pure herbal substances produced as the result of a complicated manufacturing process as being just merchandise. Being both supplier and user of reference substances, we are familiar with the problems presented by the practical handling of reference substances from our own experience. We therefore offer our customers complete packages, comprising substance, (registration) documentation and advice, right through to the project-specific isolation and structural characterisation of new markers that are tailored to their individual requirements. You can find details of our analytically pure reference substances at

[www.phytolab.com](http://www.phytolab.com)



## Efficacy and safety

The last ten years have not only been marked by the creation and establishment of quality standards in Germany. Authorities and market participants are now concentrating their attention on the efficacy and safety of herbal products to an increasing extent. Medical competence has become a crucial factor in all stages of the process, from development, via the registration procedure and marketing strategy, right through to sustained maintenance of marketability.

Whatever your needs in terms of pharmacological toxicology or bibliographically based clinical reports, pharmacological screening for the development of herbal agents, toxicological testing within the framework of phased planning methods, controlled clinical studies for an innovative product or periodic safety update reports (PSURs), our Pharma Service department will provide the medical and/or pharmaceutical competence to support you in all issues related to the efficacy and safety of your plant-based products.

## Regulatory Affairs

A comprehensive knowledge of the registration requirements for phytopharmaceuticals is one of the core competences of PhytoLab. This does not mean that we sell ready formulated dossiers “off the peg”, however, but exclusively prepare customer-specific documents and keep them up-to-date with rapidly changing requirements.

Irrespective of whether national or international procedures are involved, we prepare the documentation necessary to ensure that your product is marketable and remains that way. The registration requirements therefore constitute the central theme that runs through a project from the product design, via the development and stability test, right through to compilation of the complete dossier.

Even if your products are not of a pharmaceutical nature, there are many requirements to be met in order to ensure the marketability of a valuable new product. This is why there are competent food chemistry and food legislation representatives at your disposal in the form of our state certified food experts in Registration.





Curriculum vitae: Prof. Dr. med. Karin Kraft

1952: Born in Göttingen

1980: Degree in human medicine, doctorate (Dr. med.)

1980 – 1983: DFG scholarship; working at the Institute for Clinical Biochemistry at Bonn University initially, before moving to the Institute for Pharmacology at Heidelberg University

From August 1983: Working as a doctor and scientist for the Medical Polyclinic at Bonn University

1989: Internal specialist, head of the hypertension outpatient clinic

Since 1992: Senior physician at the Medical Polyclinic in Bonn: Establishment of the naturopathy outpatient clinic

1993: Qualification as university lecturer (internal medicine)

1999 – 2000: Head of a scientific project at the rehabilitation clinic in Bad Doberan

From 2001: Continued employment as senior physician at the Medical Polyclinic in Bonn

Since 1.12.2002: Professor of naturopathy at Rostock University

Focal points of research: phytotherapy, research into the care provided within the framework of naturopathic rehabilitation

## Quo vadis, phytotherapy?

Guest paper: Prof. Dr. med. Karin Kraft

### Developments in the health service

Glaring structural weaknesses and the consequences of demographic development led to a situation in which the quality of the German health service was classified as merely average within the framework of the OECD comparison, in spite of a total outlay of 226 billion € for health during 2001. Consolidation of preventive measures and the elimination of excess and inappropriate medical care, in particular, are being discussed in an effort to improve the situation.

According to a recent EMNID survey, 57% of health insurance policyholders would like to have more responsibility and involvement in their own health care. However, people are still showing a preference for passive measures, such as taking medication or massage therapy, for example, which can be consumed with the least possible personal effort. This is clearly illustrated by the current boom in dietary supplements, which also include extracts from medicinal plants and preparations of these, in the USA and in many other countries. It is absolutely essential that such preventive measures are supplemented by active measures to a greater extent, particularly including exercises and sport therapy.

Incorrect and excessive care costs around 13 billion € in Germany every year and can be attributed to a number of causes. The health insurance companies are not informed about the exact nature of the services charged by each registered doctor for an insured patient and are therefore demanding greater transparency. In hospitals handling acute diseases, the average bed occupation period of 10.7 days is much longer than in other countries, whereas the bed capacity is 71% higher than the OECD average. This category also includes what is referred to as disease mongering, i.e. the marketing of therapies for minor functional disturbances and psychological problems, which are souped up into diseases. In this respect the health service is expected to pay the costs of social dysfunction by applying medical criteria to our normal daily lives.

