Proceedings of the One Day Symposium on "Safety and Risk Assessment Approaches for Materials of Herbal Origin" Organized by Unilever Research India, along with Ayurvedic Drug Manufacturers Association, and Indian Drug Manufacturers Association, at Bangalore, on 3 September, 2010

Scientific Contributors

Dr. Vilas P. Sinkar, *Vice President, R and D and Site Leader, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Dr. Julia Fentem, *Vice President, Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ*

Dr. S.K. Sharma, *Advisor (Ayurveda),Department of AYUSH, Ministry of Health, Indian Red Cross Building, Room No. 219, 1 Red Cross Road, New Delhi - 110001*

Dr. Vasantha Muthuswamy, *Senior Deputy Director General (Retd.) ICMR, New Delhi. Presently - 5 / 1(old), 8 / 1(new), Padmalaya Apts., Balakrishnan Road, Valmiki Nagar, Thiruvanmiyur, Chennai – 600041.*

Dr. Ram Manohar, *Director, Research, Arya Vaidya Pharmacy, Ramnath Nagar, Coimbatore, Tamilnadu.*

Dr. C.K. Katiyar, *Vice President, Health Care Research, Dabur R andD Center, 22, Sahibabad, Ghaziabad-201010*

Dr. (Mrs.) P. Kakkar, *Scientist-F and Head, Herbal Research Section, Indian Institute of Toxicology Research, P.O. Box-80, M.G. Marg, Lucknow-226001*

Dr. Bobbie Bradford, *Product Toxicologist, Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ,*

Dr. D.B.A. Narayana, *Director, Regulatory Affairs, South Asia, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Dr. Nimish Shah, *Head, SEAC Bangalore, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Dr. Paul Hepburn, *Program Leader, Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ,*

Dr. Vijay Gadgil, *Head, Herbals Research, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Dr. Christine Boucheron, *Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ,*

Dr. Paul Russell, *Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ,*

Dr. Adip Roy, *SEAC Bangalore, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Mr. Rajendra Dobriyal, *Clinicals CFC, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Panel Discussion

Chair

Dr. Y. K. Gupta, *Professor and Head, Department. of Pharmacology, All India Institute of Medical Science, New Delhi.*

Moderator

Delhi, **Dr. D.B.A. Narayana,** *Director, Regulatory Affairs, South Asia, Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066*

Panelists

Dr. K. C. Gupta, *Director, Indian Institute of Toxicology Research, M.G. Road, Lucknow- 226 001*

Dr. Julia Fentem, *Vice President, Unilever, Safety and Environmental Assurance Center (SEAC), Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ*

Dr. Vasantha Muthuswamy, *Senior Deputy Director General (Retd.) ICMR, New Delhi. Presently - 5 / 1(old) ,8 / 1(new), Padmalaya Apts., Balakrishnan Road, Valmiki Nagar, Thiruvanmiyur, Chennai – 600041.*

Dr. C. K. Katiyar, *Vice President, Health Care Research, Dabur R and D Center, 22, Sahibabad, Ghaziabad-201010*

Dr. G.G. Gangadharan, *Joint Director, Foundation for Revitalization of Local Health Traditions, 74 / 2, Jarakbande Kaval, Post-Attur, Via. Yelahanka, Bangalore– 560 064*

Dr. N. Deshmukh, *Director, INTOX Pvt. Ltd., 375, Urawade, Tal. Mulshi, Dist. Pune, INDIA, 411 042*

Safety Risk Assessment Approaches for Materials of Herbal Origin – Welcome

Vilas P. Sinkar

Vice President, R and D and Site Leader Unilever R and D, 64 Main Road, Whitefield, Bangalore – 560066, India
E-mail: vilas.p.sinkar@unilever.com

It is a great pleasure and privilege to welcome you all on behalf of ADMA, Indian Drug Manufacturers' Association (IDMA), Safety and Environmental Assurance Center (SEAC), and Unilever Research and Development (R and D), Bangalore, to the symposium on 'Safety and Risk Assessment Approaches for Materials of Herbal Origin'. Ayurveda and the Traditional Chinese Medicinal (TCM) System are two ancient medicinal systems still used by the masses in the two most populous countries in the world. Besides a renewed interest in these medicinal systems, use of herbal materials in functional foods and personal care is gaining momentum the world over. Use of such materials in non-traditional areas necessitates development of appropriate science-based, risk-assessment approaches, and as you know, this is the theme of this symposium. Unilever, has been evaluating naturals for the last several years and one of the issues has been, how does one look at and review its safety, especially when used in products mostly for external use and in some cases for internal administration, although not as drugs. We have gone through our own learning curves and we have developed and adopted an internal system of assessment, which takes into consideration, appropriately, the history of their use in the traditional knowledge of Ayurveda, TCM, and so on. At times there have been requests to share our approach. What better opportunity than to do so in this forum of experts, which will make us learn further and help to promote what we are doing in a more dynamic manner.

I am happy to see the strong participation in this symposium. I am particularly happy to see renowned experts from toxicology, pharmacology, modern medicine, and Ayurveda and Naturals, coming from the Government, Academia, and Industry, to attend this symposium. Please join me in welcoming the speakers and panel members of this symposium.

I welcome all of you to this symposium on 'Safety and Risk Assessment Approaches for Materials of Herbal Origin,' and hope the deliberations in this symposium will evolve newer and more potent methods for the safety assessment of materials of herbal origin.

Safety Risk Assessment Approaches for Materials of Herbal Origin — An Introduction

Julia Fentem

Vice President, Unilever, Safety and Environmental Assurance Center (SEAC) Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ
E-mail: julia.fentem@unilever.com

Good morning Ladies and Gentlemen. Just for a few minutes, at the beginning of this symposium, I thought it might be helpful to set some context as to why we are interested in hearing from you and learning from your experiences. It is excellent to have so many experts in a room together, to share our personal expertise and insights with regard to the best methods for assessing the safety of materials of herbal origin. I think it is also equally important that we try to identify where the key knowledge gaps are, so that we understand where we need to invest in new research. There is increasing consumer interest in natural products, including outside of traditional medicinal uses, cultures, and markets. Global consumer product manufacturers have responded to these consumer insights by looking at using herbal materials increasingly in foods and personal care products.

I think this direction sets some interesting and different challenges for assuring the safety of these new product types, which will potentially be used in different ways by diverse groups of consumers. We need to think about how the exposure of consumers may change from that with the traditional use of herbs in medicinal applications. It is increasingly important that we understand how best to apply the most up-to-date scientific knowledge and approaches in this area.

Unilever's Safety and Environmental Assurance Center (SEAC) has a role within Unilever that covers the discovery of new materials and technologies and their incorporation into new product formulations by development scientists, and their subsequent manufacture, transport, consumer use, and disposal of these products. In an integrated approach, we assess the consumer, occupational and environmental safety risks, and environmental impacts of new technologies and innovations throughout their development and implementation. Thus, we ensure that the new products and processes in Unilever are safe and sustainable, both in their design and in their execution. SEAC scientists provide scientific evidence and expert guidance on safety and environmental sustainability for the discovery, product design and development, and supply chain teams within Unilever. Our core science and technology expertise is in toxicology, ecotoxicology, analytical chemistry, microbiology, process safety, and life cycle assessment, with a focus on the capability for hazard, exposure and safety risk assessment, and environmental impact assessment.

There are six main R and D laboratories in Unilever, including the one where we are today, in Bangalore. The SEAC teams are based at the Colworth Laboratory in the UK and here in Bangalore, and between them they support Unilever globally.

The SEAC uses scientific risk and impact assessment methodologies to provide the evidence and framework for making decisions on whether a technology or product is safe and environmentally sustainable. In a safety risk assessment, both the hazard and the exposure are considered in an integrated manner. Exposure is particularly important, if we want to understand the real risks to our consumers, workers, and the environment. Initially, we would need sufficient scientific evidence on consumer safety to be able to undertake some early clinical or consumer studies. Subsequently, of course, it becomes a matter of building our scientific knowledge and understanding, through an integrated and iterative approach.

The SEAC scientists work collaboratively with many scientific research partners throughout the world. We have a broad research program in terms of developing new scientific capability in safety risk and environmental impact assessments. These are fascinating times for toxicology as well as other fundamental biological sciences. There is a great modernization agenda within toxicology, driven to some extent by the US National Research Council report in 2007 on "Toxicity Testing in the Twenty-First Century: A Vision and a Strategy". The strategic direction is to move away from some of the traditional hazard characterization approaches (typically using laboratory animals) to a far greater application of new cellular and molecular methodologies, and to a better understanding of the human biological pathways and networks, and how these are affected by exposure to chemicals. Ultimately, such approaches will improve the scientific quality and vigor of our toxicological (human health) risk assessments and risk management decisions.

It is very important that we chemically characterize and analyze the materials we are interested in. As complex mixtures, herbal materials are often extremely challenging from a characterization perspective. This is an area where we are investing to develop the analytical capability needed. For example, we have been looking at how to use various analytical techniques in combination, to study and compare the chemical 'fingerprints' of herbal mixtures. This underpins the framework we have developed in the SEAC for safety risk assessment for herbals and other naturals, based on a concept of demonstrating a safe history of use. We have found that it is important to develop and implement a consistent, transparent, and scientifically robust framework for these types of risk assessments, where you are integrating data of many different types and from various sources, to enable decisions on safety. Our approach will be described later today, in the presentation by Bobbie Bradford.

In closing this brief introduction, I wish to express my sincere thanks and appreciation to the speakers and all of the delegates who have taken time today to participate in this conference.

Regulatory Status and Recent Developments Relevant to Herbals

S. K. Sharma

Advisor (Ayurveda),Department of AYUSH, Ministry of Health, Indian Red Cross Building, Room No. 219, 1 Red Cross Road, New Delhi – 110001, India
E-mail: adv_ayurveda@yahoo.com

I have been asked to speak in this one day Symposium on the important Topic of Safety and Risk Assessment Approaches for Materials of Herbal Origin. Being a regulator and working in the area of Ayurveda and other holistic systems of healthcare, it is difficult for me to understand what would be relevant from a regulatory perspective on this topic. Furthermore, in Indian regulations, there are either synthetic drug-based medicines or medicines based on traditional holistic sciences, namely, Ayurveda, Unani, Siddha, and Homeopathy. The term herbals or 'herbal medicines' is not defined in the current regulatory provisions in India, although a fairly high proportion of the recipes, formulations, and products that are employed by Ayurveda are made by using herbs as their ingredients.

One of the organizers of this Symposium, who worked with a leading research-based organization like Dabur, had been in discussion with the Department of Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH) and suggested a number of initiatives based on science and technology, to promote Ayurveda and Ayurveda-based products. These initiatives have been in discussions, evaluation through science, intensive negotiations among Ayurvedic and contemporary scientists, and have seen the light of the day through various amendments to the regulations. Some of these have taken a long time, as much as ten years; however, these regulations are aimed at promoting the use of Ayurvedic herbal remedies for the public and many of them, which I will briefly discuss, impact on ensuring the safety and quality of these products.

