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TOXICOLOGY
NEWSLETTERS

"A nation that destroys its soils destroys itself. Forests are the lungs of our land, purifying the air and giving fresh strength to our people."

- Franklin D. Roosevelt

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Safety of Botanicals in Regulated Products

K.S. Rao[1] M.V.Sc. Ph.D., DABT ✉ and S. Gopumadhavan[2],M.Sc., Ph.D., DABT ✉
[1]Eurofins Advinus Limited, Bangalore, [2]The Himalaya Drug Company, Bangalore

1. Preamble

Herbal (botanical) natural plants (or derivatives of them) have been used by humans from time immemorial for its immense value as medical, food (or supplements), Personal Care Products (PCPs), flavoring, coloring agents etc. Early humans recognized their dependence on nature for a healthy life and since then humanity has depended on the diversity of plant resources for food and medicine to cure myriad of ailments. *Herbal remedies and alternative medicine have been and still are, used throughout the world and caters 85% of the world population for their health needs. It is estimated that about 25% of all modern medicines are directly or indirectly derived from plants, which has led to the discovery of number of new drugs, and non-drug substances.* Examples of herbs whose active ingredients have been synthesized and are now used as registered pharmaceutical therapeutic agents include willow bark (aspirin), poppy (opium), foxglove (digitalis), angels trumpets (scopolamine), deadly nightshade (belladonna), and moldy clover (dicoumarol, coumarin). Although, aspirin (acetyl salicylic acid) and digoxin (digitalis) are synthetically manufactured for pharmaceutical therapy, their herbal origins are still relevant in number of cultures. However, one should always keep in mind finished products or mixture of herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal or traditional herbal products.Herbal products, foods/supplements, medicines and PCPs made from leaves, flowers, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be used in the entire form, fragmented, powdered or extracted. *Herbal medicines include in addition to herbs, fresh juices, gums, fixed oils, essentials, resins, etc. Use and precautions associated with herbal medicines can be confusing for some as they are considered as ''naturally occurring'' rather than ''man-made'' compounds and hence presumed to be ''safe.''* Added to the confusion of the consumer regarding the similarities and differences among herbal remedies and dietary supplements, regulatory bodies do not regulate these products in a manner similar to synthetic therapeutic products. To

Editor
Alex Thomas
Bioneeds India Pvt Ltd
+91-974-545-0045
alexthomas.a@gmail.com

complicate matters further, many countries either do not regulate these products or treat them as foods rather than drugs. Regulation of herbal remedies and alternative medicines has been slow. As a promulgation of regulations is hindered by the public's view that these products are commonly used traditionally for decades, if not centuries, hence, there is no need for regulation. In addition, tardiness towards regulation may be a result of the complexity of their chemical content and variety of bioactivities, challenges in controlling the quality of the product, and less scientific evidence to support its efficacy and safety. People turn to supplements for a wide variety of performance enhancing, cosmetic, or health maintenance reasons such as: balancing the diet, compensating for lack of nutrition in diet or exercise, improving appearance, wellness or mental conditions. In many cases, large quantities of an individual supplement are consumed with little regard for their interactions with other supplements or recreational drugs. *In addition, negative interactions with prescribed drugs, cosmetics (PCP's) have been noted, despite the insufficient regulation and monitoring systems that exist. As a whole, herbal medicines/products can have a risk of adverse effects and drug-drug and drug-food interactions, if not properly assessed.*

Use of nutritional supplements is especially common in sports. It is used as a supplement by athletes of all ages, from all countries and in a wide variety of sports. Non-prescription supplement use has been observed among adolescents, students, physically active adults, post-menopausal women, cancer patients and people at high risk of cancer, those with chronic diseases, elderly and children.
Toxicology profiles have yet to be determined for many herbal products currently on the market. *Owing to the peculiarity of the regulation, these herbal products, and plant extracts marketed as dietary supplements were not required to undergo clinical trials for effectiveness, or toxicity before marketing.* The purpose of this document is to provide an overview of issues surrounding regulation and risk assessment of herbal products in medicinal preparations, nutritional supplements, and personal care products, to ensure safety.

In this issue of the newsletter, I will not be addressing the longest-standing ones such as Traditional Chinese Herbal Medicines, Japanese Kampo Medicine, and Indian System of Ayurvedic Medicine. These time-honored products often contain combinations of several plant extracts in specific proportions as described in respective pharmacopoeias. Approved as drugs in other countries, herbal agents are marketed in the United States as dietary supplements and are regulated as such under the 1994 Dietary Supplement Health and Education Act (DSHEA). In European Union the submission of dossiers for registration as Herbal Medicinal Product (HMP) and Traditional Herbal Medicinal Products (THMP) should be as per the format of Common Technical Document (CTD) which includes quality, safety (preclinical and clinical), herb-drug interaction studies and efficacy (preclinical and clinical) (EMEA, 2008).