### Consequences for naturotherapy and phytotherapy in particular

Nature-cure therapies are frequently the first thing that comes to mind when asked about incorrect and excessive care. This is not justified, however:

1. Because the health insurance companies do not reimburse the costs, many patients pay for nature-cure therapies themselves and considerable savings are achieved as a result of this, even if the exact amounts are unknown.
2. Around one billion packets of drugs are sold over the counter every year, corresponding to 60% of all drugs supplied by the trade, whereby more than two thirds of these are bought without consulting a doctor beforehand, i.e. prescribed by the patient himself. This led to an estimated saving of 2.45 billion € for the statutory health insurance companies (GKV) in 2002.
3. Phytotherapeutic agents are frequently administered for minor illnesses and, as such, are not refundable.
4. With OTC drugs costing 8.16 € per packet on average, the costs are frequently covered by the additional payment ruling.

The drugs associated with specialist therapeutic approaches, including phytotherapy, have been classified according to the appendix of the so-called positive list, which contains the drugs which are refundable by the statutory health insurance companies (GKV). The fact that some herbal drugs appear in the main body of this list and have therefore fulfilled the most important admission criterion – positive proof of efficacy – illustrates their excellent position in terms of scientific evidence. The positive list was also intended as an instrument to combat disease mongering. In the meantime, however, the German government and the opposition have instead passed a resolution to remove all OTC drugs from the list of those refunded by the GKV within the framework of the discussion leading to consensus. Incidentally, these drugs do not require prescriptions because the associated side effects and risks are particularly low. The intention is to make refundability for children up to 12 years old and adolescents with developmental disorders an exception to this ruling, as well as patients with certain, as yet unspecified serious diseases. The hoped-for savings are expected to amount to around 1 billion €. This is questionable, however, as the doctors are then more likely to prescribe ethical drugs which therefore have more side effects and are usually more expensive. Whether the patients actually take them is another question. At all events, the consequences are more far-reaching:

1. Phytopharmaceuticals will be affected to a greater extent than the drugs associated with other types of therapy (anthroposophic or homeopathic medicines), which will continue to be refundable without having to give details of the indications.
2. Medical competence in working with these tried-and-trusted medicinal products will get lost, particularly in the field of phytotherapy, because interest is not being upheld by well organised groups of doctors as is the case for anthroposophic or homeopathic medicines.
3. Hardly any phytopharmaceutical research will be conducted because of the anticipated financial cuts.
4. The strict segregation of phytopharmaceuticals and dietary supplements brought about by the German Drug Law (AMG) will be weakened in the public awareness. The detrimental effects of this are particularly pronounced for monograph-conforming phytopharmaceuticals, which are occasionally referred to as “rational” medicines and are approved for specific indications and/or diseases. They are therefore subject to much more stringent quality control and have to comply with cost-intensive requirements.
5. Economic considerations will often motivate the consumer to resort to “traditional” phytopharmaceutical products, which contain a lower dosage but are seldom clinically tested, as he is unaware of the evaluation criteria and the differences between the two groups of phytopharmaceuticals.

What we should really be asking ourselves is whether it is acceptable to outcast drugs which have minor side effects or none at all, or their manufacturers, for having achieved this desirable state by excluding them from the list of refundable drugs.

## Phytotherapie as an important element of integrative therapeutic concepts

According to a survey conducted by the Allensbach Institute in 2002, more than 80% of the population showed a preference for natural remedies. As therapeutic concepts which are not in accordance with the patient's wishes are frequently not pursued, or only in part – particularly where long-term therapy is needed to treat a chronic disease – the patient's cooperation is actually the factor which decides whether the therapy is successful or not. As indicated by a number of studies, especially in the USA, integrative therapeutic concepts, including the use of such natural remedies as phytopharmaceutical products, are becoming increasingly popular among patients.

