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*This manuscript is dedicated to Prof. Dr. Helmut Lieth and Peter Menke-Glückert*

## **Information gain in environmental monitoring through bioindication and biomonitoring methods ("B & B technologies") and phytoremediation processes—with special reference to the Biological System of Chemical Elements (BSCE) under specific consideration of Lithium**

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**Dedication:** Helmut Lieth, the first, who developed in the 1960s a so global Net Primary Productivity Map of plants by use of computer technologies, influenced different of the authors - since beginning of the 1980ies - by stressing the topic for scientific investigations of ALL chemical elements of the Periodic Table and their positive, negative or neutral effects to ecosystems, organisms and environments. In 1968 Peter Menke-Glückert developed already the Ten Ecological Commandments for having some practical rules for living in "freedom in responsibility". His goal was to get a more balanced and harmonized behaviour of man to the global environment through human's day by day life.

**ABSTRACT**

Different definitions for the concepts of information, information transfer, i.e. communication and its effect and efficiency of false, but also correct information, especially from the environmental sector, are given.

"THE TEN ECOLOGICAL COMMANDMENTS" developed by Menke-Glückert at the end of the 1960s, the 9th commandment "Do not pollute information", in particular, is examined in more detail and understood practically as a currently unchanging law in our existing world societies.

The "Ethics Consensus", derived from "THE TEN ECOLOGICAL COMMANDMENTS" and developed by Markert at the end of the 1990s, reflects

both theoretical and practical levels of action that many people in our highly diverse world societies can support.

From a scientific point of view, this article deals with the so-called B & B technologies, i.e. bioindication and biomonitoring of chemical elements, their chemical speciation as well as organic substances.

B & B technologies, which deals with the biological detection of atmospheric deposition of chemical substances on a regional, national, and international level, are taken into account.

From both an academic and a practical point of view, mosses have prevailed here in the last decades in addition to lichens. The use of mosses is a major focus of international air monitoring, especially in Europe.

Furthermore, the phytoremediation of chemical substances in water, soil and air is described as a biological and sustainable biological process, which does not yet have the full scope as it is used in bioindication and biomonitoring, as shown in the example of mosses.

However, the phytoremediation is considered to be an excellent tool to have the leading role in the sustainable pollutant "fight".

In the future qualitative and quantitative approaches have been further developed to fit scientifically and practically B&B Technologies as well the different forms of phytotechnological approaches.

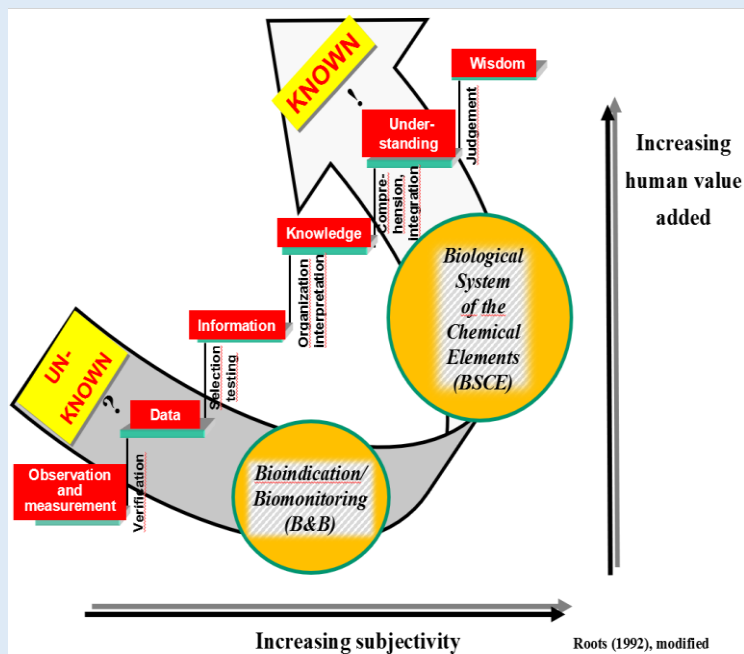
Finally, the example of lithium, which is optionally derived from the Biological System of Chemical Elements (BSCE), becomes a chemical example that the administration of lithium to ALL mentally conditioned diseases such as manic depression to smoking cigarettes becomes one of the most valuable services for the recovery of human society on a global level.