2. Approaches to Adverse Effects

All medicinal agents have potentially unexpected effects including toxicity, and herbals are no different. *Toxicity of herbal preparation may be attributed due to the inherent toxicity of plant constituents and ingredients as well as due to the*

presence of contaminants and adulterants. As with other drugs, the risk of unexpected effects may also be influenced by a user's age, gender, genetics, nutrition status etc.

3. Food Supplements

Plant-derived ingredients used as food are subjected to novel food regulations in the EU, US, New-Zealand, and Canada. *''Novel foods'' are defined as foods without a traditional history of use*. Briefly, the safety assessment of novel foods and novel food ingredients is based upon the principle of substantial equivalence. This principle focuses on differences between the new food and its traditional counterparts if they exist.

Plant-derived dietary supplements are popular products in the EU and the United States. *To protect human health, the US Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994*. Since that time, the US FDA issued a series of regulations to ensure both the quality and safety of dietary supplements, including that of plant-derived dietary supplements (FDA, 2003; Federal Register, 2007). Accordingly, the US National Toxicology Program has performed toxicological studies including carcinogenicity bioassays on several plant-derived ingredients used as dietary supplements including *Ginkgo biloba* leaf extract, *Aloe vera*, *Panax ginseng*, and Kava (NTP, 2003). The US Food and Drug Administration published a guidance document to assist academic and industry sponsors to develop drugs from botanicals (FDA, 2004). *In the US, most herbal products are marketed as dietary supplements, which may not claim to diagnose, cure, treat, prevent or mitigate a specific disease.*

In the EU, the use of plant-derived ingredients as food is regulated under the General Food Law (EC, 2002), which attributes the primary legal responsibility for the safety of botanical ingredients to the producers. EU regulations, however, provided no guidance on the safety assessment of these products. In 2004 the European Food Safety Agency (EFSA) expressed concerns about the quality and safety of plant-derived ingredients that have become available to EU consumers. Subsequently, the EFSA Scientific Committee provided guidance on the data required in order to carry out a safety assessment of a plant-derived ingredient used as food supplements which also considered previously published and proposed guidelines (EFSA, 2009).

In Europe, traditional herbal drugs are regulated by the Directive 2001/83/EC as amended by Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004 (EC, 2001, 2004). The chapter 2a of the amended Directive 2001/83/EC established specific provisions for the simplified registration of traditional herbal medicinal products with long-standing medicinal use of at least 30 years (including at least 15 years within the Community). Accordingly, the EMEA issued guidance documents on the quality and safety of herbal medicines (EMEA, 2006 and 2008).

4. Personal Care Products (PCPs)

Personal care products include a large variety of product and formulation types, such as soaps, shampoos, and shower products, sunscreens (EU), skin and hair

care products, hair dyes, makeups, lipsticks, toothpastes, dental care products, deodorants, personal hygiene products and many others. There is a growing consumer demand for PCPs containing natural and/or organic ingredients. *Botanical ingredients used in PCPs include a variety of preparations, such as plant extracts, expressed juices, tinctures, waxes, vegetable oils, lipids, plant carbohydrates, essential oils, as well as purified plant components, such as vitamins, antioxidants or other substances with biological activity.* The variety of plants providing these ingredients ranges from staple food plants (cereals, fruits, vegetables, roots, bulbs, spices) to herbs used in traditional medicines or teas as well as exotic plants and their ingredients.

Concerning the safety of all PCP ingredients, whether traditional or botanical, the cornerstone of European and US cosmetic regulations include the principles that *(a) a cosmetic/PCP must not cause damage to human health and (b) the manufacturer is responsible for the safety of a PCP placed on the community market.* To this end, a safety assessment of finished products has to be performed taking into consideration the toxicological profile of the ingredients, their chemical structure, nature (nanoparticles, skin penetration enhancers etc.) and the human external and systemic exposure in order to arrive at the systemic exposure dosage as well as the margin of safety of individual ingredients used in the formulation. *Safety assessment guidelines of personal care products (PCPs) and their ingredients have been updated by the EU Scientific Committee on Consumers Products in order to arrive at the systemic exposure dosage as well as margin of safety of individual ingredients used in the formulation*. However, current EU Guidelines primarily focus on the safety assessment of chemically well-defined ingredients and cannot be easily adapted to the safety assessment of natural substances.

In the US, personal care products (PCP) are regulated under the US Food, Drug and Cosmetic Act. The US Food and Drug Administration was designated to be responsible for the safety of PCP. Overall, the safety of PCP and their ingredients is the responsibility of the manufacturer.