Unless the diseases are potentially fatal, doctors generally try to offer integrative therapeutic concepts. Nevertheless, they do have to orient themselves to guidelines which now exist for a very large number of different diseases as the basis for treatment. These guidelines primarily allow for the results of evidence-based medicine, i.e. the results of clinical studies which are often concerned with the treatment of acute ailments. Natural remedies are rarely mentioned, even if informative studies exist, as is the case for many phytopharmaceuticals. At the same time, such guidelines suggest that a lack of evidence for a drug's efficacy is the same as a lack of efficacy. Apart from this, the increasingly stringent requirements to be met with respect to proving the efficacy of medical treatment are also resulting in the gradual elimination of previously refundable, cost-effective methods of treatment. Because of the cost-intensive requirements, hardly any medium-sized company is capable of funding the performance of clinical studies, e.g. to prove efficacy, which legislation now requires for those phytopharmaceuticals which are to be registered in accordance with § 105 of the German Drug Law (AMG). Nevertheless, the so-called rational phytopharmaceuticals offer an excellent solution for combining with other therapeutic measures and are exerting a positive influence on acceptance. Medical experience must therefore be the deciding factor for development of a therapeutic concept and guidelines should merely play a supporting role.

## Safety of phytopharmaceutical products

A few years ago, government research sponsorships for nature-cure therapies were established in certain countries, including the USA and England. The high prices of drugs and large deficits in the funds available to the national health service led to the emergence of an enormous market for nature cure and complementary therapies in those countries. Furthermore, many parties were heard to express their fears that such therapies would detrimentally affect the medical care given to the people and would even jeopardise their safety.

Compared with chemically defined drugs, the safety aspect played a very insignificant role as far as phytopharmaceuticals until a few years ago. The few, mostly harmless side effects were known as a result of decades or even centuries of use. This was also the reason for their being available over the counter. Nevertheless, in recent years, reports of side effects associated with numerous medicinal plants have been appearing in scientific journals. Most of these are sadly lacking, however, when subjected to closer scrutiny:

1. The characterisation of the used herbal extract is often missing and not only for phytopharmaceutical products which are used as dietary supplements. Incidentally, because of the generally low level of official monitoring, dietary supplements frequently contain substantial quantities of undeclared constituents.
2. As a rule, there is no analysis or description of nutritional habits which can exert a considerable influence on the break-down of drugs in the body.
3. The simultaneous administration of mostly chemically defined drugs, which in some cases can also be responsible for the described side effects, is rarely discussed.
4. The construction of connections between the administration of a herbal drug and the undesirable side effect is often incomprehensible. In many cases, the connection between taking the phytotherapeutic agent and the occurrence of the side effect could be purely incidental.
5. There are considerable gaps in the medical description of the case.
6. The treatment with the product in question was not repeated under controlled conditions in order to verify the reproducibility of the effect. Ethical problems play an important role in this respect, however.

The many general papers based on these case studies, which have been published in the meantime, should therefore be viewed with a very critical eye. As yet, there is no evidence to support the frequently made assertion that many more side effects occur but have not been noticed sufficiently by doctors or patients, in spite of the fact that patients pay more attention to tolerance and compatibility when they are paying for the medicines themselves.

The reports from the spontaneous adverse effect reporting scheme play an important role in assessing the relationship between benefits and risks in addition to the case studies. The unfortunately often poor quality of these reports – not only for phytopharmaceutical products – should provide sufficient grounds for the generation of internationally accepted guidelines for adverse effect reports relating to drugs. The revocation of the German licence for extracts taken from the kava-kava rhizome in June 2002, for example, was based on case studies and spontaneous reports of liver damage, massive in part, virtually all of which proved to be fairly paltry when examined more closely by acknowledged hepatologists. The revocation is maintained in spite of this. This means that only chemically defined pharmaceutical products are available for the treatment of anxiety disorders in Germany, most of which with considerable side effects.

Another, very well-known medicinal plant, St. John's wort, has proven effective in the treatment of mild to moderately severe depression in a number of reputable clinical studies. The majority of patients show a preference for the OTC St. John's wort extract for no other reason than the extremely minor subjectively perceived side effects, compared with those experienced with those encountered by patients taking chemically defined anti-depressants. However, influential effects of St. John's wort preparations were recently discovered in one of the liver's intrinsic systems, leading to a situation in which certain drugs, such as ciclosporin, anti-coagulants or Digoxin, the cardiac stimulant, are broken down more rapidly and their efficacy is restricted. Studied more closely, however, it would appear that many of these interactive effects – some only generated at experimental level – are virtually irrelevant in therapeutic terms and are only caused by certain, highly concentrated preparations. Incidentally, the not always critical echo in the trade journals was remarkable, as was the response to these reports in the normal media.