As a conclusion of these tremendous effects of lithium can be considered: pulled out, to make clear that only this chemical element beside a psychiatric care and the involvement of family members, friends, physicians, psychologists and psychiatrists.

In addition, it is a must that there is a strong relationship between patient, psychiatrist(s) and strongly related persons to the patient. First an intensive information transfer via communication must be guaranteed. After it, psychological support by doctors and, only if it seems necessary Lithium is to be given in a patient specific dose.

**Keywords:** Bioindication, Biomonitoring, B&B Technology, Phytotechnology, The Biological System of Chemical Elements (BSCE), Lithium. Neurological diseases, Functional Food.

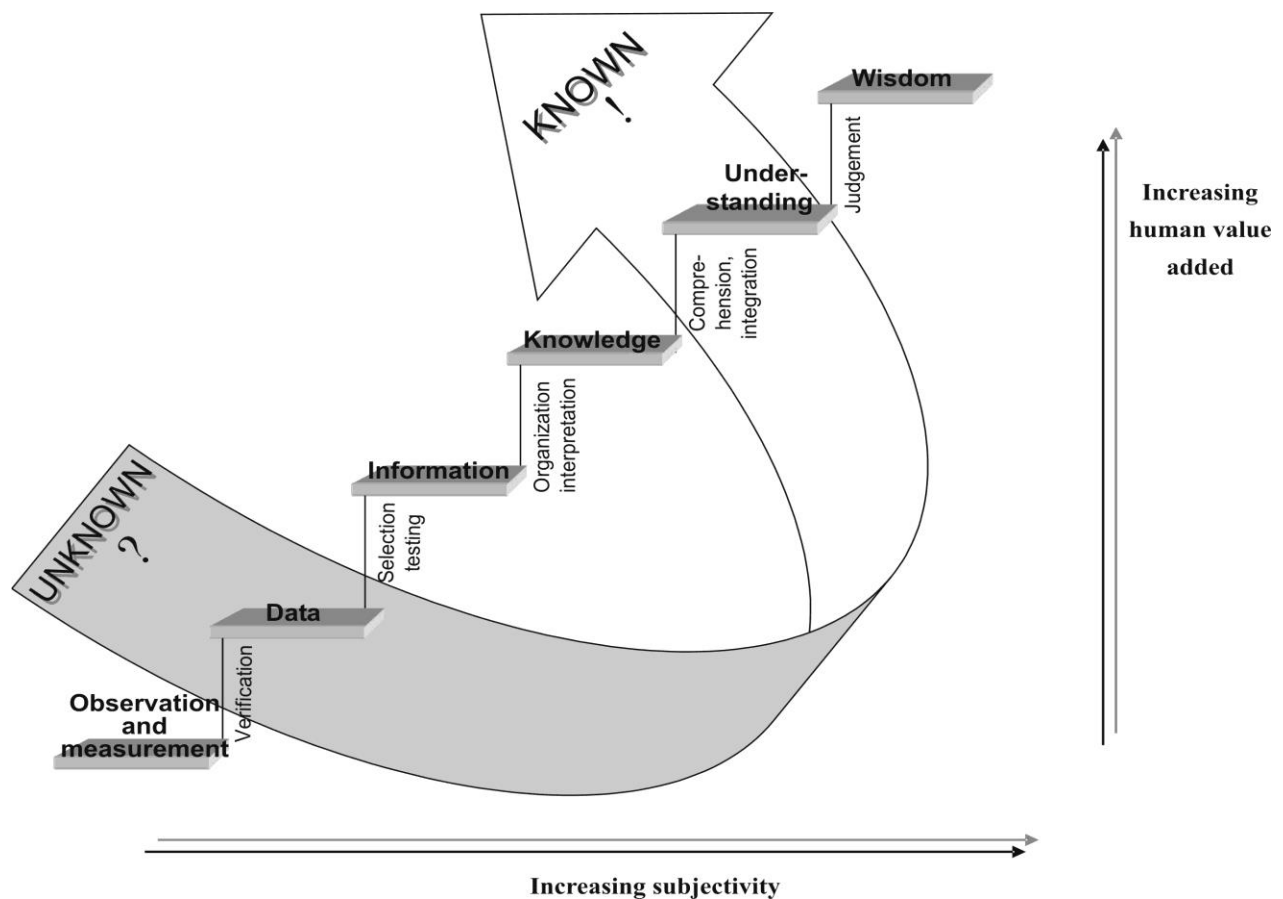
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**1.1 “Do not pollute information”:** Information means to convert hitherto unknown into established knowledge (the Latin verb informare means to educate, to give things an intended shape). Fig. 1 is to show how information is gained in a stepwise, open but never really completed multi-stage process [1]. As a rule, measurements and other kinds of observation produce some set of data, thereafter, selecting some of these data to obtain specific pieces of information and finally knowledge and recognition. If the things thus understood can be judged about also in the later

future, both the individual and society end up with a generally valid, secure plus of knowledge.