In 1976, the Cosmetic, Toiletry and Fragrance Association (CTFA, today named ‘‘Personal Care Products Council’’ or PCPC) established the Cosmetic Ingredient Review (CIR) which provides a mechanism for the self- regulation of the industry. The CIR provides an independent Expert Panel to review relevant data on cosmetic ingredients and to decide whether they are safe under their current conditions of use (CIR, 2010).

In the EU, PCP regulations were introduced in 1976 (European Cosmetic Directive 76/768/EC). According to this regulation, cosmetics products do not require a pre-marketing clearance. However, the safety of cosmetic products and their ingredients is the responsibility of the manufacturer. Exceptions are certain ingredients, such as UV filters (Annex VI of the Directive), preservatives (Annex V), colorants (Annex IV) and, most recently, hair dyes that require approval prior to marketing. Banned ingredients are listed in Annex II. Concentration-limited substances are listed in Annex III of the Directive. In the EU, the approval process includes submission of a safety dossier to the EU Scientific Committee of Consumer Products/Safety (SCCP, recently re-named SCCS) that issues an Opinion on the safety of the respective ingredient. Safety

requirements for cosmetic ingredients are listed in the ‘‘Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation’’ (SCCS, 2018).

5. Essential Oils and Flavouring Agents

Essential oils have a long history of use as perfumes, flavoring agents and spices. *There are more than 1500 flavoring substances in use in the United States, and the great majority of these are ingested at minute levels at which no cogent scientific evidence of hazard can be visualized.*

Many flavoring substances are closely related chemically, and follow common metabolic pathways, and can be evaluated within structurally related groups, thus reducing the massive burden of testing that would be imposed, if each substance were to be evaluated individually.

Flavoring agents, the major constituents of essential oils, represent secondary metabolites of plants. All chemical constituents present in essential oils are formed by five or six major biosynthetic pathways. Since all these pathways operate to some extent in most plants, the same or similar chemical constituents are present in a wide variety of essential oils. The limited number of plant biosynthetic pathways result in a limited number of structural variations of chemical constituents in essential oils. *Essential oils tend to contain 5–10 distinct chemical classes/ congeneric groups, for example, terpenes, aliphatic or aromatic hydrocarbons.* Therefore, chemical grouping is also a practical tool for the safety assessment of essential oils used as cosmetic ingredients.

Majority of flavoring substances, daily intake is low and many of these substances have, or would be expected to have, simple routes of metabolism, often to endogenously occurring substances. The combined use of structure-activity relationship, human exposure thresholds, metabolic data, and intake is proposed as a basis to perform safety evaluations on flavoring substances. The approach set forth provides a sound scientific basis to ensure that flavoring substances can be efficiently and adequately evaluated.

6. Interactions of Herbs and Pharmaceuticals

The question of herbal interaction requires further consideration and is the subject of public concern. Most interactions seen between herbal remedies and pharmaceuticals are based on more than just pharmacodynamic interactions. Pharmacokinetic interactions with pharmaceutical agents are quite common. Factors that affect the absorption include physical properties, such as the pH, pKa, etc. of the mixture, which may accelerate or retard absorption. *Adsorption of the prescription drug onto the herb may either decrease absorption of the pharmaceutical agent, or reduce the drug’s effectiveness (e.g., cholestyramine, colestipol, and sucralfate).* It is possible that medications and ingesta create a solvent drag for both pharmacologically active compounds (e.g., the cannabinoids) and lipid soluble prescription drugs. Regardless, altered motility resulting in decreased absorption has been well established.

Once across the mucosal barrier, herbal remedies may affect the distribution of a prescribed medicine by altering the protein binding of the drug. Of importance are those drugs that have a narrow therapeutic window, and are protein bound,

that may be displaced, e.g., warfarin. Biotransformation of pharmaceuticals and herbal remedies is affected in several ways. The most common method of alteration of the metabolic pattern occurs with inhibition of phase one enzymes used in biotransforming the drug. *To demonstrate how prevalent such interactions are, grapefruit juice contains the bioflavonoid naringenin, which blocks cytochrome P450 (CYP3A4) resulting in an elevated concentration of the pharmaceutical treatment, e.g., calcium channel blockers. Perhaps the best example of herbal alteration of biotransformation is that of St. John's wort. Several compounds can induce the nuclear receptors controlling cytochrome enzyme increases, presumably to assist in the elimination of xenobiotics with bile acids. One of the active ingredients of St. John's wort (hyperforin) induces CYP3A better than any other inducing agent.* The mechanism of induction has been shown to be through activation of CYP3A via the Pregnane X Receptor (PXR). The result is a considerable decrease in the half-life of drugs metabolized by CYP3A. Efficacy problems have been noted with the antiviral drug indinavir that is also biotransformed by CYP3A.