These examples are representative for many other herbal drugs, because it has now become evident after in-depth testing that there is seldom conclusive evidence for the assumption that phytopharmaceutical products often have serious side effects, in spite of intensive research in the field of adverse effects.

## Looking into the future

Despite constant improvements in the efficacy documentation for a large number of herbal drugs and a risk profile that is still extremely favourable in spite of intensive research, the current situation regarding phytotherapy cannot be described as favourable, due to the regulative measures in the health system planned by the government. Nevertheless, the diverse qualified contributions to quality assurance and documentation of the efficacy of phytopharmaceutical products made over the last few years cannot be simply ignored.

One way of viewing the current development in the health service is as a battle between two scenarios: high-tech medicine representing increasing efficiency but accompanied by much higher costs in the first of these, whereby the real benefits must be validated in a better manner and there is still the discussion on ethical issues. The alternative scenario regards human health as a whole and puts the psychosocial competence of the patients in the foreground. This medical concept uses nature cure and natural remedies, "alternative" therapeutic methods and psychosocial forms of treatment. Still better evidence of efficacy must be demanded here in the future.

This battle will eventually be decided by health-conscious citizens and patients, whereby it will basically be a matter of defining the boundaries for the two scenarios, both of which have their justification. Everybody will be forced to assume more personal responsibility for themselves to the extent demanded by the health politicians by being required to pay a share of the health costs and this will also ensure that the patients determine the nature of the service they are given. The trend of a fundamentally changed understanding of health will be superimposed onto this: in the future, health will be regarded as being a personal competence, i.e. it will become a virtue. As a consequence, patients will assume more and more personal responsibility for their health and will be more critical in questioning the therapeutic proposals made by the doctors. This will ensure that the therapeutic guidelines are repeatedly subjected to acceptance testing. The relationship of dependence on the doctor will be replaced by a partnership based on mutual respect and trust, reinforcing the position of the family doctor to a particular extent. The statutory health insurance companies will support this development vehemently, as they will be hoping to save costs and possibly also to have better control of curative measures. Because of the high level of acceptance among the population, the many documents providing evidence of its efficacy and, last but not least, because of its documented high quality standard, phytotherapy will survive the current crisis if it recognises and uses the considerable chances offered by this development.

# Contaminants through the ages

## Is the quality of our food declining or are we adopting a healthier lifestyle?

Dr. Lothar Kabelitz

We have frequently been on the receiving end of terrifying reports on the poor quality of foodstuffs in recent years. Nearly all types of food were affected, beginning with Salmonellae in pasta, acrylamide in crisps and chips and ochratoxin in liquorice, and going through to poisonous substances in tea. The press admittedly survives on sensational reports, but we should ask ourselves whether it is right to instil doubt in the consumer, particularly as he is unable to do anything to change the situation.

We should also consider the effects of this type of reporting; after all, if the consumer changes his behaviour, for instance, and stops drinking herbal tea for fear of some sort of contaminants, then he will replace it with something else that is likely to hold other dangers. Nobody could wish for this to happen as herbal teas are not only safe, refreshing beverages, but also have properties which are conducive to health. Responsible reporting should also concern itself with its consequences, particularly where the health of the consumer is involved.

Another question that emerges here is whether the information propagated by the press is really new. The reports often refer to familiar things which are featured as sensations. The consumer is unable to judge whether something is to be regarded as dangerous or not. Could it be that the idea of a healthy lifestyle has changed? What is referred to as prudential consumer protection changes our world completely if it does not originate from responsible, sensible members of the community. I would like to illustrate what this is all about with reference to a few examples from my work at PhytoLab.

### Microbiological quality of herbal tea

Requirements for the microbiological purity of ready-made herbal drugs were published for the first time in the German Pharmacopoeia of 1991 (DAB 10). A distinction was made between drugs used in medicinal tea, where the aerobic count is reduced when brewed in boiling water (category 4a) before drinking, and other preparations containing comminuted herbal drugs (category 4b). The total viable aerobic count may amount to 10 million organisms in category 4a, but only 100,000 organisms in category 4b; the "absence of Salmonellae" requirement applied to both categories.