Within about 100,000 years, humans developed patterns of thinking and acting which permitted a successful spreading across continents over the most of the earth. Using education in a skillful and intelligent way – that is, selecting and applying solid pieces of knowledge – renders education the principal and crucial factor of future life.



**Figure 1.** The staircase of “knowing”, modified after [1].

Healthy ecosystems and environments are necessary to the survival of humans and other organisms. The Ten Ecological Commandments [2]

are important catalysts for permanent activities to solving global ecological problems.

They were already formulated by Peter Menke-Glückert at OECD in Paris during 1966 to 1970. He firstly presented them at an UNESCO conference “Man and Biosphere” in Paris on March 9, 1968.

The Ten Ecological Commandments support humans to identify ways of reducing negative human impact by environmental-friendly chemical engineering, environmental resources management and environmental protection. The information is gained from green chemistry, earth science, environmental science, and conservation biology. Ecological economics studies the fields of academic research that aim to address human economics and the natural ecosystem. Moving towards sustainability is also a social challenge that entails international, national law, urban planning, transport, local and individual lifestyles, and ethical consumerism. Especially the international and global, ethically sound, and sustainable information transfer will be catalyzed by permanent sustainable activities to solve global ecological problems.

The Ten Ecological Commandments of [2] represent a sustainable decalogue for Earth Citizens bearing responsibility by birth for sustaining planet earth and its exuberant nature and creative wisdom.

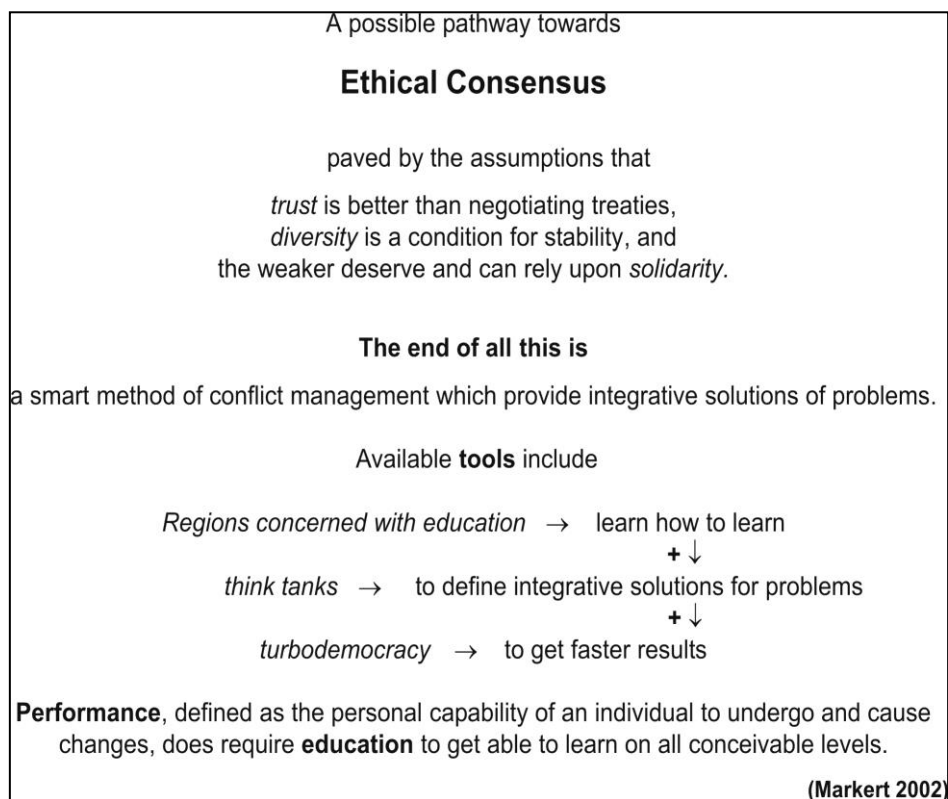
To protect nature and to overcome environmental damage needs courage to tell the