The Department of AYUSH is aware that Ayurvedic products come with a long history of safe use, having been codified in official texts, recognized by the law, many of them also fall into the 'Herbals' area, which could be either the same or modified versions of the Ayurvedic products. This herbal area has not been fully evaluated by the Department of AYUSH and no new registration / licensing procedures were available till recently. The current law recognizes the extrapolation of the safe use of Ayurvedic products, and hence, does not ask for new safety or risk assessments. However, adoption of scientific and many new technologies of herbs used in Ayurvedic products have raised the need to look at the regulations, especially with a view to ensure the safety of herbal materials. After lot of debate, discussions, and evaluations, the Government has notified changed provisions for rules related to proprietary Ayurvedic medicines. According to this notification, while the category of proprietary Ayurvedic medicines will continue, three more categories have been defined, and the safety and efficacy data required for regulating them have been specified. Ayurveda is known to have a number of preparations, which are primarily nutritive, health promoters and belong to the category of 'diet as medicines'. This category has been listed in the amended regulations as '*Balya / Poshak dravya'*. This category will promote and provide to common consumers, what, in a simplistic way, can be termed as 'Ayurvedic health supplements' required to maintain the health of healthy individuals and also to help in preventing or reducing the risk of certain diseases or disorders. The second new category defined in this notification relates to '*Soundarayaprasadhan*', which is a category of those Ayurvedic products meant for supporting the health of skin, hair, oral hygiene, and primarily for external usage. Ayurveda is replete with a number of recipes and procedures for these purposes and many of them provide benefits similar to but not limiting them to that of cosmetics. The third category actually addresses a longstanding need of the industry to permit them to use the modern technology of extraction and use it to get some of the solvents by extraction. Recognizing this need has gone through a thorough debate for many years, but the need to balance a change in regulations with a focus on safety was of primary interest. As even the Ayurvedic industry, apart from the herbal industry, has been slowly moving to the use of ready prepared extracts rather than handling large quantities of raw herbs, the need to modify the regulations has been accepted and a third category of '*Satvas or Ghana Satvas*' (extracts of herbs) has been recognized. However, a cautious approach has been clearly enunciated in the new regulations, where water extracts, which are well known and have a long tradition of use, have been accepted as the best solvent for human beings or animals, and have been allowed without any additional safety data to be generated, apart from documentation of the history of use. A second solvent system of hydroalcoholic (water plus ethanol)

extracts has been permitted, with some additional safety data to be generated apart from the documentation of information known about such hydroalcoholic extracts. The regulations have clearly indicated that if the herb recipes are the same as in the official texts or have been processed in the same way as known in the classical use of these extracts, no new safety or toxicity data needs to be generated. However, if there is any deviation in either the herb or recipe or in the processing technologies from the classical texts, additional safety and efficacy (through pilot human studies as per protocols) have been specified.

Many requests have been received from the industry to also permit solvents other than water and ethanol, and still allow them to call it Ayurvedic materials. This has not been accepted and complete acute toxicity, subacute toxicity, chronic toxicity, Genotoxicity, and the mutagenicity data have been made mandatory, so as far as the standards are concerned.

There are a number of other regulatory provisions that have undergone changes and many of them have taken a long consultation process, some of them as long as two to three years. The process of regulatory changes involves discussions among various stakeholders – namely the industry, scientists from the academia and industrial research, practicing clinicians, ayurvedic scholars, and also bureaucrats. Results of such consultations get discussed in expert committees and are then put up to the Drug Technical Advisory Board appointed by the Government, as per the statutes, the decisions of which then get published as draft gazette notifications. After receiving further inputs and objections, which are carefully reviewed, the final modified regulations are notified in the gazette. I have been involved in advising and taking forward this process in the Ministry of Health, Department of AYUSH.

It is important that I cite a number of other regulatory changes that have been notified in a fairly rapid and regular way in the last two years, as a result of the extensive consultation and review process. As many as eight such changes have been notified in the gazette in the last two years, which is a contribution of the small department that we have. All these that are being described have a direct bearing and impact on the safety of herbals whether marketed as an herbal product or as an ayurvedic product. Considerations have been adequately given and a careful assessment has led to notifying permission to use what are known as 'Excipients' for use, while formulating ayurvedic products, with a view to make them more robust, with proper shelf-life and transport worthiness, as well as, improved product appeal. This notification has allowed various pharmaceutical aids that are official in the Indian Pharmacopoeia, all additives with and without restrictions as listed in the Prevention of Food Adulteration Act and Rules, and the approved ingredients listed in the Bureau of Indian Standards. This has been welcomed by the industry and we at the Government feel that the industry will use a proper scientific rationale when using these pharmaceutical aids.

In March 2009, Good Manufacturing Practice (GMP) guidelines were made mandatory along with separate GMP guidelines for Metals and Metallic preparation and manufacture. Persistent pressure from the consumer bodies and different view points expressed by the industry led to a lot of debate on marking the shelf life (expiry dates) for ayurvedic products. Assessment of shelf life of herbal products and ayurvedic products is not easy when compared to synthetic chemical-based drug products. Ayurveda has recognized and has even mentioned in the official texts under what conditions and after what period from the date a *Vaidya* prepares a recipe they should not be used, as they would have gone bad. However, in many instances, this period is very short, as these recipes are made using the current industrial scale of operations as well as adopting modern packaging technologies. On 15 October, 2009, a final notification was issued, bringing to end the long discussions, fixing the maximum shelf life that can be marked on various ayurvedic dosage forms, and making such shelf life declaration on labels of products mandatory. This notification has taken into consideration the ayurvedic wisdom, scientific work done by the Central Councils of Ayurveda, Unani, Siddha, and data provided by the industry. This should further help in building confidence among consumers about the safety of ayurvedic / herbal products offered for sale in the market.

March 2010 saw another notification where one of the official books listed in the first schedule to the Drugs and Cosmetics Act had been reviewed thoroughly and updated.

It is known that quality is to be built into a product and not just merely checked by testing. This used to be achieved by two different regulations — one, the issue of a manufacturing license to the premises where production of ayurvedic products took place and the second was related to an inspection, to check for compliance to GMP. These two needed some harmonization. This was achieved in May 2010, where both GMP and License inspections happened concurrently and the certificates / license issued was valid for a period of five years.

A number of activities are going on in developing and publishing monographs for the quality of raw herbs and raw materials as well as finished products in the ayurvedic pharmacopoeia. An amendment to a regulation has also been issued recently, where the analyst who issues a certificate of analysis after testing any raw material / herb or finished product has to state clearly whether the analysis results show that the material tested 'meets the specifications applicable or does not meet the specifications applicable'. This simple change will also support the further strengthening of the safety aspect of compliance to quality requirements.

Currently, there is no separate license required for the sale of ayurvedic products in India, unlike those for drugs of synthetic chemical origin, which are to be sold only through outlets of licensed chemists. It is recognized that most ayurvedic products have a long history of safe use and do not really need regulations on their sale. However, this view is under review and discussion among the concerned specialists, clinicians, as well as industries. A view is developing that there could be some ayurvedic products that need to be regulated for their sale and usage in a manner that is different from today, would need to be sold against the prescription of a qualified *Vaidya* under whose supervision and guidance such products need to be taken, to avoid serious overdosing, side effects, accumulation, and other toxicities. It is being contemplated to amend the regulation and make the sale against a prescription as a requirement for a specified and limited number of such identified products, and treat them differently from the over-the-counter type of sales.

Ayurvedic physicians and scientists have been engaged in a fruitful dialog and discussions with the contemporary scientists

and many collaborative projects, including human clinical trials, are being undertaken. These clinical trials are generally of a confirmatory nature, to confirm and document the safety and efficacy of ayurvedic products, and in many cases of herbal combinations, which have an origin in Ayurveda, and base their safety assessment on the history of safe use. In order to support such studies in a proper manner, keeping in mind the ethical and scientific aspects, a procedure for the issue of permission for pre-clinical as well as clinical studies has begun. Encouragement to transparently declare such study details on the Clinical Trial Registry of Indian Council of Medical Research (ICMR) is being done.

Another important aspect is to either regulate or provide the necessary guidelines, providing details of the mechanism for all clinical trials involving ayurvedic and herbal products in India. This aspect has a number of issues that need clarity, and is evolving through discussions. Integrating ayurvedic wisdom in terms of diagnosis, treatment, mid-course evaluations, measuring the benefit and outcome of treatment, and adoption of multiple routes (dietary controls, behavioral modalities, drugs, as well as *shodana* processes) with that of controlled trial mechanisms of the Pharma industry is a big task. One of the important requirements for such trials is the availability of a quality monograph for the ayurvedic product that one wishes to study in a human clinical trial. Monographs on 100 such ayurvedic products have already been published in the Ayurvedic Pharmacopoeia of India, Part-II, and work on publishing monographs and more finished products is continuing. A coordinated large project involving eight reputed institutions like I.P.G.T and R.A., Gujarat Ayurveda University, Jamnagar, National Institute of Ayurveda, Jaipur, Arya Vaidya Sala, Kottakkal, and so on have just begun to undertake human clinical trials in a multicentric study. Work on developing broad guidelines for such clinical trials has produced a second version of the document, which is undergoing further review. Inputs and comments from scientists and knowledgeable persons are welcome, to make the guidelines practical and robust.

A number of other measures are already notified or under discussion. These measures primarily aim to provide quality ayurvedic and herbal products and help in ensuring the safety of these products.

It would be very useful to receive the deliberations of this important Symposium and any decisions suggested for consideration by the Department of AYUSH.

Challenges in Herbal materials (Herbs, Herbal materials, Herbal products, Natural sources)

Vasantha Muthuswamy

Senior Deputy Director General (Retd.) ICMR, New Delhi. Presently - 5 / 1(old),8 / 1(new), Padmalaya Apts., Balakrishnan Road, Valmiki Nagar, Thiruvanmiyur, Chennai – 600 041, India
E-mail: vmuthuswamy@hotmail.com

Thanks to the organizing committee for inviting me to deliver the keynote lecture. This is an august gathering where everybody is a specialist in the area of herbal extracts. I will share my thoughts about whatever I have learnt in the last 10 years in the area of herbals, mainly what is the need for safety of herbals.

There are several factors influencing the use of herbal products. The global market for herbal healthcare is estimated at $ 62 billion and the estimated size of the herbal healthcare and personal care market in India is estimated to be more than Rs. 5000 Crores. The main reasons for the increased use of herbals are:

- Self Medication and Preventative Health Care
- Growing aging population preferring to take herbal products
- Growing Healthcare Costs demanding cost-effective herbals
- Accessibility, affordability, availability
- Growing Research Backup and Media Publicity
- Opportunities offered by the tools of Biotechnology

Since earlier times, herbal medicines have been used for edible and poisonous purposes, for killing, hunting, as appetite suppressants, stimulants, and so on. Given the varied use of these materials, safety is one of the concerns associated with herbals.