These requirements were derived from microbiological data from previous years, but the regulatory background has changed in the meantime. Instigated by the Food and Drug Administration (FDA), a discussion began concerning the risks of treating drugs with ethyl-

ene oxide and led to a prohibition on such drugs throughout Europe in 1990. Ethylene oxide leaves traces of mutagenic ethylene chlorohydrine in the treated material. The USA and Canada have tightened up their regulations dealing with ethylene oxide and ethylene chlorohydrine residues, while the EU has imposed a ban on ethylene oxide treatment.

The microbiological requirements of DAB 10 have therefore given rise to a special problem situation. Enteric bacteria, such as Salmonellae are naturally ubiquitous. Snails crawling over plants, birds and locusts flying over plantations, foxes, hares, geese, ducks etc.; all of these creatures can cause plants to become contaminated with Salmonellae, which means that Salmonella contamination of herbal tea is unavoidable.

Based on an evaluation of 17,000 samples of herbal tea drugs, each weighing 25 grams, analysed by PhytoLab, it is true to say that, on average, more than 3% of the samples contained Salmonellae. This correlates with an "Opinion of the Scientific Committee on Veterinary Measures relating to Public Health on Salmonellae in Foodstuffs" dated 14th - 15th April 2003, which says that the frequency of positive Salmonella findings in herbs and spices amounts to 1%, compared with a frequency of 10% in oriental spices and vegetables. This means that Salmonella contamination is not restricted to just a few isolated plants, but can occur in all herbal drugs.

The Microbiological Expert Group of the German Pharmacopoeia has been tackling the Salmonella problem. The requirement for absence of Salmonellae was dropped without replacement in the 1996 DAB. According to the comments published on the 1997 DAB: "Category 4a designates herbal drugs to which boiling water is added prior to use". Around 99% of the bacterial flora found in plants and parts of plants is deactivated when treated with boiling water. Salmonellae are sensitive to heat; they must therefore only be excluded from those drugs which do not undergo treatment with hot water. This ruling was adopted in the European Pharmacopoeia with suitable comments in 1997 and still applies today.

It is a very different matter in the food sector. In its 1998 specifications, the European Herbal Infusion Association (EHIA) stipulates that herbal tea and fruit tea must be tested for the presence of Salmonellae. The fact that this gives rise to problems becomes evident when one considers that, based on the test of 25 gram samples, 1 - 10% of the drug lots contain Salmonellae. When testing larger numbers of samples in each lot, the likelihood of positive Salmonella findings increases according to the number and size of the samples.

In statistical terms there is also a problem in meeting a zero requirement in that positive Salmonella findings can not be cancelled out by any number of negative findings.

Now that ethylene oxide treatment for herbal and fruit teas is prohibited in Europe and there is a ban on treatment with ionising radiation in this country, we are definitely facing a problem with food teas in Germany. Antimicrobial treatment can only be performed on a few tea drugs without considerable detrimental effects on the quality. We became painfully aware of this unfortunate situation this summer.

The food supervisory body decided to screen food for Salmonellae because of a few cases of salmonellosis and, in the course of this, positive findings were recorded in herbal teas. There was no evidence for a direct connection between the consumption of tea or infusions and salmonellosis in any of the cases. Nevertheless, district administrations ordered the recall of herbal teas for a complete range of products because of positive Salmonella findings, as instructed by the competent state ministry.

If at all, the cases of salmonellosis could only have occurred as a result of not preparing the herbal tea properly, which means that the tea was made without boiling water. Although this is indisputable, the authority draws attention to predictable improper use. Authority and industry are unanimous in their opinion that public relations and consumer education work is necessary to ensure that herbal teas are prepared properly.