truth about the effects of certain industrial practices. About consequences of certain political actions and affluent energy-wasting lifestyles - even if it hurts common beliefs, traditional views, and interests. One of the great sins of our Media, and Public-Relations-Culture, is manipulation of information. Therefore, resist this distortion of information! Earth Citizens have a fundamental right to access precise environmental information! Included in the United Nations Charter of Human Rights belongs Freedom of Access to environmental information including environmental assessment of technology innovations and its health results. Industry Advertising in green marketing is not sufficient! The coming knowledge and computer society needs a new Codex of Information-Handling-Ethics, needs a world campaign against “information pollution”, one of the biggest and most dangerous environmental sins, confusing fair, precise, understandable and honest communication.”

This relates to an ethical consensus already developed by [3]. This means education and professional education will decide about life chances in the foreseeable future (Figure 2).

#### THE NINTH ECOLOGICAL COMMANDMENT

**“BELONGS INFORMATION ABOUT ENVIRONMENTAL DAMAGE TO MANKIND – NOT TO PRIVILIGED BIG BUSSINESS! NOT TO ANYONE ALONE! AVOID INFORMATION POLLUTION! GENERATE SURVIVABILITY INFORMATION TO LASTING KNOWLEDGE AND DAILY ROUTINE! DO NOT MANIPULATE INFORMATION BECAUSE OF COMMON PRACTICE AND BECAUSE OF POSSIBLE LOSS OF PRESTIGE OR CAREER POSITION OR ECONOMIC LOSSES!**



**Figure 2:** Trust, variety and solidarity provide an indispensable blueprint for solving problems in regions of education, think tanks and approaches of turbodemocracy” [3].

To reach the Ethical Consensus by human mental and practical management The Ten Ecological demands will be of tremendous assistance, because The Decalogue [2] is

- easy to understand
- intercultural
- dealing on an interregional and international level
- having an interdisciplinary approach of ecology, economy, and sociology
- reflecting communication and information transfer on a modern level
- coupling freedom and responsibility
- being an argumentative basis for lifelong learning and education
- mobilize and catalyze nature’s wisdom

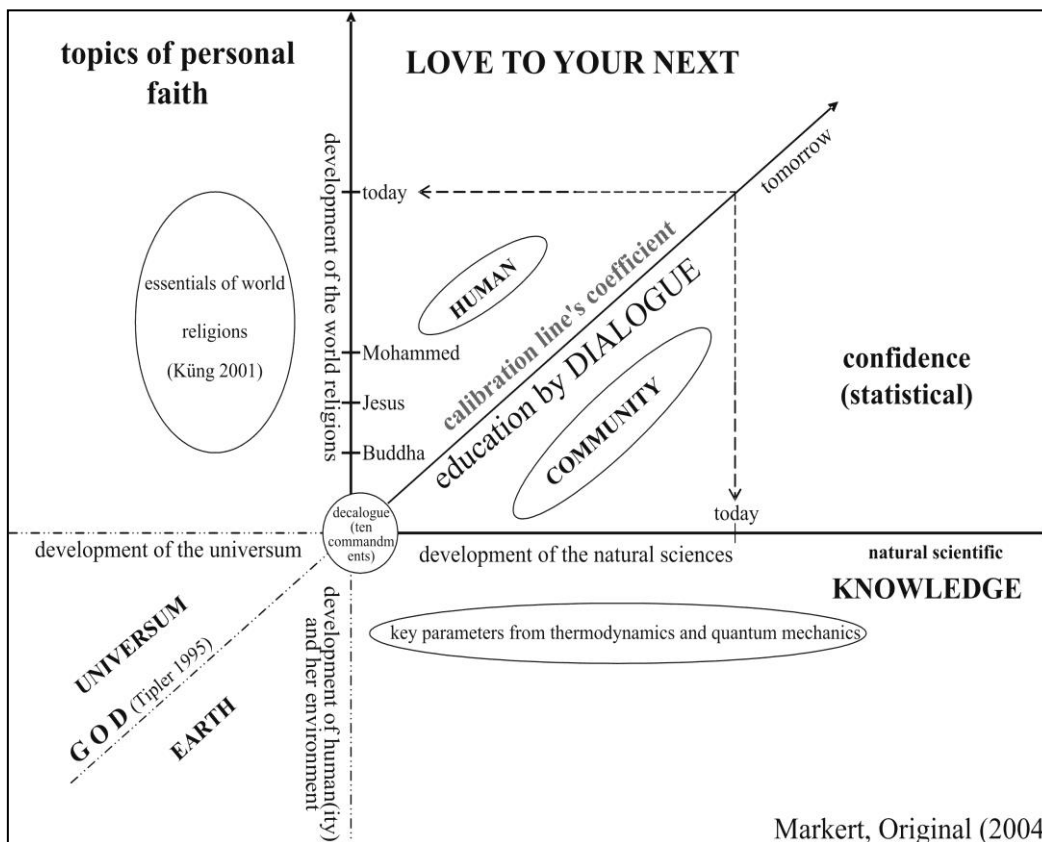
**1.2 How to shape dialogic education processes (DEP) as a future principle of communication:** One needs to develop some generalizing concept to conceive a pathway into some information process which is all economically reasonable, ecologically responsible and maintaining peace among nations and societies. This concept requires it to be theoretically sound and applicable to the economy, yielding corresponding information effective and improving the present situation.