Pharmacodynamic effects include those of toxicity and pharmacodynamic interaction. Toxicity can be direct organ-related toxicity. *An example is the pyrrolizidine alkaloids (eg., comfrey and butterbur), which, when taken in excessive amounts, are hepatotoxic resulting in hepatocellular necrosis.*

In contrast, indirect toxicity can be subtler. Phytoestrogens are found in many plants and have been suggested as a treatment for menopausal symptoms. There are three main classes of phytoestrogens: isoflavones, lignins, and coumestans. Excessive consumption of phytoestrogens may result in hyper-estrogenism. Excess licorice consumption for the herbal treatment of inflammation can result in potassium depletion, which in addition to being a problem alone can exacerbate the effect of potassium-depleting therapies. Interactions are the major cause for concern regarding herbal remedies. Generally, the pharmacodynamic interactions seen are addition or potentiation of the pharmacodynamic action of prescription medication by the herbal remedy. Some of these interactions can be serious resulting in excessive pharmacological activity of both the prescribed and non-prescribed medicines. Interactions are numerous and examples include St. John's wort with Paxil, Prozac, and other antidepressants, kava with Valium (all benzodiazepines), valerian with barbiturates and sedatives, and licorice with digoxin and diuretics.

Herbal bioenhancers have been shown to enhance bioavailability and bioefficacy of different classes of drugs, such as antibiotics, anti-tuberculosis, antiviral, antifungal, and anti-cancerous drugs at low doses. They have also improved oral absorption of nutraceuticals like vitamins, minerals, amino acids, and certain herbal compounds. Their mechanism of action is mainly through the absorption process, drug metabolism, and action on drug target.

The concept of bioenhancers of herbal origin can be tracked back from the ancient knowledge of Ayurveda system of medicine. *Use of Ayurvedic preparation "Trikatu" from the period between the 7th century B.C. and the 6th century A.D., which is a Sanskrit, word meaning three acrids*. It refers to a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.), *which contains active component*

piperine and gingerol, which enhances the bioavailability of drugs, nutrients, and vitamins. However, these interactions are subjected to the concentration of the bioactive fraction present in the final formulation (Dudhatra *etal.*, 2012).

7. Challenges in Standardization of Herbal Products

Reliable and consistent quality is the basis of safety and efficacy of herbal medicinal products. Given the nature of products of plant origin, which are highly variable and complex products with numerous biologically active components rarely completely identified, therapeutic results and safety issues vary greatly from product to product, even within a single class. Therefore, the evidence of both benefits and risks is specific to the product tested and cannot necessarily be extrapolated to other products, as is the case for synthetically derived compounds.

For these reasons, and due to the inherent variability of the constituents of herbal products, it is generally difficult to establish quality control parameter and maintain consistent batch-to-batch quality; variation in the absence of reference standards for identification can start from the collection of raw materials and increase during storage and further processing. *Quality issues of herbal products can be classified into 2 categories; external and internal. External issues include contamination (eg. toxic metals, pesticide residues, and microbes), adulteration and misidentification, whereas complexity and non-uniformity of the ingredients in herbal products are the internal factors.* The rigorous implementation of Good Agricultural and Collection Practices and Good Manufacturing Practices would undoubtedly reduce the risk of external issues. Internal issues can be managed through the application of modern analytical methods and formulation techniques. The use of traditional medicines, phytotherapeuticals, personal care products, and dietary supplements should be based on quality, safety, efficacy, and consistency (QSEC). Therefore, standardization is an essential measurement for ensuring the quality control of herbal products.

WHO guidelines for quality standardization of herbal formulations include (WHO, 2002; 2007; 2011):

- Quality control of herbal drug material, plant preparations and finished products. In general quality control is based on 3 important aspects of identity or authenticity of herb (macroscopical and microscopical examinations, DNA Fingerprinting), purity and assay of active constituents. A vast array of analytical methods like UV-Visible spectroscopy, TLC, HPLC, GC, ICP-MS, mass spectrometry (MS) or a combination of GC and MS can be employed for purity (also includes microbial contamination, aflatoxins, radioactivity, heavy metals, and pesticide residues) and assay of active constituents.
- Herbal extract should be standardized on the basis of biological or analytical markers along with the chromatographic fingerprints.
- Stability assessment and shelf-life. The physical and chemical stability of the product in the container in which it is to be marketed should be tested under defined storage conditions and the shelf-life should be established.