### Mycotoxins in herbal drugs

Mycotoxins are secondary metabolites of moulds. They remain stable when subjected to heat to a great extent and are not usually destroyed during the processing of foodstuffs. Symptoms of acute mycotoxin poisoning include damage to the liver and kidneys, the central nervous system, the skin and mucous membranes. However, they may also be deleterious to the immunological system and hormone balance. Mycotoxins may cause trembling, spasms and death without any visible cause. Quantities of toxins which may not trigger any acute symptoms may cause carcinogenesis, genetic damage or embryonic deformities. The discovery of mycotoxins has frequently been preceded by a disaster, as was the case when more than 100 000 turkeys died of Turkey-X disease in England in 1960, which was triggered by aflatoxins produced by species of *Aspergillus*. Mould-infested turkey feed was responsible for the disease. The fact that

aflatoxins produced by moulds can also be present in human foodstuffs and cause diseases only became evident when the accuracy of analytical methods had improved and offered a means of examining a large number of foodstuffs and food constituents.

1976 saw the first mycotoxin directive being published in Germany with the following maximum concentrations: 5 µg/kg aflatoxin B1 and 10 µg/kg total aflatoxins. The maximum levels were reduced to 2 µg/kg aflatoxin B1 and 4 µg/kg total aflatoxins in 1991. These are completely at odds with the situation in India or Israel, where people may consume food containing 60 µg/kg, and the USA where 20 µg/kg aflatoxin is tolerated.

As far as Europe is concerned, aflatoxins are "imported" toxins. The *Aspergillus* species require temperatures of between 25 and 40° C to produce toxins, which means that, in spite of the toxin-producing moulds presence all over the world, it is the products from subtropical and tropical regions which are primarily at risk. The corn-producing industry in the USA is affected, for example, as well as in tropical countries. So are harvested products, such as oil-bearing seeds and nuts, peanuts, almonds, pistachios, poppy and sesame seeds, as well as rice, millet and broad beans. Pistachios are currently among the foods with the highest contaminant concentration of aflatoxin B1. But drugs used for medicinal purposes are also jeopardised, such as senna pods from India, nux vomica, ginger, figs, peppers and cayenne pepper.

Ochratoxin is produced by species of *Aspergillus* and *Penicillium*, which are found in such crops as corn, oats, barley, wheat, rye, buckwheat, rice, millet, soya beans, peanuts, Brazil nuts and pepper. Residual quantities of ochratoxin have recently also been identified in coffee, beer and wine, as well as buckwheat, raisins, lime blossoms and, above all, in liquorice root. However, the heat resistance of mycotoxins is such that ochratoxin is also present in products made from the liquorice root, as well as in products treated with liquorice extract, such as pipe tobacco. Maximum levels of ochratoxin A were stipulated in EC Directive 466/2001. Nevertheless, it is still interesting to note the speed at which mycotoxin research has been progressing since the end of the 1990s. There are now more than 9 mycotoxins to be examined in the future. It would go beyond the scope of this article to go into all of the relevant mycotoxins here, particularly as there is insufficient data concerning the prevalence of many of them.

However, PhytoLab is already testing numerous samples for other mycotoxins mentioned in the opinions published by the EU's Scientific Committee on Food within the framework of the strategic quality management of the MB Holding. These are not only concerned with aflatoxins and ochratoxin, but also patulin, for which the EU published a maximum concentration recommendation in August 2003, as well as the Fusarium toxins fumonisin, zearalenone and Fusarium toxins combined under the heading trichothecenes like nivalenol, deoxynivalenol, T2-toxin and HT2-toxin.

## Heavy metal concentrations in herbal drugs

Heavy metals get into plants used to produce herbal and tea drugs as a result of the nature of the soil, the climate and the irrigation. Since 1986, the Central Registration and Evaluation Office of the Federal Public Health Agency for Environmental Chemicals (ZEBS) has been publishing guideline values for the concentration of heavy metals in herbal products. In 1987 saw the ZEBS specifying a guideline value of 0.3 mg/kg for linseed, a drug described in the DAB for the first time because a high concentration of cadmium was determined on the basis of market observations. Since then, a distinction has been made between small-grain linseed, which complies with the requirements of this guideline, and large-grain linseed, which can only be used for technical purposes because of its high cadmium content.

On 17th October 1991, the then Federal German Minister for Health announced the following maximum concentrations of heavy metals in drugs of plant or animal origin in a draft recommendation: 5 mg/kg of lead, 0.2 mg/kg of cadmium and 0.1 mg/kg of mercury. Exceptions were defined for the maximum levels of cadmium in certain plants. By publishing the extensive data collected by a Contaminant Working Group within the German Association of Drug Manufacturers (BAH), the authorities could be persuaded that higher values were tolerable in starting materials for pharmaceutical preparations as long as the preparations of the drugs complied with the requirements of the contaminant ruling.