By now, correct information from economy, environment and social living conditions are not delivered to most people in the World and, moreover, lack integrative reflection [4-13].

E.g., Chinese citizens—some 20% of all mankind—are kept from uncensored access to the Internet; additional billions of men cannot afford it. Is a “war for education” imminent?

Needs and demands cannot be met anymore on the scale of entire (though still affluent) societies in either Germany or all of Europe. This once again calls for a concept which takes regards for specific

conditions and demands related to cultural history and the individual likewise. Therefore, research on intelligence must integrate cognitive and emotional processes of information. Fig. 3 depicts a scheme which combines multicultural common positions and parameters from natural sciences into a line along which “dialogical education” might arise and grow with time.



**Figure 3:** Creation of information as „de-novo synthesis “produced by linking knowledge from natural sciences, belief in world religions [from 10] and by use of a dialogue education process (DEP).

People of most diverse backgrounds need a common code of values and education which likewise regards individual demands and obligations towards society. Intelligence apparently includes a peculiar ability to produce relationships among different sources of information, with love and power being at odds ever since. While love (to all yourself, to others

and to nature) is in favor of positive relationships, power can be abused and thus promote negative relationships [14].

Distribution and processing of information in this broad sense are and will remain crucial to analyze and understand whatever processes in environment, economy, and society. So-called “quasitruths” will



vanish in the long term. Goudevert postulated years ago that “technical education without general education tends to produce knowledge without conscience”, “Ethical aspects of the society”, following 3.

## **2. Information in environmental monitoring of chemical elements with bioindication and biomonitoring (“B & B Technologies”):**

All the environmental compartments air, water, soil and the biocoenoses associated with them are considerably influenced by a larger number of both biotic and abiotic factors [15-17]. Owing to an increasing extent of industrial activities, the environment is also influenced by chemical pollutants. This diverse group of potentially hazardous substances contains a larger number of organic compounds as well as metals (e.g. mercury and tin), so-called semi-metals (e.g., arsenic and antimony), and organometal compounds (e.g. tributyltin). Once they accumulate in soil, ground water or organisms, drawbacks for certain members of a trophic chain may become unpredictable yet grave [18-27] which is likely what J.O Nriagu [28] saw a silent global epidemic of environmental metal poisoning.

Already ancient high cultures used metal(loid)s to an extent emission from which can be detected globally by corresponding depositions in e.g. Greenlandic ice cores. During the last 150 years, however, anthropogenic emissions got so large that negative effects on man and his environment were no longer restricted to the regional surroundings of emission sites [29].

Accumulation being a slow, inconspicuous process which, however, causes a likewise slow damage to living organisms requires a meticulous and

constant monitoring of deposition of metal(loid)s (and likewise organic compounds, also) and of their impacts to living nature. However, among the anthropogenic pollutants, metals and metalloids represent a major threat because, while organic pollutants can be soon or late be degraded by the Earth microbiome owing to its genetic plasticity and metabolic infallibility, metallic species are only transformed by chemical speciation.

Emissions into the atmosphere are often monitored by means of deposition collectors whereas in aquatic monitoring a – however not continuous but intermittent – sampling of water samples is employed.