Modern drugs are known to produce serious side effects. Latrogenic diseases are the fourth leading cause of death in USA and developed countries (JAMA 1998) and the side effects of drugs kill more Americans annually than those killed in World War II and the Vietnam war combined (N. Roth, NY Times 28th Feb 2003). Around 2600 persons died in the Twin Tower tragedy in USA, on 11 September, 2001 and JAMA had reported earlier that about the same number die in USA every 10 days from side effects of prescription drugs (JAMA April 1998). Several drugs, for example, rofecoxib, have been withdrawn from the market due to side effects.

Traditional medicines are popular as remedies for diseases by a vast majority of the world's population. The promising pharmacological agents from this branch include nootropics, anti-diabetics, hepatoprotective agents, and lipid-lowering agents. The popularity of traditional medicines is due to:

- A strong widespread belief of safety, as they are from 'natural sources'
- Often, in villages, herbal medicines are the only option available
- Cheaper than modern medicine, which also require a lot of investigation
- Inability of modern medicine to offer relief to the common man
- The lay public is often unaware of the risk of untested and unregulated remedies

There are, however, many limitations with regard to the safety and efficacy of Traditional medicinal preparations, such as, (1) Knowledge about the active principles of herbal preparations is not well-defined, (2) Information on the toxicity and adverse effects of these formulations is inadequate, (3) Information regarding the pharmacokinetics and bioavailability is not available, (4) Details regarding the safety and warning are not required for sale of these, which are available as over-the-counter preparations, and (5) The abuse of these systems by unqualified medical practitioners, or quacks. Several areas in herbal medicines need focus; there is a need to improve the quality and acceptability of herbal preparations as safe and effective pharmacotherapeutic agents. The selection of plant material based on the quality and standardization of methods of preparation should be ensured. There is a need to identify the active principles of these medicines, enforce regulations regarding appropriate labels, and document them in research publications.

The science of Indian traditional medicine has come a long way from when it was considered unnecessary to subject these products to stringent quality tests for the introduction of Good Manufacturing Practice guidelines. More such measures are needed and indeed are being taken up on an urgent basis to address the safety and efficacy issues of traditional medicines. Apart from safety and efficacy, the access and benefit sharing issues should also be addressed where a part of the financial gains from herbals should go to the community who owned the initial knowledge.

A strategy for drug discovery from natural products addressing both safety and efficacy should be adopted. A possible approach can include, (1) Treatment of cells with herbal extracts, fractions or pure compounds, (2) Construction of c DNA Libraries, (3) Identification of Novel induced proteins, (4) cDNA Micro arrays for gene expression assays, (5) Isolation of active compounds or standardized fraction, (6) Drug Development-Additional Pre-Clinical and Clinical Research, (7) Manufacturing and Marketing, and (8) Reverse Pharmacology Strategy for speedier results.

There are several diseases for which there is no cure in modern medicine and people look toward knowledge from traditional medicine to find cures. The formation of the 4-kDa amyloid beta peptide is a key factor in the development and progression of Alzheimer's disease. Importantly, herbal treatments (providing Anti-inflammatory, Anti-oxidant, and Anti-amyloid benefits) have been tested in the animal and cellular models of Alzheimer's disease and in clinical trials with Alzheimer's disease subjects. Similarly, *Berberine*, a Chinese herb has been found to reduce Abeta levels without cellular toxicity. *Bacopa monniera*, a traditional Ayurvedic medicine, has been used for centuries as a memory enhancing, anti-inflammatory, analgesic, antipyretic, sedative, and antiepileptic agent.

When using herbal medicines, ethical issues should also be considered and in the ICMR guidelines issued in 1980, a section was made for traditional medicines. As per the guidelines, traditional medicines have been divided into three categories:

- Traditional Herbal drugs, as per classical text and prescribed pharmacopoeia — limited pre-clinical toxicity evaluation is required for use of this material.
- Traditional formulations for a new indication or new process or new combination — all Schedule Y guidelines to be followed.
- New Herbal Drugs or plant-based New Chemical Entity (NCE) — entire Schedule Y guidelines to be followed and all pre-clinical data to be generated before submitting for consumer trials.

The World Health Organization (WHO) has guidelines for the safety of herbal medicines and the main reasons attributed to the adverse reactions from herbal medicines are due to the problem of quality, adulteration with undeclared other medicines like steroids, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), and so on, use of wrong species of plants, incorrect dosing, errors in use, drug–herb, herb–herb interactions and contamination with toxic metals, pathogenic microbes or agrochemical residues. To address these issues, we have to look into the Pharmacognosy, Phytochemistry, and Standardization for ensuring the identity of pesticide, heavy metals, and microbial and adulterant contamination, to ensure the quality of the herbals. The preclinical considerations, for example, botanical verification, pharmacological activity, standardization and quality control, and safety and efficacy, need to be considered.

With the diversity and amount of knowledge of traditional medicine available in India, the government has initiated a golden triangle program in which the Department of AYUSH selects formulations for different diseases (joint disorders, memory disorders, menopausal syndrome, bronchial allergy, fertility and infertility, cardiac disorders, etc.), and the Council of Scientific and Industrial Research (CSIR) laboratories do the pre-clinical safety studies and finally the ICMR conducts the clinical trials. There are a number of problems in carrying out these studies, for example, obtaining informed consent is difficult, especially for double blind studies, with drug–herb interactions causing adverse reactions. Most ethics committees are not aware of the Indian / ICMR guidelines and lack compliance with GMP standards / GCP training and have constraints on resources / infrastructure. International collaboration is another issue, as knowledge and benefit sharing needs to be addressed.

The main issue for the future is, will the new approaches consisting of development of biologicals through biotechnology processes, discovery of new indications for existing drugs, new delivery systems, use of traditional systems both as medicines and sources of medicines, deliver cost-effective and safe and effective drugs for diseases for which treatment is not available or available treatments are not appropriate?

We are using natural products with the proof of science, and the safety of traditional medicines is very important for conducting human studies and I believe that this symposium will help to progress in this area.

Principles and insights from Ayurveda and safety of herbals

Ram Manohar

Director, Research, Arya Vaidya Pharmacy, Ramnath Nagar, Coimbatore, Tamilnadu, India.
E-mail: rammanohar@gmail.com

I am happy to speak in this one day Symposium on the important Topic of, 'Safety and Risk Assessment Approaches for Materials of Herbal Origin'. I am very happy to be here to share my views on how Ayurveda looks at safety and risk assessments for herbal medicines.

Codification of Knowledge in Traditional Texts: There were a lot of limitations for writing in ancient times, therefore, there was limited scope to document anything in detail and no scope for it to be very detailed. Therefore, experts wrote in a codified manner. Thus, when the text was studied again, one needed to use a lot of techniques to decode it and elaborate the ideas.

Vaghmela, one of the prominent codifiers of ayurvedic knowledge, classified traditional texts in three classes: (i) *Leshoktha* (ii) *Vyathasoktha*, (iii) *Alpoktha*: The subject is dealt with in an indirect manner and requires a lot of interpretation. There are certain concepts that one cannot see directly in the text, but when textual analysis is done, there is sufficient evidence to show that these ideas have been actually discussed in the text. This is because of the

traditional manner of communication, which is very different from the modern scientific treatises. Therefore, I have tried to interpret it in a manner that will be understandable to the modern audience.

Nature of drugs in Ayurvedic pharmacopeia: The title of my talk is, 'Principles and insights from Ayurveda and safety of herbals'. Ayurveda believes that anything under the sun can be used as a medicine. Its pharmacopeia is very open. There is a classical text which states *'Jagatheva manokshitham na kinchith vidyathe dravyam, vashathat Jnanaath trayoga yo,'* which means that Ayurveda has looked at it's own pharmacopeia as a dynamic phenomenon, where new substances can be continuously added and new drugs discovered. It further states that Ayurveda can accept drugs from any source, not just naturals.

In those days there were not too many artificial substances, but even man-made artificial substances were actually incorporated in medicine if they were found to be useful. Thus, any artificial or natural substances from plant, animal or mineral origin could in principle become potential drugs in Ayurveda.

Moreover, *Shushruta Samhita*, which is a further extension of the *Charaka Samhita* advises one to search the earth at every nook and corner — the earth is bountiful and there are many medicines waiting to be discovered. Therefore, the verse *'Nadishu, Shaileshu, Sarasu chaapi vanyeshu aranyeshu thatha shrameshu sarvathra sarva praimargitavya sarvathra bhoomi vasu thatha'* states, everywhere there is a potential drug waiting to be discovered. Although anything in the world can be used as medicine, we find that a very limited number of substances actually get codified and listed in the formal Ayurvedic pharmacopeia.

Selection process for incorporation of an unknown substance in the Ayurvedic Pharmacopeia:

Ayurveda also believes in principles that do not use an unknown substance. *'Oushadham ki anabhi Gyanam'* means any medicine that cannot be adequately understood in terms of *nama*, that is, nomenclature, *roopa*, that is, identity, and *guna,* that is, properties, will lead to undesired effects. So Ayurveda has been continuously looking for new medicines and new products, but then it is also trying to bridge the gap between what is adequately known and unknown. Anything that is not adequately known cannot get officially codified in the pharmacopeia. Thus, using unknown substances has been correlated with playing with poison, with a deadly weapon, with fire or even lightening. It has been stated that it can have very dire consequences. Therefore, one can state that there is a safety conscious approach when it comes to using medicinal substances.

Ayurveda has very elaborate protocols for evaluation of new substances, so much so, only few substances have been introduced in the Ayurvedic pharmacopeia over last 3000 years.

There are the three very important principles on the basis of which Ayurveda develops its pharmacopeia, (i) first is that anything can be used, (ii) second, no unknown substance should be used, and (iii) third, a known substance should not be abused.

They are also well aware that even if one has fully understood the nomenclature properties, there is still a chance of abusing. This is described in the verse *'vidjnanam chaapi duryuktham amarthayopi prateethe,'* which means, even if one knows the substance adequately, and still abuses or misuses it, then it will cause a safety concern.

I will just give you a quick overview of everything that went into the understanding of a drug.

Nama Jnanam: The first thing was nomenclature; an enormous amount of nomenclature had to be developed in order to help the practitioners in the system identify a particular drug without any confusion. This was further compounded due to multiple names for one object and many objects have the same name in the Sanskrit language. *'Ekam tu namam prateetham bhuna'* — our texts have recognized this problem. We used to have what is called the polynomial system of nomenclature; there were some benefits of this,

(I) First, it was that it was done intentionally, to make sure that unauthorized people could not easily access this knowledge. Therefore, they were coded and only people who had access to this code could exactly know which drug should be used.