When analysing the data, it became evident that special problems were encountered with the concentrations of heavy metals in certain drugs. It was discovered, for example, that St. John's wort and willow bark actually enrich cadmium. The 90th percentile of the cadmium content amounted to 1.3 mg/kg of St. John's wort and 1.8 mg/kg of willow bark. These plants have since been cultivated in soil with a particularly low cadmium content.

The European Pharmacopoeia (Ph. Eur. 4.4) contains a monograph on the subject of heavy metals in plant-based drugs and fatty oil, describing methods of testing for 8 heavy metals, namely cadmium, copper, iron, nickel, lead, zinc, arsenic and mercury. We must expect limits to be defined for these metals in the Ph. Eur. in future, which is why it is necessary to have a collection of data. Future maximum levels should be oriented to feasible limits. The European Pharmacopoeia has defined limits for one drug on the basis of the BAH database, and that is bladder wrack, with 90 mg/kg for arsenic, 4 mg/kg for cadmium, 5 mg/kg for lead and 0.1 mg/kg for mercury. This paves the way for the definition of maximum levels in drugs in the years to come.

Maximum concentrations of lead, cadmium and mercury in herbal products have been specified in a binding manner in EC Ruling No. 466/2001. However, it looks as though considerably more heavy metal concentrations will have to be monitored in the future.

## Residual quantities of pesticides in herbal drugs

When looking through an analytical certificate for chamomile flowers issued by the Institute for Applied Botany at Hamburg University in 1993, I noticed how few pesticides were tested for in those days. The certificate contains the results of tests conducted to determine 24 pesticides. That was the usual scope of testing for plant-based drugs then for a number of laboratories. Residual quantities of pesticides in drugs presented relatively few problems at that time as § 1 (2) of the German Ordinance on Maximum Permissible Residual Quantities (RHmV) provided for the highest permissible maximum concentration of each substance when analysing spices and condiments, raw coffee beans, tea, infusion products and oil seeds, when a specific maximum level was not expressly stated. I also considered that to be a sensible course of action as infusions account for less than 0.1 % of the average consumption of herbal foodstuffs in the official German shopping basket.

The ruling laid down in § 1 (2) of the RHmV was rescinded when the ordinance was reformulated and adapted to EC legislation in 1994. A procedure that differed completely from those for all other foodstuffs was regarded as being no longer appropriate. There was and still is no provision for application of the majority of substances to the foodstuffs laid down in § 1 (2), which is why the pesticide manufacturers are required to conduct field trials, where necessary, in order to derive and define maximum concentrations for specific products, as is provided for with respect to other foodstuffs.

This ruling had fatal consequences. The previously applicable maximum concentrations no longer applied to herbal teas. Maximum levels for infusions were merely stipulated for 7 persistent chlorine pesticides and 6 other substances, including bromide and cyanide. That meant that where no plant-specific maximum levels were given – as was the case for hops, – for example the maximum limit for the category “other plant-based products” was to be applied. This is always the lowest quantity quoted for the substance and generally amounts to 0.01 mg/kg.

This state of affairs led to a situation in which the associations established pesticide databases in order to record the actual residue situation and to issue proposals for acceptable maximum limits for infusions on the basis of retrospective data. This course of action was accepted by the responsible German ministry, which then implemented the procedure in the form of a national ruling. Nevertheless, the opinion that it is not worth defining maximum concentrations for such small product groups as herbal teas, is still upheld within the EC.

A contaminant database only makes sense if it contains as many of the more than 400 substances recorded in the RHmV as possible; this is because specific maximum concentrations cannot be defined with respect to any substances for which no data exists. The German Ordinance on Maximum Permissible Residual Quantities (RHmV) contains specific maximum levels for residues of more than 60 substances found in herbal teas (infusions), which have been stipulated by the legislative body on the basis of the submitted database analysis. Furthermore, maximum concentrations have been adapted to practically feasible values for a number of products.

The price of the information required for this process is a high one. In 2002, PhytoLab tested in excess of 7000 drugs for more than 150 substances defined in the German Ordinance on Maximum Permissible Residual Quantities (RHmV). The scope of testing will have been extended to include up to 250 substances by the end of 2003.