- Safety assessment based on the weight of evidence from literature, traditional experience and toxicological studies with the final formulation as required depending on the product category.
  Assessment of efficacy by ethnomedical information and most importantly biological activity evaluations (preclinical and clinical).

8. Risk Assessment

Risk assessment of plant materials should exploit all available data. *The first step should be the decision whether a) the available data are enough or insufficient to assess the safety of the material or additional safety data have to be generated. Finally, the safety assessment should be consistent with the current safety assessment paradigm, i.e., identification of potential hazard(s) of a botanical ingredient, its hazard characterization, and intended use, assessment of the human external and internal exposure, risk characterization and management.* Particular attention should be given to the assessment of local exposure and local safety in addition to systemic exposure in case of PCPs. Flexibility should always be a pivotal aspect of the safety assessment of botanical ingredients; given that any novel botanical ingredient will present new and unique safety issues, its safety assessment should always follow a case-by-case approach. Following are some of the approaches that can be considered on a case–by-case basis.

8.1. The comparative approach

8.1.1. Risk Assessment Natural Food or Food Ingredients

The safety assessment of plant-derived products is usually conducted by applying the ‘‘comparative approach’’ (CA) that is currently accepted for the safety assessment of novel foods and food ingredients. Historically, the CA has been based on the concept of ‘‘substantial equivalence’’. In the comparative approach, the first step of the safety assessment of a novel food is to determine what (if any) existing food(s) should be used as comparator(s). *Once a comparator(s) has been identified, the comparison should be performed based on ingredient characterization, chemical composition, and novel analytical techniques, such as protein profiling by gel electrophoresis, methods of processing, previous human experience, intended intake as well as target groups.* Whenever inherent plant toxins are known, it is important to compare their concentrations in food or herbal preparations with those intended for its use. This approach is designed to highlight equivalence, similarity or differences between the new food and the comparator, i.e. its traditional counterpart. The result of the safety assessment should be accepted by the regulators and consumer. Recently, the application of the comparative approach has been extended to the safety assessment of plant-derived food supplements in Europe (EFSA, 2009).

The determination of human exposure to the comparator(s) is a crucial issue in the comparative approach. For foods, exposure data should include an estimation of the serving size, daily intake, frequency of consumption and duration (number of years of consumption of the product).

8.1.2. Risk Assessment of Plant-derived PCP Ingredients

Just like for foods (above), once the comparator has been identified and characterized for, the safety assessment may proceed to the compositional comparison with the plant-derived ingredient intended for PCPs. If there is no evidence for significant differences, human exposure to the comparator will be evaluated relative to the exposure to the intended cosmetic exposure.

It should be kept in mind that the human systemic exposure resulting from a topical application of any substance will generally be limited when compared with that after oral ingestion. Therefore, it is necessary to measure or to estimate the cutaneous absorption of the constituents of both the comparator(s) and the cosmetic plant-derived ingredients. The percutaneous absorption of PCP-ingredients may be estimated from *in vitro* data. When no data are available on a substance, default values based on physical/chemical properties (molecular weight, log Po/w) or values from structurally and chemically related (similar class, functional groups, molecular weight, log Po/w) substances should be applied to conservatively estimate the skin absorption/penetration rates.

In the risk and safety assessment of a cosmetic ingredient the calculation of the Margin of Safety (MoS) is critical. *MoS is calculated as the ratio between a Point of Departure (usually historical NOAEL or BMD values from oral studies) and an estimate of the exposure for individual ingredients used in the formulation.* A default value of 100 (10x10) accounting for inter- and intraspecies differences is generally accepted and a MoS of at least 100, therefore, indicates that a cosmetic ingredient is considered safe for use (SCCS 2018). The risk assessment should also be based on a case-by-case basis, like hair dyes, the exposure is once in 15-30 days and deodorants or antiperspirants wherein it is used as sprays one need to assess the risk arising due to inhalation exposure as well.

8.1.3. Flavoring Agents

Historically, the chemical grouping approach was applied to the safety assessment of flavoring agents by the JECFA (1998) and the EFSA (2004). The procedure applied by JECFA to the safety evaluation of flavoring substances integrated data on intake, metabolism, and structure–activity relationships with toxicity data. For their safety assessment, flavoring substances were first compiled into groups of structurally related materials, named congeneric groups. Members of congeneric groups were expected to have common routes of metabolism and, therefore, similar toxicity. *According to the JECFA approach, substances with simple structures, which are known or presumed to be readily metabolized to innocuous products, may be evaluated without toxicity data. In contrast, the safety assessment of substances for which the metabolism is poorly defined or that are expected to be metabolized to reactive products requires toxicity data.* Given that metabolism or toxicity data are rarely available for all members of a congeneric group, the safety evaluation of substances lacking data depends upon the availability of data from other group members. Using this approach, the safety of more than 1400 flavoring substances were evaluated between 1996 and 2004.