II) *Roopa Jnanam:* Second was identity — *Roopa jnanam* — in which one had to look at the morphological as well as pharmacological identification. People used whatever techniques were available in those days. Adulteration and contamination were also dealt with and there were clear instructions on how a herbal specimen had to be collected for medicinal use, what type of land it should have been grown in, in what condition, in which season, and so on. All these details were very well laid out so that the identity of the drug was not compromised.

III) *Guna Jnanam:* Then you had the properties, *Guna jnanam*, which included both pharmacodynamics and pharmacokinetics. Ayurvedic explained from *rasa* to *vipaka,* which meant, it discussed a drug as it was and what happened to the drug after it got transformed in the system. Ayurvedic pharmacology was a complete understanding of what the drug did to the body and what the body did to the drug.
Vipaka was the ultimate final state of the medicine in which it exerted its pharmacological action.
Safe Medicine: There is another interesting principle from the *Charaka Samhita,* which states that there is nothing called safe medicine. So, Ayurveda has never claimed that just because it is herbal it is intrinsically safe. In fact Ayurveda states *'na kinchith dosham na gunam,'* meaning there is no substance that will not have the potential to produce one unwanted effect or the other. So, *'guna bhuyastwam atho vichintitha'* just look at the risk benefit ratio, so an assessment of any particular substance has to be in terms of this risk benefit assessment. One can never presume any drug to be fundamentally safe. Ayurveda has never advocated this position. But unfortunately, in modern times, this misconception has spread that just because the drug is herbal it is safe. However, the text or the tradition does not endorse this view. It is unequivocally mentioned that *'na kinchith adosham na gunam':* there are *doshas* and *gunas* that have to be evaluated for each substance.

IV) *Yukti Dyana:* In Ayurveda, there is nothing called a perfectly safe substance, but there is something called as a perfectly safe use and that is called *yukti* or application. Thus, that is beyond properties; safety is more about how you use a substance. That is how Ayurveda looks at safety.

Only those drugs for which adequate information was compiled, on all the four aspects mentioned above, got developed over several years, sometimes over centuries. Only then did they get formally accepted in the Ayurvedic formula. That is why we find that although there are 9000 or 10000 species of medicinal plants in the Indian ethonobotanical database, only one-tenth of these have been recognized in the classical Ayurvedic text.

Substance abuse: Substance abuse is very much highlighted in the traditional texts. So they say, *'yogaath api vishamadikshma'*, even a poison if it is used properly becomes medicine, whereas, a medicine if used wrongly becomes toxic. Thus, it is all about how you use it. And that is where the entire focus needs to be. This is mentioned in the text composed 3000 years ago that it is possible to discover an application, a therapeutic intervention, which cures one disease without causing another problem.

It is observed that the patients prefer the disease more than the side effects of the medicine; and this is exactly what Ayurveda also recognizes. Furthermore, this is possible even when we are using a toxic substance. Therefore, there is no perfect substance, only a perfect application and that is the goal of Ayurvedic therapies.

Evaluating safety using animal models: Both the intrinsic safety of the *dravya aushadha* (the substance) and the risk in its *yukti* or *prayoga*(application) are considered in Ayurvedic texts. A new plant or any new substance is looked at with great suspicion. Both short-term and long-term safety issues are considered.

However, many other issues for evaluating the safety have been referred to in Ayurveda in a chronological manner, which is beyond the scope of discussion. Even use of procedures involving animal testing for knowing the toxicity of substances is definitely endorsed by the literature. The procedure may not be as refined as modern LD 50 experiments, but there are textual references, very clearly recommending testing of not only drugs, but new food substances, using animal models. Later on one can extend the use of that anywhere. Ayurveda is also open for receiving initial clues from animals to know how a drug might act. Even the *Atharva Veda* refers to mongoose nerves, rat nerves, snake nerves, and the like, for getting rescued from diseases.

There is an indication that even long-term safety evaluation must have been taking place in those days. This can be concluded from the fact that in spite of several Ayurvedic doctors working on several herbs / drugs only 600 drugs have been added to the first traditional text – *Charak Samhita* in about 3000 years. This translates to about 200 drugs every 1000 years or roughly one plant / herb or drug every five years. Of course this is a very rough estimate to stress the fact that new herbs / drugs must have been evaluated carefully for a long time by several doctors, before they appeared in the Ayurvedic pharmacopeia.

Vishavarga: Modern medicine teaches us how to use toxic substances in a safe way by reducing the doses. However, Ayurveda describes several other ways of using toxic substances in a safe manner.

Indications, contraindications, and *Vidhi:* Ayurveda describes in detail all the three aspects related to use of drugs: If one used them insufficiently, inappropriately or in excess. Using the substance in the effective manner is referred to as *Samyak yoga* and in case of any adverse events an Ayurvedic practitioner must be prepared to handle the situation. Before using the drug, the Ayurvedic doctor must ensure the purity of the material he is using and all the methodologies available at his disposal. Using substitutes for the herbs / drugs is unavoidable at times, however, substituting *'Pradhan Dravya'* is not permitted. There are elaborate procedures for collection of substances, to probably ensure the microbiological safety, and very passive / preventive procedures are used for this purpose. There are guidelines to collect the substance from very pure places or to purify these places using 'two-burner fumigation'. Guidelines for avoiding certain substances are also present, for example, curds should be avoided by people living in marshy lands and alcohol in a tropical region. Ayurveda recognizes the physiological changes in the body with seasons, therefore guidelines exist for variation in drugs depending on the season.

Age factors: Ayurveda recognizes that needs for children and aged persons are different. Ayurveda does not recommend treatment of children with *Rasa aushadhi*. Ayurveda recommends *mrudu-bheshaja* (very mild drugs) for children and intervention should only target stabilization of the condition. For infants Ayurveda recommends that the treatment should be given to the mother so that it passes on to infant through the breast milk. All *'tikshna-aushadhis'* should be avoided for pregnant women or to women breast feeding their children. A separate concept of *tikshna-aushadhi* has been described in Ayurveda.

Prakriti and medicine: Unlike modern medicine, Ayurveda prescribes modification of treatments depending on the *prakriti* of the person, for example, *Kantakari* should be avoided for *pitta prakriti* persons or suitable mitigating herbs need to be co-administered to prevent loss of mucus membrane in the intestine, if one chooses to use *Shigru* for *pitta prakriti* people.

Viruddha concept: Disease drug interactions are also considered in Ayurveda, for example, one should avoid drugs that will put a stress on the kidneys, if the patient has kidney problems. So, there are certain examples mentioned in Ayurveda, in such great detail that sometimes one thinks that Ayurveda is being too cautious about safety. Even subclinical safety issues should be given importance, for example, a combination of fish and milk in the diet should be avoided. Thus the safety regimens span across drug behavior, drug–drug interactions, drug-disease interaction, drug-food interactions, and food–food interactions. Thus, this covered in *'Viruddha'* concept.

Purification of drugs: Ayurveda describes three ways of using toxic substances: by minimizing the dose or by co-administering a substance that will mitigate the side effects of the toxic material or by purification of the toxic substance before use. If one processes the toxic material in a manner described in the traditional texts it becomes non-toxic.

Adverse Events: Adverse events have been described in Ayurveda as *'Vyapath,'* that is, an unexpected or unwanted outcome of the treatment. In fact, Ayurveda states that the success of a physician depends on one of the key skills of anticipating *Vyapath* and his ability and preparedness to handle such situations. Iatrogenic diseases are also recognized as *'Vaidyopcharjan Vyadhies,'* that is, diseases created by wrong treatments by physicians. Therefore, Ayurveda recommends a very careful approach when using any medicine or drug.

Now I will quickly go through a few substances:

Pepper: Ayurveda states that you should use it only after purification. It is an irritant, if you use it continuously it can harm you, so purify and use.

Honey: Is also to be purified. I was a bit surprised about this, but then I found that honey is the only food source that has botulism bacteria. If you give it to infants it is suspected to be one of the major causes for infant botulism. Ayurveda advises honey to be given to infants. We are doing a study in which we see whether Ayurvedic method of purification will render it free from the force of these bacteria.

Callamous root: *Vacha: Chakradatta* clearly states never use it without purification. I was involved in a small animal study which we did when I was doing my PG where one of my colleagues looked at *Vacha* before and after purification. In mice we found that after purification it is safe, before purification it kills with just one injection, the mouse just dies in your hands, but when purified it does not create a problem.

Ghee*:* Substances like ghee of course are not herbal. So, I will not go into it, but Ayurveda states ghee can be as dangerous as poison and as useful as nectar.

Marking Nut: This is a known irritant, and has to be used only after purification.

Nux Vomica — Also can be used after elaborate purification.

Aconite — Can be lethal. This is interesting, because aconite poisoning cases have been reported in allopathic cosmetics. Generally it is concluded that it has been used in a wrong way. However, an animal studies have been done by Dr. Sharadini Dahanukar. In these studies aconite was purified using cow's urine and cow's milk, and in combination it was found that when the complete procedure of purification was done even the highest dose of aconite was non-toxic. This has been published in a permanent indexed article, it is a very interesting study and the title of the article is, 'Can we dispense with the Ayurvedic *samskaras*?'

Therefore, the conclusion, the message that I would like to place before this audience is that Ayurveda has developed and embedded a detailed comprehensive protocol for assessing risk and safety of herbal substances. These need to be evaluated, better studied, and expanded using modern research methodologies. We have a whole foundation on which we can work further. I am not claiming that this is the final thing. If we use traditional wisdom then there will be only some fine tuning of these aspects that need to be done in many areas. We will get more knowledge in a short period of time. Hence, we do not have to start on a clean slate.

Thus, these are the risk and safety statements. (Sanskrit *shloka*). The *vyapath* is the risk factor, *vyapath sidhi* is the safety measure, and the chapter is called the *Sthana* of success in clinical intervention. This success is achieved not just by knowing how to use the medicine, but rather success comes when you are able to anticipate *vyapath* risks and are equipped to take safety measures. Thus, this has been a fundamental principle, which still looks very modern today.

So with these words I would like to conclude. Thank you very much.

Modern Challenges for Safety Assessment of Herbal Materials

C. K. Katiyar

Health Care Research; Dabur R and D Center, Sahibabad, Ghaziabad, India
E-mail: Chandra.katiyar@dabur.com

The main triggers of the challenges for safety assessment are: The growing global interest and competition and scientific discovery along with changing regulatory requirements. In US, Europe, and also in India, many new regulatory notifications have come in recent years, which in itself is a regulatory challenge in the field of herbals.