While investigating herbal medicinal drugs, we have discovered that around 86 substances are regularly found in them. On the other hand, the Ph. Eur. monograph on the subject of residual quantities of pesticides only contains 34 substances and groups of substances and therefore reflects the status quo in 1995. The Contaminant Working Group within the BAH will therefore be submitting a proposal to the European Pharmacopoeial Commission containing maximum concentrations for the 86 designated substances, which have been derived from the 90th percentiles of the findings entered in the database by the end of the year.

## Assessment of the situation

Using a few examples, it has been possible to show that the quality of our food is not declining, but that increasingly subtle testing methods are providing more and more information concerning substances that can damage our health. The maximum concentrations are no longer defined according to the scientific principle of “what is tolerable”, but are stipulated along the lines of the political orientation for precautionary consumer protection according to the principle of “as little as possible”. This concept will certainly be of slightly greater benefit to people's health with the average life expectancy increasing all the time, whereas the improving quality of our food is also resulting in higher costs in production and testing. With the economy in such a strained state, one should certainly be allowed to question the extent to which we intend to pursue this type of quality thinking and whether we will be able to afford it in the future.

I believe that we should reconsider and redirect our focus away from a quality ideal and towards a reasonable standard of quality. In spite of and because of this, we can still say that our food is the best there has ever been and that people could never enjoy such a healthy lifestyle as they can today, if they actually do so. But here too, everything in excess is bad for your health.

## Networked for even greater dependability

In your capacity as a PhytoLab customer, you automatically benefit from a variety of synergetic effects within the nature network. This global alliance of strong brand names and resources for everything related to plants offers top quality customised products and services to the food, cosmetic and pharmaceutical industries, from the acquisition of raw materials and production, right through to research and first class service.

### Specialists at your service

Apart from PhytoLab, the nature network is made up of many other specialist companies from the international phyto sector: Martin Bauer, for example, the supplier of herbal raw materials, herbal and fruit teas, as well as black and green teas. Or Plantextrakt, supplier of herbal extracts and decaffeinated tea to the food industry. Finzelberg, manufacturer of extracts for phytopharmaceuticals and dietary supplements, and many other brand names belong to this unique global alliance of specialised companies associated with herbal products.

At the same time, the nature network offers extraordinary synergetic effects to all of our customers. After all, you can use the entire knowledge and infrastructure of the network. With success: a customer satisfaction survey conducted in 2001 indicates that 96% of all nature network customers are either satisfied or very satisfied.

### Double benefits

The benefits of the nature network that you enjoy as a PhytoLab customer are two-fold. You can profit from the strengths of each individual company. And you can take advantage of the synergetic effects of the complete alliance at the same time. This means, for example, that PhytoLab offers you direct access to the most diverse services, such as acquisition of raw materials or product development.

We can increase your success to an even greater extent from the nature network, with new tailor-made products. In doing so, we safeguard your future growth. The concentrated research and development know-how in the nature network will also add impetus to your innovation rate. This is because critical pulses for the most diverse markets are being emitted by companies within the network all the time. The network offers you maximum supply security and you will receive up-to-date information via fast, secure channels.

### Reliable acquisition of raw materials

You can purchase herbal raw materials of first class quality through the nature network. Cultivated under controlled conditions and in accordance with your chosen conditions, it is even possible to modify the properties of the plants to suit your specific requirements. The transparent cultivation concept also exerts positive effects after the harvest: e.g. on laboratory analysis. After all, testing can be simplified to a great extent if the origins of a product are known. This for its part reduces your costs and improves product reliability at the same time.

Our customers also reap the benefits resulting from the large number of samples examined at PhytoLab. This is because the knowledge gained in the course of this work is directly incorporated into statutory regulations and specifications and ensures that practical limiting values are defined.



### Partner in new markets

The international orientation of the nature network is particularly valuable when entering new markets. This is because our companies are already active in many countries around the world. They have therefore established contacts with official authorities and potential local partners. Valuable resources which are freely available to PhytoLab customers.

Our extensive experience and contacts in the Eastern European countries entering the EU and in Russia are of particular interest at the moment. The nature network has been actively involved in this important region for years now. And is therefore an ideal partner for your future.