8.2. Chemical Grouping

The term Chemical Grouping describes a general approach to assess more than a single chemical at the same time. It may include the definition of a chemical category or identification of a chemical analogue to which a read-across approach can be applied. The latter is a predictive technique regarding a toxicological endpoint for a substance by using data on the same endpoint from another substance, which is sufficiently similar on the basis of structure, properties, activity, and metabolism. *A chemical category is a group of chemicals whose physical/chemical, toxicological, human health and ecotoxicological properties, as well as their environmental fate, are likely to be similar or to follow a regular pattern as a result of structural similarity (or other similarity characteristics).* Application of the group concept requires that physico-chemical properties, human health effects, and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every toxicological endpoint (EU, 2006).

8.3. Threshold of Toxicological Concern (TTC)

The Threshold of Toxicological Concern (TTC) is a theoretical human exposure threshold value below which no appreciable risk to human health is expected. *TTC is based on the concept that safe human exposure levels may be identified for a substance without determination of their toxicological profiles by estimation their toxicity based on their similarity to known substances.* The US FDA developed the Threshold of Regulation, i.e. a daily human intake of 1.5 µg of indirect food additives that poses a negligible carcinogenic health risk. The concept of a TTC evolved from Cramer Decision Tree (1978) classification of substances into three different chemical classes consisting of 33 structural aspects that classify a chemical as Class I (potential low order of oral toxicity); Class II (unknown toxicity, no presumption of safety or significant harm); or Class III (no strong presumptions of safety; structure may suggest significant toxicity). The calculated human exposure thresholds were 1.8, 0.54 or 0.09 mg/day for Cramer Classes I, II or III, respectively.

8.3.1. Plant Food Ingredients

The starting point in the quality and safety assessment of plant-derived ingredients should always be the comprehensive botanical characterization of the plant, its origin as well as a chemical characterization of the plant ingredient under evaluation. Given that many plant-derived ingredients have a history of human use as foods, spices and/or herbal medicines, the next step should be a comparison of the plant material under assessment with one or several comparators that have an established history of safe human use by using the comparative approach. A comparative approach may be completed by *in silico* analyses, such as chemical grouping and read-across approaches.

The extent of experimental investigation required, such as in vitro, animal, and/or human studies, depends on the adequacy of this information. A decision tree is presented as an aid to determinining the extent of data requirements

based on product comparison. The ultimate safety in use depends on the establishment of an adequate safety margin between expected exposure and identified potential hazards.

For substances used in small concentrations that are predicted to produce minimal systemic human exposure, the concept of the Threshold of Toxicological Concern (TTC) may be applied. Risk characterization of botanicals and botanical preparations for use in food and food supplements should assess all of the available hazard characterization data in relation to the potential or predicted human intake, both the daily intake and the duration of intake.

8.3.2. PCP Botanical Ingredients

The TTC concept has gained extensive acceptance for the human safety assessment of compounds that result in oral exposure. In 2007 (Kroes*et al.*), expanded the TTC concept to PCP ingredients that produce human exposure via the topical route for PCP ingredients. This is based on the use of up to 0.1% of a plant material in a personal care product that is applied to the body at 18 g per day, i.e. maximum amount of total daily consumer exposure to PCP as defined by EU SCCP (SCCP, 2006).*The Scientific Committees (SCs) consider the TTC approach, in principle, scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels of exposure.* The application of the TTC should, however, be done on a case-by-case basis and requires expert judgement (SCCP 2018).