In 2004, the Government of India exhibited knee-jerk reaction to an article published by Saper *et al.,* JAMA. Dec. 15; 292(23): 2868-73, which mentioned that 17 out of 70 Ayurvedic / Unani medicines contained heavy metals; therefore, they were not safe for human consumption. In 2005, Health Canada and UK banned few Indian Ayurvedic medicines. In October 2005, the Central Government of India made testing of heavy metals mandatory for exported products. In November 2005, some of the products having heavy metals were withdrawn in the UK. These were the triggers that actually led to setting of heavy metal limits for herbals by the Government of India. Herbal materials can be crude herbs or herbal extracts like aqueous extracts, hydro-alcoholic extracts, and so on. As per a recent notification by the Government of India, other solvent extracts have also been permitted with the condition of safety studies.

For export of herbal products to few European countries, the respective regulatory authorities ask to submit the data on individual plant toxicity beside the formulations. In different Ayurvedic formulations, a single plant actually may go into many products. Therefore, either the final formulation is tested for its safety or the ingredients are tested individually, only after this is the product declared to be safe.

In the last 3000 years, a number of things have changed, but the basic rules of safety have been embedded in the formulae itself, as per the classical Ayurvedic texts on herbals, and we are following the same even today. But today, can we say that because of traditional use and because of the formulation being mentioned in the classical texts, a toxicity study must not be done? We need to understand that the plants used centuries ago on which data is available in classical texts may not be the same today because of changes in the geographical and climatic conditions; even the inherent genetic make up of the plants may have changed.

For preparation of some formulations, toxic or even poisonous substances are used, but these are subjected to *shodhana* (detoxification process) before their incorporation into the final product. In certain such cases, their safety after *shodhana* has been validated, while in others it is yet to be done. An improper manufacturing process is another safety concern, along with contaminants, in the formulation, including heavy metals and the like. However, does the mere presence of heavy metals make a product toxic? Has some one conducted a toxic study on two samples of the formulation? In most of the cases, heavy metal limits have been picked up from the food and not from the drugs. Food is taken in grams, while the herbal drugs are taken in milligrams, leading to much lower intake of heavy metals as compared to

food. Poor quality and misuse and abuse of Ayurvedic drugs are also other safety concerns.

In the allopathic medical science, the same material which goes into drugs goes into clinical trials. On the contrary, in Ayurvedic formulations, the herbs used from two different geographical locations might have a different profile as far as toxicity and efficacy is concerned. Therefore, conducting clinical trials with these different varieties of herbs in a single study may not be justifiable. Therefore, it is a challenge how we ensure that the same material is being subjected to toxicity and clinical trials.

Proper harvesting practices and time of sample collection also play a role in both the safety and efficacy of herbs.

Herbs are different from chemicals. A single plant has more than one active component or alkaloid or chemical, which might have different biological activities when used separately. Different compounds have different actions. These chemicals may have synergistic actions. The individual chemicals may counteract with the adverse drug reactions of each other. They may have effects on the bio-availability and help in the absorption of the other active ingredients of the formulation. So, even taking a single plant would mean taking a number of chemical constituents, and hence, it becomes a challenge to identify them.

Ayurvedic products differ in their consistency too, for example, the bulk density, specific gravity, physical form, and so on, have a direct impact on the dose. The dose of Ayurvedic formulations also depends on whether crude herbs or herbal extracts are used in the formulation. Like pure chemicals may have a dose range from microgram to milligram, the plant as a whole may have a dose range from milligrams to grams and the large dose of herbals itself poses logistic challenges for conducting toxicity safety studies.

Different parts of a single plant may have different actions and may have different toxicity profiles too. The uniformity of the samples used in the formulation is required for standardization of the final formulation. Hence, the selection of the parts of the plants itself is a challenge for the safety of the formulation.

The secondary metabolite plays a major role in determining the action of the product. Berberine, an antimicrobial product, has poor absorption when given alone, while the extract of Berberis aristata, having berberine as major constituent, resolves this issue, and the bioavailability of berberine gets enhanced. Each extract may have different metabolites and the absorption of the extract will also depend on it.

The absorption, distribution, metabolism, and excretion of herbs are not fully known. Hence, it remains a mystery as to how these herbs act inside the body. This lack of facts regarding the pharmacokinetics itself poses a challenge to determine the safety of the formulation.

As per Schedule Y of the Drug and Cosmetic act, if a product is used for up to two weeks, a toxicity study of four weeks is required. Hence, the duration of toxicity studies is linked with the duration of its use. According to the Organization for Economic Cooperation and Development (OECD) guidelines, the no observable adverse effect level (NOAEL) limitation is 2000 milligrams per kilogram. Moreover, these guidelines are applicable for allopathic medicines too. Therefore, these guidelines, if used as such for herbal medicines, may not actually be giving the validated safety outcomes.

Ayurvedic treatment follows few strict principles and ideologies, which cannot be extrapolated by the modern method of toxicity study. The Ayurvedic treatment regime typically includes diet, drug, vehicle, and behavioral modalities, but a part of the treatment cannot be evaluated by any kind of toxicity. In Ayurveda, not all medicines are prescribed to be taken with water; some are prescribed with honey and some are given with other vehicles like juices, and so on. The herbal practitioner follows the ethics by giving the treatment as described and taught. So, while conducting the toxicity studies, should the medicine samples be given with honey, water and the like? Therefore, in this complex scenario of herbals; it is advisable, if possible, that one sample be given with the standard vehicle and another sample without the standard vehicle and only then some conclusion about the safety of the regime can be drawn. However, the concept cannot be established by the current methods of toxicity studies, as Ayurvedic physicians have their own unique way to prescribe the medicines. One may prescribe different products concomitantly along with some other thing, like *aahar, vihar*, and *anupana,* to different patients with the same disease, depending upon their psychosomatic constituents. Modern toxicity methods would not be able to capture this variable.

Along with the oral preparation, topical formulations are also described in Ayurveda. There are appropriate methods available to find out the rate of absorption, the depth of absorption, and methods to study whether the topical formulations go and accumulate somewhere inside the skin or do they accumulate in some other organs of the body. By-and-large only few toxicity studies such as the dermal irritation test and the mucosal irritation test are conducted on these products Therefore, there is a need for some elaborate discussions on the desirability of toxicity and safety studies on topical herbal products.

Allopathic medicines may have an onset of action say within 30 minutes, however, the onset of action of herbs is not definitely known and it actually might be much longer, say days or weeks. So, if the drug does not produce efficacy within 30 minutes, how can it produce toxicity in a model that has been chosen based on the concept of toxicity studies on Allopathic formulations. Therefore, there is a need to look at a different paradigm, and the guidelines for the toxicity studies in herbals need to be changed accordingly.

To cite the example of lead, if it takes six months to produce the clinical symptoms; while conducting a toxicity study on Ayurvedic formulations having lead as an ingredient, it may not actually show any toxicity if the studies are conducted just for one month or three months. So the question arises, how then can we conduct the toxic study on it? Therefore, there is a need to have total new modern protocol for that, but this needs a lot of discussion, because other considerations will be required.

According to the Drugs and Cosmetics Act and Rules of India, the clinical trials were not mandatory, keeping in view the traditional use and the reference of Ayurvedic textbooks. In Ayurvedic literature, a list of toxic substances have been mentioned, which should be used only after the detoxification process. Therefore, the law has been amended in India recently,

which states that if the formulation is known to have any of the herbs that are known to be toxic; then toxicity studies need to be conducted.

Another guideline, which is yet to be published; mentions that a 28-day toxicity study needs to be conducted, and if the product is to be given for a longer period a 90-day toxicity study is required. Also, if any of the products contain the listed toxic ingredients, then the words 'To be taken under medical supervision only' need to be mentioned on the label.

According to the Indian Council of Medical Research (ICMR) guidelines, every product needs to undergo a toxicity study if the product is reported to contain schedule E (1) drugs or if it is to be given for more than three months. The available guidelines for toxicity studies are the WHO guidelines, International Conference on Harmonization (ICH) guidelines, OECD guidelines, Schedule Y guidelines, and so on. The basic methodologies in almost all these guidelines are more or less the same. They revolve around the principles of the safety of allopathic medicines.

A recent publication on the safety evaluation approach for TCM (Traditional Chinese Medicine) relies more on the known *in-vitro* techniques, rather than going for direct animal studies. One of the modes of conducting toxicity studies can be *in-vitro* studies. The cell viability assay is a very simple method, but the dose needs to be standardized to know whether the toxicity is to be evaluated at 5 mcg, at 1 mcg or at 30 mcg, and so on.

Nowadays, the *C. elegans* model is also used as a tool of predictive toxicity. This may be useful for herbal drugs as well. Therefore, instead of conducting studies in rats, mice, followed by monkeys, which are usually done for unknown medicines, these *in-vitro* models may give fast and expedited results, at least for a safety screening purpose and then the herb that is passed in the screen can be subjected to animal models to evaluate its safety. Ayurvedic medicines are not unknown substances, as these have been used since hundreds of years. So, if we still have to conduct toxicity studies in rats, mice, and monkeys, probably we need to find a method and need to debate and discuss on this issue.

As per the recent amendment notification by the Government of India, dated 10 August, 2010, for the manufacturing license requirement for a special class of products, for example, herbal extracts other than aqueous extracts, toxicity studies have to be performed on these or a total safety profile needs to be established.

So, there is a need to find out alternative means, alternative methods of toxicity safety evaluations, other than the documented use of traditional practice. One can also use pharmacovigilance as a tool for clinical safety basis documentation of actual clinical practice.

These limitations are more obvious in India, because traditions are very strong; sometimes the industry also uses this as an excuse for not conducting adequate safety studies. Probably the academicians should also come forward to guide and suggest what minimal toxicity studies are required for herbals, especially herbs that have a history of traditional use.

Toxicological assessment of herbal materials: Current status and progress in India

P. Kakkar

Scientist-F and Head, Herbal Research Section, Indian Institute of Toxicology Research, P.O. Box-80, M.G. Marg, Lucknow - 226 001, India
E-mail: pkakkar@iitr.res.in

I have been given the task of talking about the toxicological assessment of herbal materials, and also its progress in India. Now, progress in India is a very big topic, but I will try to cover whatever I can and that too in terms of Toxicological Assessment.

Let us begin with the question - Is the toxicity testing of traditionally used herbal medicines required? We must question this, because there is assured safety, as herbal medicines have been used in India for more than 4000 years as per documentation and earlier also. However, if these herbs are pharmacologically active they will have the potential to be toxic too, if used in a very high dose. Hence, toxicity evaluation is required for these materials also. It is a very systematic evaluation and we need to have our minds open when doing this toxicological evaluation.

There are two things that have happened over the past say 25 years or maybe more in India. One is, there has been a shift from individual medication by the *Vaidji* to larger scale production of these herbal medicines or herbal formulations. There is also an economic aspect attached to it. We would like our country to grow and reach the bar, which is 62 billion dollars, so let us not have the share of 1.5%, we want to have a better percentage in that market.

The safety evaluation of herbals would depend on two or three things; one is the purity of the preparation. If the preparation is not a standardized one, that particular individual preparation can cause toxicity. It does not mean that all such preparations are toxic. Second is, it should be free from contamination. There should not be any contaminant in the medicinal plant preparations and then a systematic toxicity evaluation is desired. The quality may be compromised due to a number of factors. One is misidentification — not many people know how to identify a medicinal plant and particularly a plant species. Then there can be adulteration, substitution because of economic reasons, because the species may be endangered, maybe cost-wise very high so substituted with another one, or not available so substituted with another one. There can be contamination, which is always inadvertent and not with any intention as such. Storage of the material and shelf life can also compromise the quality of the preparation. Quoting one study where 25 commercial *Panax ginseng* preparations were evaluated for seven marker compounds, they differed significantly from the ginesenosides' content on the label, that is, 15-fold in the capsules and 36-fold in the liquid preparations, which is a very high amount of variation.

The question is, 'do we really have standardization?' and AYUSH took a lead in developing pharmacopeial standards, which Dr. Sharma mentioned earlier. We have been a part of this study and we have concentrated on 17 poisonous plants; altogether 24 medicinal plants were done in this and we developed the chromatographic finger print profile and also the microscopic studies to identify the plant. Seven of these monographs have already been published. We can also go in for say genomic parameters liked RAPD,

RFLP, and identify of the species using that. In our laboratory, we have conducted it for *Desmodium gangeticum* a very important constituent of *Dashamula*. There can be an intrinsic toxic principle in a medicinal plant. This kind of information can come from literature and from reports, and that is why it is very important to report and document it.

One example that is given here is over 100 cases of irreversible nephropathy reported in young women attending a slimming clinic, since 1993, and some developed urothelial cancer also. There was an inadvertent use of the toxic *Aristolochia fangchi* root in the formulation as a substitute for *Stephania tetrandra*. A very recent report in 2010, mentions that consumption of aristolochic acid containing Chinese herbal products (studied in 4574 patients) was found to be associated with an increased risk of cancer of the urinary tract, in a dose-dependent manner. So, if we have this kind of information and we also have information about aristolochic acid being present in the preparation, then we can be cautious right from the beginning. There are certain warnings that keep coming from time to time like the Food and Drug Administration (FDA) issued a consumer advisory that *Kava* products may be associated with severe liver injury.

These types of toxic herbs may not be present in the dietary supplement or medicines, but what about topical applications. The pyrrolizidine alkaloids in *Comfrey* is one of the examples. *Comfrey* is one of the most popular herbal teas in the world, which contains pyrrolizidine alkaloids and FDA took action to remove *Comfrey* from all dietary supplements in 2001. But you see, there are creams and cosmetics which contain this and they are being marketed. Some of the families of medicinal plants in which pyrrolizidine alkaloids are present are Boraginaceae, Asteraceae, and Fabaceae. Pyrrolizidine alkaloid has minimum toxicity, but when it is metabolized in the liver then the pyrroles formed are toxic, so it causes liver damage. Apart from liver damage it also causes damage to other organs; it can infiltrate the lung fluids, it can cause pulmonary edema, and in high doses it can be fatal. So there are the non-target toxicities also.

That was about quality and intrinsic toxic principles that may be present in the medicinal plant and now coming to the contaminants; herbs should be free from contaminants. What are the contaminants that we should look for? Heavy metals, pesticides, microbial load, and radioactivity. Radioactive load may be related to the location, so one has to exercise one's own wisdom to see whether it is required to be tested or not. However, with regard to the other three, they do require testing. Heavy metal may be present as an ingredient, as in some of the ayurvedic preparations or as a contaminant. The commonly tested pesticides, synthetic pyrethroids, and organophosphates, have limited half-life, so they do not cause much of a problem but organochorines do cause a problem because they are residual in nature and persistent, and studies show that even 25 – 30 years after banning DDT in the US, the residues are present in the soil. So, the persistent nature of these pesticides requires that these should be tested. Now with this knowledge, in our country DDT is not allowed to be used for agricultural purposes, but it is used for vector control because we have a problem of malaria.

Hence, we took up a systematic study of heavy metals and persistent pesticides in medicinal plants. Since 2002, taking up studies in three simultaneous projects, we have analyzed more than 1800 plant samples. You can see the map and the red dots in more than 100 locations in the country from where the samples were collected, belonging to 312 plant species, and heavy metals, volatile and non-volatile; both were tested. We tested for DDT (op' and pp'), its metabolytes, all the four isoforms of HCH and alpha endosulfan and tried to collect samples equally from each zone. If you would see, the data generated from the analysis of all the 1800 plants, for lead, cadmium, arsenic and mercury (Pb, Cd, As, and Hg), then the level of heavy metals is not very high. In our study, hardly 1.5 to 2% of the plants contained lead over the permissible level.

Also, different countries have different permissible limits. In Singapore the permissible limit for lead is 20 mg, whereas, in our country it is 10 mg. But now we have the directive that lead, cadmium, arsenic and mercury are to be tested in all herbal raw material extracts and all the finished products. Among the persistent pesticides, most of the time they were below the detection limit, but the data that you see here is just for the detected ones; although it does not mean that if it is detected, it is above the permissible limits. As we have sophisticated equipment we can detect it at a very low level.

Just a finding that some heavy metal or pesticide has been detected, does not mean that it is toxic. We have to exercise our wisdom to see what is toxic and what is not toxic. It does not have to be alarming if DDT is just detected in a number of plants. The Commerce Ministry fixed specification limits for heavy metals and pesticide residues, which came out in 2007. As we have generated a large data volume, we have developed a database for it, which has recently been copyrighted, where we have the names of the plants. It contains the plant part, it gives you information regarding the region from which it has been collected, and the date on which it has been collected, and from the data, one can generate a report according to one's own need. It will give you a picture of all the plant parts that we have analyzed.

We have also analyzed the microbial load in medicinal plants as per the WHO permissible limits, bacterial count should be equivalent or less than 10^5 colony forming units (CFU) and fungul count should be less than 10^4 CFU / g crude plant material. *E. coli* and *Salmonella* must be absent in the plant material.

Now coming to toxicity testing, it depends on the intended use. Here I am citing one example of garlic; it can be used as a food additive, conventional food, dietary supplement food, for special dietary needs, can be used as a biological drug or a medical device — some people use it as an ear plug and in some of the cosmetics. There are several toxicity testing guidelines available, for example, OECD, ICH, FDA, WHO, and so on, which outline the testing requirements. The minimum testing required is Acute toxicity: 14-day study, Sub-acute toxicity: 28-day study, and Chronic toxicity: 90-day study. The duration of the repeat dose studies depends upon the intended use of the herbal medicine (e.g., single or repeated clinical exposure for less than one week, the administration period for toxicity study is two weeks to one month; for long-term repeated administration > 6 months, the administration period for toxicity study is 9 to 12 months, and so on)

The use of animals has also been reduced. Now we have a test for acute toxicity (OECD 420) which we can do with only five

animals (female rats). One animal is taken for a sighting study, with a fixed dose and observations done for 14 days for toxic symptoms and mortality. The main study is conducted with four animals. The cage side observations are done, which are routine, and the gross pathology after the sacrifice of the animals. So with just five animals you can do the fixed dose acute toxicity study for herbals, which have a history of use.

Coming to metal toxicity, it is a function of the specific metal, which metal has been used, the form of the metal that is used, whether it is a sulfide or an oxide, as also the exposure, how long has the person been exposed to it. Thus, the dosage and the duration are very important and the question to be asked is: are these heavy metals present in the herbometallic preparations? Are they bioavailable after specific processing, especially if using the herbometallic preparation, with presence of toxic heavy metals as an ingredient? Whether prepared according to the ancient text, has there been any quality control, how to assess the metal present in the desired form like oxide or sulfide or it is in some other form or is it retained by the vital body organs? As far as quality control is concerned we did a metal estimation in *Tribhanga Bhasma* prepared by three different Centers (this was done in a project with AYUSH). The heavy metal contents were similar in the preparations across the three Centers. So the quality is maintained if it is prepared according to the text. We were also involved in the preparation of the protocol for evaluation of herbominerals. We have done some study for coded herbometallic preparations and we found that subacute toxicity with recovery and a subchronic oral toxicity study showed no toxicity at all of these herbometallic preparations. This was an initiative to clear doubts regarding the safety of metal containing herbal preparations, because that is one line of Ayurveda which is very effective and poses a lot of questions and needs answers.

Another milestone has been the golden triangle partnership project that Dr. Vaidya has been very instrumental in bringing out. In this program, Ayurveda meets the modern medicine and the basic science. The CSIR, Department of AYUSH and ICMR together went into this project, which was started sometime in 2006, and the idea was to validate the traditional Ayurvedic drugs and develop new herbal formulations. IITR has been involved in the development of eight of the new formulations out of which dossiers have been submitted for six. For three herbomineral drugs (*Ras kalpa*), 90 days oral toxicity was also done and they were found to be safe. In one of these, its toxicity studies were done as well as metal content estimated in all the vital organs. When we used 10 times the therapeutic dose, there was a slight increase in the metal content, which went down during the recovery period. There was a recovery period of 30 days and after that the metal content was quite close to the level in non-treated animals. So this was an answer to whether metal was getting accumulated in the vital organs or not. It would cause toxicity if it got accumulated in the vital organs in high amounts. Some specialized tests that could be required were the immunotoxicity parameters. Here the Ayurvedic text can give you indications, because many of these side effects and other things are already mentioned there.

Specialized tests required may include immunotoxicity and allergenictiy parameters (IL1 b, IL 4, IL 6, IL 10, TH1, TH2, histamine levels, etc.), mutagenicity tests (Ames, micronucleus assays), and medium- and long-term animal tests for carniogenicity as per the international agency for research on cancer guidelines. Reproductive studies may be required for some special cases, not always. This includes a teretogenecity study and reproductive toxicity, besides the classical parameters that are already studied.

Herb-drug interaction is another aspect less worked on, but requires a lot of documentation. Here we need help from the pharmacovigilance centers, because the adverse reaction reports are given there, so we have to improve the quality and quantity of the adverse reaction reports due to herbal products. Some training is needed and people are to be made more aware of pharmacovigilance. Then, the data available with the Poison Control Centers should be used for toxicity evaluation. We cannot ignore the importance of literature for reported toxicity that can be traditional as already mentioned in Ayurveda, any of the traditional text or other sources, and sharing of information is important.