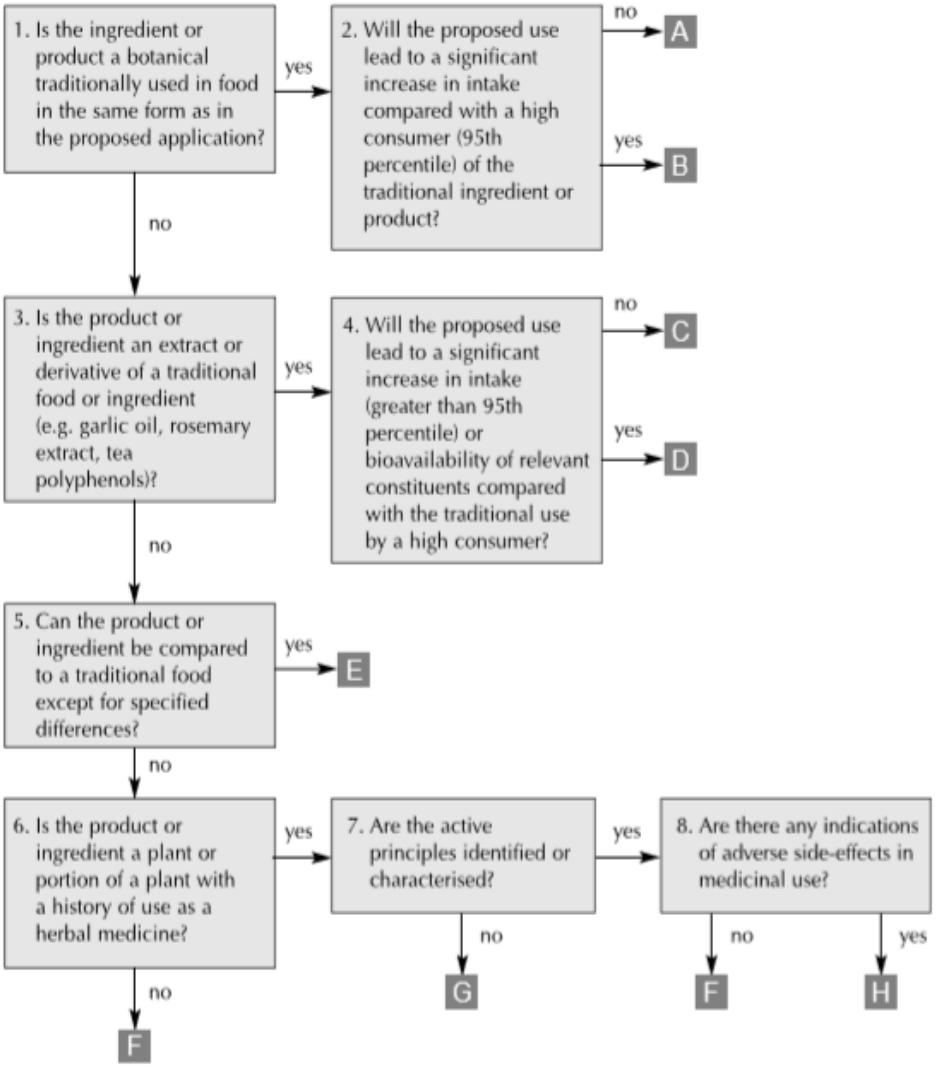
8.4. The Decision Tree Approach

A decision tree can be used as a guidance tool to assist in determining the information that needs to be considered for the safety evaluation of botanical ingredients or products (Scheme 1). *The decision tree allows the classification of new products or ingredients according to their previous history of human uses: botanicals with a traditional use, extracts from botanicals with traditional use, botanicals or botanical preparations with a history of medicinal applications, botanicals with no history of human exposure.* For each case, key general information required to demonstrate safety is defined.

The first question (box 1) identifies botanical ingredients or products used traditionally in food and which are used as such without significant processing. For such ingredients or products, the key question is whether the exposure resulting from the new application is comparable with the exposure from traditional use (box 2). If the exposure is within the 95th percentile of the exposure from traditional use, the information necessary to provide assurance of safety consists in an appropriate characterization of the ingredient or product and documentation of the traditional uses and resulting exposure. If the exposure is significantly higher than the 95th percentile of the exposure from traditional use, additional information allowing benefit and toxicological assessment is required.

The second set of questions deals with extracts derived from botanicals traditionally used in food (box 3). In such a case, the key question is to compare the exposure of relevant constituents of the extract with the exposure resulting from traditional products (box 4).

The next steps of the decision tree refer to products or ingredients, which do not have any history of prior use for that application. *If the new product or ingredient has no history of human use but is comparable with a traditional food product except for specified differences (box 5), information should be available to permit an assessment of the safety significance of such differences.* If the new product or ingredient is a plant or a portion or extract of a plant with no history of food use but with a history of application as a herbal medicine (box 6), information on the identity of the active principles is considered necessary to conduct a proper safety assessment (box 7). If not available, such information should be generated.



For products or ingredients sufficiently characterized, information on the potential side effects associated with medicinal applications should be critically analyzed (box 8). If no side effect has been reported, the full package of information relevant for safety should be thoroughly reviewed to ensure that it fully supports the safety of the specific new application.

For botanicals with no history of human exposure (box 6), a complete package of information is necessary to demonstrate safety.

9. Regulations

With the 1938 Food, Drugs and Cosmetic Act (FDCA), herbs not listed in the USP no longer were recognized as drugs and only as food articles that could make no claims. In 1958 the list of food additives Generally Recognized As Safe (GRAS) contained some herbs. For these additives, the proof of safety burden was on the seller. Pursuant to the 1962 Kefauver–Harris amendments requiring drugs to show efficacy, panels were formed in 1972 to evaluate the active components of over-the-counter (OTC) drugs. Many older agents, including herbals, were exempted under the 1938 FDCA, not requiring evidence of safety before marketing, and under the 1962 amendments, not requiring proof of efficacy; they were considered OTCs. The panel results were released in 1990 with few herbals receiving category I status (i.e., generally recognized as safe and effective [GRASE] and not misbranded), and most as category II or III (not GRASE, misbranded, or insufficient data). *Products sold with a label indicating claims of efficacy were considered misbranded if not identified as category I ingredients.* Because it was not cost-effective to seek required data for herbals, many became relegated as foods or food additives without labeling claims.

European phytomedicines are officially approved products, often with standardized active compounds. *The German Commission E, starting in 1978, prepared over 350 monographs in its review of 1400 medicinal plants, with about 250 of them positive (found to be safe and approved).* They required absolute proof of safety for premarketing approval. *The World Health Organization (WHO) established medicinal plant monographs in which it divides the use of each botanical into one of three categories: use supported by clinical data; use described in pharmacopeias and traditional systems of medicine; and use described in folk medicine, not supported by experimental or clinical data.*

The assessment of botanicals and botanical preparations under food regulations requires the establishment of adequate safety, and any health benefit to the individual would not be considered, as this would make the risk characterization equivalent to a medicinal botanical product. Owing totheir inherent biological activity, i.e. the benefit, it is unlikely that a wide safety margin will be available for botanicals and botanical preparations, and therefore the advice to risk managers may not be as the equivalent of an ADI but may take the form of specific advice on the safety margin available for specific groups of the population in relation to intake, duration, and contraindications.

10. Conclusion

Herbal products (remedies, alternative medicines, nutritional supplements, and PCPs) are used throughout the world, and in the past herbs were often the original sources of most drugs. In most countries, alternative remedies are regulated as foods, provided that no medicinal claim is made on the label. The European Agency for the Evaluation of Medicinal Products has drafted test procedures and acceptance criteria for herbal drug preparations and herbal medicinal products. In the US, the Food and Drug Administration classifies these natural products as dietary supplements.

Safety assessment of botanicals is more complex and associated with a higher degree of uncertainty than that of conventional ingredients. Given that novel botanical ingredients may contain unknown substances with novel toxicological properties, new approaches to their safety assessment are needed.

The nature and extent of toxicological testing required will depend on: nature of the supplement, prior knowledge of human consumption, likely exposure and nutritional impact, and intended beneficial effects. Generally, for herbs or complex extracts, it is not possible to make a risk assessment based on a single active component as more than one may be of toxicological significance and matrix effects may affect bioavailability. Nevertheless, studies on single components may be useful in elucidating potential interactions. *Botanical supplements are intended to produce physiological effects, so there is a need to distinguish a No Observed Effect Level from a No Observed 'Adverse' Effect Level and the margin of exposure between that producing the desired effect and the upper safe level may be smaller than that adopted for food additives and contaminants.* Human studies of efficacy and possible side effects may help in determining the acceptable margin of exposure.

As of now stringent practices based on QSEC in respect of herbal products from seed to shelf is adopted only in few organizations/institutions as it requires state of art facility and subject experts from interdisciplinary areas. In conclusion, there is a need to develop standardized, pragmatic and conservative approaches for appropriate quality and safety standards of plant-derived ingredients, keeping in mind that consumer safety should always be the first objective of the safety assessment of conventional as well as botanical ingredients.

Questions

1. *Write a few examples of Interactions of Herbs and Pharmaceuticals?*
2. *Write about Challenges in Standardization of Herbal Products?*
3. *What are the WHO guidelines for quality standardization of herbal formulations?*
4. *Write about Risk assessment of plant materials?*
5. *Write about Risk Assessment of Plant-derived PCP Ingredients?*
6. *Write about the Threshold of Toxicological Concern (TTC)?*
7. *Discuss about the Decision Tree Approach?*
8. *Write about regulations for Botanicals?*

---------End of the Document----------

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Risk Assessment for Safety of Personal Care Products including Cosmetics

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ToxGurukul is a group of professionals in the field of toxicology who are in search of a platform to learn and share the vast knowledge in this area. This syndicate belongs to independent professionals from different backgrounds of toxicology who share their knowledge to un-puzzle the Rubik's cube that each face in their daily work routine.

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S. No. 135/136 Part, Kothrud, Pune-411038

Corporate Identity Number: U80904PN2019NPL182886

Emai Id: toxgurukul.india@gmail.com