Another important effort that has been ongoing is developing a mechanism to safeguard our traditional knowledge and this was the turning point which brought in a Traditional Knowledge Digital Library, which was initiated with the effort of AYUSH and National Institute of Science Communication and Information Resources (NISCAIR). This is an electronic database containing a translation of 36000 *shlokas* in five languages. The languages are English, French, Spanish, Japanese, and German. It has more than 10 million pages of information. And this has now been made available to patent offices. In the year 2009, it was made available to the European patent office, Indian Patent office, and German patent and trademark offices; and in December the United States Patent and Trademark Office (USPTO) has also been given access to it and this has saved many claims. Another aspect is, now we have a comprehensive traditional knowledge digital library, where a network for database expansion was launched in 2004, to cover approximately 2600 medicinal plants used in Ayurveda. The available toxicity data has been documented for most of the medicinal plants. Like for one particular plant *Digitalis lanata* (digoxin, digitoxin, digoxigenin), toxicity data is given for the oral route, for adults, for pediatric population, and individually for digoxin, digitoxin, and digoxigenin; with all sets of symptoms, usage, and antidotes. All this information is present in this database as a value addition, which is being constantly updated. So, a lot of toxicity-related information can be availed from it. Of late, we have started adding the 3D structure of the active constituent to the database. Citing this particular example, there are three constituents and the 3D structure is given there. Digitoxin has been the most worked out but docking these structures, studies show that digoxigenin may be a better / more potent therapeutic compound. So, apart from giving toxicity-related information, it also gives information regarding the possible efficacy.

What are the future approaches and challenges? Predictive toxicology is needed to prioritize for safety / toxicity testing. Like we have thousands of chemicals, we have a large number of medicinal plants and among the medicinal plants we have a whole lot of phytochemicals, so how do we prioritize them? Using Quantitative Structure Activity Relationship (QSAR) studies and building a consensus model, not taking information from one or two databases, but taking information from many models and then taking information from toxicity databases and data mining software, and then combining all of them, one comes to a conclusion. There can be an omics approach like genomics, transciptomics, metabolomics and what would it give us? These

can give us noble biomarkers of toxicity, potential tissue or cellular location of the toxicity, and clues to the mechanism or mode of toxicity.

In future we would also be facing nanotized herbals because they may be more bioavailable, effective at lower doses. For example, any constituent may be an alkaloid which may be toxic, it can be nanotized and the dose-reduced, hence, reduced toxicity. Encapsulation or slow release forms can also be customized for reducing toxicity. These modifications would post some safety issues also, for which I am leaving these questions with you. Does nanotization affect the stability of herbals? Is the bio activity of nanotized herbal products similar to the parent herbal product? Do we require different safety parameters for nano herbals? Is the material used for nanotization natural or synthetic? So, whatever material is used for nanotization, its toxicity also needs to be evaluated. Leaving you with these questions and a futuristic approach.

I thank you all for your patient listening.

Unilever's risk assessment strategy for herbal materials

Bobbie Bradford

Product Toxicologist, Unilever, Safety and Environmental Assurance Center (SEAC) Colworth Science Park, Sharnbrook, Bedfordshire, U.K. MK44 1LQ
E-mail: bobbie.bradford@unilever.com

I would first like to thank the organizers and my colleagues in Bangalore for inviting me to come to this conference and make a presentation, because it has given me the opportunity to visit India for the first time. So thank you very much. It also gave me the opportunity to listen to distinguished speakers and learn more about Ayurveda and the purposes and essence behind it.

Therefore, what I am going to talk about today is how we can actually look at safety and risk assessments for Unilever products. As Julia established this morning, SEAC does the safety risk assessment for consumers, for our workers, and the environment. We also look at the sustainability of the ingredients in the Unilever products. I am going to concentrate today on consumer safety, but of course that can also have an impact on worker safety as well. I am going to be talking about why Unilever is interested in the use of herbal materials, how we approach the risk assessment looking at both hazard and exposure, and the different ways that we can do that — by using testing strategies and / or also using the history of safe use. I will also discuss the 'history-of-safe-use model' that we have developed to conduct the risk assessment of herbals and use some case studies to show different ways in which we can look at risk, risk assessment, and risk management, using as examples green tea extracts and *Brahmi*.

Unilever is a global company with lots of brands and we have to make sure there are no safety concerns with any brand, because that can obviously affect the reputation of Unilever in other brands as well. We need to make sure that when we do safety assessment we are very robust in that. This is also relevant for herbal materials; the reason being that the number of different product types fortified with herbals is increasing.

The risk assessment varies for herbals being added at emotive levels (e.g., herbals added to shampoos at very low levels where they do nothing functionally) to when a herbal ingredient is added to a product to give a functional benefit (e.g. functional benefit in food or having an effect in a cosmetic product). When we are looking at ensuring consumer safety, we conduct the risk assessment as we would for any material, whether it is a herbal material or a synthetic chemical. We look at what type of hazards and potential harmful effects could occur and the exposure. This risk assessment is very different from the one that is done for herbal medicines. With herbal medicines we have a patient, and the practitioner will be giving a dose. When we have a consumer product we have to model exactly how much we think the consumers will use, by finding out about normal habits and practices. The habits and practices can be completely different from one area compared to another; how people use deodorants in UK, in India or in Brazil can be very different. We use that information about product usage and put that alongside how much of a particular material is going into the product and this gives us the daily exposure to that material.

When carrying out the risk assessment of herbals that give functional benefits, both hazard and exposure can be affected by functionality. In our risk assessments we need to look at the hazard and exposure scenarios. I will talk about exposure first. To determine exposure for foods and drinks we model what the consumer will be exposed to based on the food intake data. We use both the median intakes and take into consideration high intakes using different databases. This is where we struggle, sometimes getting the right sort of information from different parts of the world. There are databases based on general intakes of various food products from the US (NHANES) and the UK (NDNS), but we often have to rely on our colleagues in India and China to give us information about how consumers there would typically use our products. As mentioned earlier, we also need to take into consideration high intakes — some people consume more than the normal (median). So we have to cover those as well in our risk assessment.

For cosmetic ingredients it is a combination of the frequency of the application and the amount used per application put together to get the exposure to a particular product type. We collect data on how much of the product is used on each occasion and how often the product is used, and using the level of ingredient in the product, we can determine the total amount the consumer would be exposed to each day. It is also important to know how the consumer uses the product. For example, whether it is a face cream or a body cream determines the surface area of the skin that will be exposed, or for an anti-perspirant, whether it is an aerosol spray, in which case lung exposure will be important. We also look at who uses the product - whether it is a product used by the whole population or more likely to be used for babies or by the elderly or whether it could be targeting a particular sector of the nation. We also look at susceptible individuals, for example, for a skin cream - whether it might be used by people with underlying skin problems (such as eczema or psoriasis). How much is retained on the skin is important, whether a skin cream will be left on the face or body or whether it will be washed off. We have skin surface area data for different parts of the body and we use this to give us our consumer exposure levels for different product types (for example a face cream or an underarm deodorant). We put all of this together to determine how much of an ingredient a consumer will be exposed to and what are the likely endpoints of concern.

There is an influence of functionality on exposure predictions and this has to be included in our exposure calculations. Functional materials like herbals from Ayurveda and TCM may have previously had restricted uses or different exposure scenarios and we need to take that into consideration, whether or not this affects how they might be used in consumer goods. For some cases, where the levels are very low, we can use what we call exposure-based waving (EBW). This can be used when a herbal ingredient is used at such a low level that there would not be any safety concern. There are methods like the threshold of toxicological concern (TTC), a method developed many years ago for looking at safety of flavors in foods. Using rules based on the chemical structure the TTC provides for inclusion of ingredients in products at thresholds below which one can say that an untested material will have a very low risk to human health. However, this can be difficult to do for herbal ingredients, where there are both many chemicals present and a lot of them are not identified.

For herbals ingredients added for functional effects it is unlikely that EBW will be useful, as the levels are likely to be above those that could be supported in this manner. Therefore we need further work to characterize the hazards. When we are looking at the hazards we need to think about the intrinsic properties of the herbals, which might be a safety concern. For an Ayurvedic material, for example, we start with what is known from the literature and what is known from the history of use of that herbal. To do that we need to start with the identification of the herb, which part of the herb is being used, is it the same as has been used traditionally, is it the root or leaf? In consumer products it is not typical that we would use the whole herb. It is more typical to use a preparation or an extract, and it is important to see if the composition of the extract is the same as what has been traditionally used and whether we can actually compare that with what has been prepared traditionally. To do this we need to use analytical techniques to confirm the similarity. SEAC has done a lot of work in analyzing naturals and using different approaches to compare materials. There are different methods to carry out these analytical comparisons. One can look at one or two chemical constituents or markers if we know exactly which constituents are effective, but it does not tell the whole story. There are better methods of conducting chemical analysis in terms of using multi-component approaches and using fingerprints, this means different types of pattern and spectrum profiles from a lot of different analytical techniques put together, comparing one with the other, and seeing how similar they are. This provides unique visual patterns representing the presence of unknown or known characteristics coming from the components. These techniques help us to compare the fingerprints of the herbals with what has been traditionally used.

Hence, now that we know what we are dealing with, we know that we have got the same herbal, and we know that the specification is the same, so we can start to look further into whether we can support the material based on the history of safe use. At SEAC we developed the history-of-safe-use model based on the knowledge and questions we already used within SEAC to make risk assessment decisions, but we wanted to make it more robust and more standardized. So, we all sat down as a big group and discussed the questions we would normally ask if we were trying to support a material based on the history of use, how we would get the answers to those questions and what would lead us to make the safety approval decisions. We used a technique called the multi-criteria decision analysis (MCDA), which takes a lot of different pieces of information and puts them all together, comparing both the positive (supportive) and negative data. This then gives you a scoring system so that you can compare one material against another. The main basis of the history-of-safe-use tool is that you are looking at the similarity of the ingredient that you want to use in a product and comparing it with an appropriate comparator, which is already in use. On one side of the tree we have the history of use, which includes parameters such as the degree of similarity of specifications and the origin and identity of the herbal ingredient. This is supported by many of the earlier presenters today, that it is very important to look at the herbal material that you are dealing with — has it come from the same place as in traditional use, has it been grown in the same way, prepared and processed similarly (e.g., water extract or solvent extract?) and how does the specification compare using the fingerprint analysis?

We also look at the population exposure, has it been used in the entire population or has it just been used in a small proportion of people. For example when we were looking at an extract of *Hoodia gordonii*, this plant was used only by some tribes in South Africa, so we could not really use this approach. In comparison when we were looking at traditional medicines that are used in China or in India, there are many more people who have used these herbals previously, so we can use that sort of evidence. Duration of exposure, whether it is something that has only been introduced quite recently or whether it has been used for 1000s of years, the patterns of frequency of use, something that has traditionally being used on a daily basis compared with a material that would only be used only on very rare occasions. How much has been used each day and how many times a day, and finally is there any effect on the bioavailability by processing or using the material in our products.

That is the side of our history of use, and then on the other side we have 'evidence of concern' and this is looking at whether the material has got any biological effect either pharmacological or toxicological. The evidence of concern includes information on what the material has been used for in traditional medicines and if there are any toxicological data reported. Have any adverse effects been reported in man or any contraindications and is there any evidence of concern due to mechanism of action. With some materials we will score very low there because we do not know anything about it.

Overall what we would like to see, to support a material using history of safe use, is that the history of use branch should have a high score and the evidence of concern a low score. We have put a number of ingredients through this tool (history of use and evidence for concern) and scored them based on this model and based on that we validated as the model for use for further ingredients.

If we look at the history of safe use and we decide that a particular material is very different from what has been traditionally used or the level needed in a product is much higher than what has been used, then we may need safety tests to identify any hazards. These will be the standard toxicity tests, for example, genotoxicity, systemic toxicity, allergenicity, and so on. We need to assess the local toxicity effects particularly for cosmetics or for household care products, so we need to consider skin irritation and / or corrosivity. For both food and personal care and sometimes for household care we also need to think about systemic toxicity, so that is when we might need to do repeat dose studies in animals,

to give us those answers. We use the results from these studies to find the no adverse effect level (NOAEL) which we then compare with our predicted exposures and that gives us our margin of safety.

For consumer goods we are not able to control the use or consumption in the same way as with pharmaceutical products, we leave the consumers to decide how much they are going to use. There is also no risk : benefit with consumer products, and so we tend to have a higher margin of safety that would be standard with medicinal products. The standard used is a margin of safety of around 100 for local and systemic effects, apart from inhalation where we have a lower acceptable margin of safety because we are looking more at local effects in the lungs. For the use of functional herbals the standard toxicity studies may not be applicable all by themselves, so we have to consider what the functionality is and how this affects the studies we do. One of the methods we can use for that is to look and see what is the health or cosmetic benefit that is wanted for a product - Whether it is blood pressure control, cholesterol lowering or boosting immune function. We also consider whether there is information on the mode of action. It is important to get as much information as possible. Based on the mode of action, relevant animal toxicity studies can be designed to address specific endpoints. We are increasingly trying to take more measurements in human studies, working more closely with our partners in the clinical groups within Unilever. We are adding safety parameters into some of the efficacy studies that the clinical group are conducting, to monitor adverse effects or identify safety or tolerability concerns not picked up in animal studies (for example nausea, vomiting, headaches).

In our safety and risk assessment, we put together the hazards and the exposures considering not only the intrinsic properties of the materials and normal habits and practices of the product uses, but also thinking about how functionality affects both the hazard and exposure.

The first case study that will be described is green tea extracts. The use of Green tea is increasing. Although it is the most widely consumed beverage in the world, its use has been predominantly increasing from the Asian countries to throughout the Western world now. The main constituents of green tea are the catechins, which are at a much higher level in green tea compared to black tea. It is believed that catechins have antioxidant properties which can lead to health benefits. We had consumption data representing the median and 95 percentile exposure to catechins using the intake from traditional green tea drinkers in Japan. In Japan there are very high consumers of green tea and this could be used as the basis for history of use, as also the history of safe consumption. There were also a number of toxicology studies published on one of the catechins, EGCG. The available data included genetic toxicity data, reproductive toxicology data, dermal and eye irritation data, and also acute and short-term toxicological studies. We used the history of use and toxicology data combined with chemical analysis showing that the catechins profile in the Lipton tea products was similar to that in typically consumed green tea products. Therefore, we approved the use of these green tea extracts in Lipton products and we did not have any safety concerns.

In the last two or three years, however, there have been a number of case reports published associating liver diseases with consumption of supplements containing green tea extracts. These reports led us to re-assess the safety of consumption of the green tea catechins and whether we should be worried. The reports published linked different liver injuries with consumption of particular green tea extract supplements. In particular the supplements were being used as slimming products by people not consuming very much food and usually consumed first thing in the morning. The Lipton tea brand included a standard green tea product already, but there was also a product launched (Linea RTD green tea) with enhanced levels of catechins with claims around reducing waist size. There were no explicit claims on it about slimming but there was an implied claim around weight reduction and effects on body shape, so it could be used by people that were slimming. Therefore, would we also see liver toxicity with this type of product? Because of the reports on liver toxicity the US Pharmacopeia also gave safety advice on dietary supplements containing green tea extracts and recommended labeling the products to say that they should be consumed with food and to include a caution that you could develop symptoms of liver diseases with such products. We looked at the published data and that seemed to indicate that the bioavailability of catechins was greatly increased when they were consumed in the absence of food and this increased bioavailability could cause damage to the liver. This was based on a dog study using EGCG, comparing blood exposure in fed versus fasted dogs, which showed an increase in exposure to catechins in fasted dogs and enhanced toxicity in these animals. We designed a human study, in which subjects consumed Linea RTD green tea at typical levels of two servings a day for two weeks. The levels of catechins in the blood were measured and compared with the levels seen in the dog study. An acceptable level (action standard) of EGCG was agreed on, based on the no adverse effect level in the dog study. If the level of EGCG in the human study was below this action standard then we would not have safety concerns. The result of the study was that that the levels of catechins (we measured EGCG and other catechins also) did differ in fed versus fasted subjects. However, the blood levels that subjects were exposed to with the Linea tea were very much lower than the action standard and well below the adverse effect level. This indicated that there was no safety concern for the Linea green tea products and so we did not need to do any risk management.

The second case study I would like to talk about is *Brahmi*. Unilever was interested in promoting the cognitive benefits of *Brahmi* in tea products. The health benefits claim and the levels that were going to be used were those that would be typically consumed within the population. There was a large amount of historical consumption information and we relied on our colleagues in Bangalore to provide this data. First we used different analytical chemistry techniques (Infrared and HPLC) to look at the specification, comparing the material we wanted to put into the product with that typically used, and that confirmed that it was equivalent, the fingerprints were very similar. We then evaluated *Brahmi* in all the other aspects of the history-of-use-tool and scoring was done for all the components, like origin of the ingredient, preparation and processing, bioavailability, exposed population, levels of use, evidence of concern due to mechanism of action, known contradictions, known toxicological effects, and so on. With the available historical information and scientific data, *Brahmi* scored high on 'history of use' and low on 'evidence for concern'. The risk assessment concluded that the *Brahmi* extract to be used was similar to the historically used material and there were no safety issues associated with it. The analysis for batch variability was recommended and the particular Brahmi extract was predicted to be safe for use in tea.

In conclusion, herbal ingredients are of growing importance in Unilever's products and risk assessment of herbal ingredients in food and home and personal care products requires exposure information of the use of the products (Frequency and amount used / consumed and levels of herbals in products) and hazard information of the herbal ingredient (Origin and characterization of the material and toxicological information).

Panel discussion

Chaired by

Y. K. Gupta

Professor and Head, Department of Pharmacology, All India Institute of Medical Science, New Delhi, India.
E-mail: ykgupta@aiims.ac.in

Chair's Opening remarks

The subjects of today's discussions have raised the issue of why such a debate, in such a depth and breadth, did not take place much earlier. It is most appropriate that it has happened at least today and the participants are of diverse learning / expertise / experience and above all with openness, driven by scientific needs, yet taking into consideration the history of its safe use (HoSU). Discussions have brought into focus how it is possible to document HoSU in new ways, how one can make it robust, creative ways of scientific thinking, the possibility to avoid falling into the trap of doing regular and conventional toxicity evaluation, but limiting such evaluations to get answers to specific concern areas.

It is natural that in a Naturals conference of this nature, in India, a lot of debate and discussions get into the realms of Ayurveda / TCM and Traditional knowledge, and there is nothing wrong in the same. However, the subject of the symposium was more on Naturals and not on Traditional knowledge base.

The symposium organizers have evolved a method for panel discussions, which will make focused discussions and a way forward possible.

As moderators of the one day Symposium on the important Topic of Safety and Risk Assessment Approaches for Materials of Herbal Origin, we record the discussions and agreements that were reached in the Panel Discussions session.

Methodology

Throughout the day's discussions, the rapporteurs documented and collected the main themes of the discussions, with consultations with the Chairman of the Panel discussions. These were drafted out as crisp statements to be put up at the end of the Chairman's Remarks - Panel discussions, questions from the participants, and answer sessions. The following records the same.

Open house discussions

Several outcomes of the discussions throughout the day in the symposium as recorded by the rapporteurs, and the following position statements were agreed upon:

- History of the use of herbal materials, recognized in traditional medical systems is a great scientific asset for Safety and Risk Assessment. This should constitute an appropriate evidence of safety in the risk assessment of herbal materials
- There is a need to improve the documentation of the history of use of herbal materials
- It is essential to establish the History of Safe Use in the context of the part of the plant, processing, format, dose, and route of administration
- It is also critical to develop relevant quality profiles, finger-prints, and specifications for all herbal materials that have a safe history of use
- Currently, there is no common globally determined acceptable level of heavy metals as contaminants (including US FDA)
- Large manufacturers are moving away from raw herbs to extracts, wherein, heavy metal levels could get concentrated

Approaches

- Common global acceptable levels
- Rigorous scientific evaluation and harmonization to avoid barriers to trade
- Develop technologies that can selectively remove or reduce levels of heavy metals in extracts, without altering the composition of the extracts
    - There is a need to develop a robust safety assessment process for Herbal extracts prepared using organic solvents as a medium, which appropriately consider any Health Outcomes Survey (HOS) data and guides additional safety data to be generated
    - Great care is to be exercised while reviewing published scientific literature / data related to Safety of Herbals. A guideline needs to be developed that can help in identifying the relevant information for safety, from the published literature (e.g., not to extend information of a chemical component to the total herb)
    - There is a need for focused education and training to enhance human resource for toxicology and safety evaluation sciences (including regulatory toxicologists), in India
    - Academic Institutions and National Laboratories need to evaluate the initiation of specific courses to develop safety professionals and regulatory toxicologists
    - In the absence of a structured pharmacovigilance program for herbals, there is a need to create greater awareness
    - Pilot projects that document the safety aspects experienced by patients / consumers when they use herbals and a system to evaluate such data needs to be initiated in the country. Such a project has a potential to generate large 'Phase-IV human use data' in a true market situation.

Additional points that came up repeatedly for discussions were:

- Need to generate more data on traditional medicine and their efficacy and safety through Pharmacovigilance and Pharmacoepidemiology
- Need for generating data on the effects of Herbals and their bioavailability, efficacy / safety and interactions, if any with other medicines taken concurrently by consumers
- Evolving a balanced safety and risk assessment approach, building on existing approaches being practiced, for example, the Unilever's History of Safe Use approach, wherever relevant

It was recommended that a core group be formed to draw out a comprehensive strategy and propose the next steps.