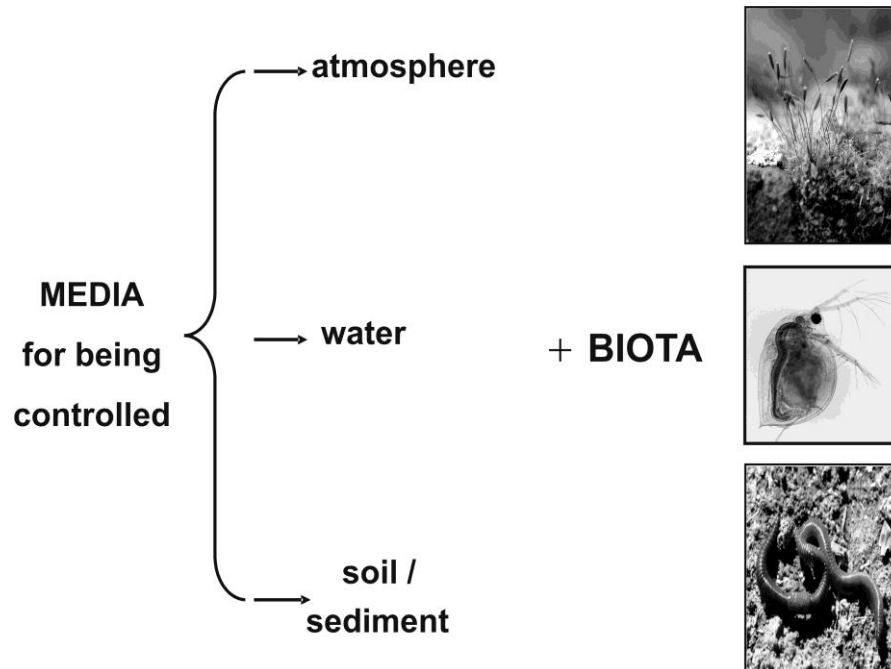
There are elegant though indirect methods to obtain data on existence, distribution, and effects of pollutants, namely, bioindication and biomonitoring (“B & B technologies”). These methods make use of the capacity of organisms to signify presence of pollutants over either short or longer periods of time ( Intensive studies of these bioindication and biomonitoring have been done (among others) following colleagues: 26, 27, 30-64.

Because bioindicators or biomonitors do integrate environmental burdens (by chemicals) over time during the experiment at their sites, short-term variations are cancelled out. As compared to “conventional” means of measuring emissions, doing bioindication or monitoring takes much less expenditures in both personnel and apparatus than e.g. running a deposition sampler. Hence bioindicators can be employed throughout large areas provided the organisms are sufficiently far spread and abundant, enabling investigations which cover entire countries or even continents which could be done otherwise only if accepting very high demands of work and money. One example is *Tradescantia* bioassay, using some parts of this

species as a sensitive test for evaluation of environmental pollution [65, 66].

Using one or several (different) organisms for purposes of estimating environmental burdens (fig. 4) brings about yet another advantage: beyond statements on the very organism which is embedded in some ecological niche within an ecosystem, hence analytical data obtained on it can be integrated into a

more comprehensive biological system. Thus, beyond the very bioindicator ecologically relevant statements are possible on larger parts of the biocoenosis due to the biotic interactions which interconnect them, unlike when using direct physico-chemical methods [67].



**Figure 4.** Environmental media and their bioindication using various living organisms (e.g. mosses, daphnia, earthworms) [67] .

**2.1 Definitions:** [26, 27, 68] gave an exact and meanwhile generally valid definition to discern among bioindication and biomonitoring:

- **Bioindicators** are organisms or communities of organisms whose content of certain elements or compounds and/or whose morphological, histological or cellular structure, metabolic-biochemical processes, behavior or population structure(s), including changes in these parameters, supply information on the **quality** of the environment or the nature of environment changes. Bioindication compares **relative data** of information (on contamination, for instance) to each other.

- **Biomonitors** are organisms or communities of organisms whose content of certain elements or compounds and/or whose morphological, histological or cellular structure, metabolic-biochemical processes, behavior or population structure(s), including changes in these parameters, supply information on the **quantitative aspects** of the quality of the environment or the nature of environment changes. Biomonitoring compares **absolute data** (on contamination, f.e) to each other.

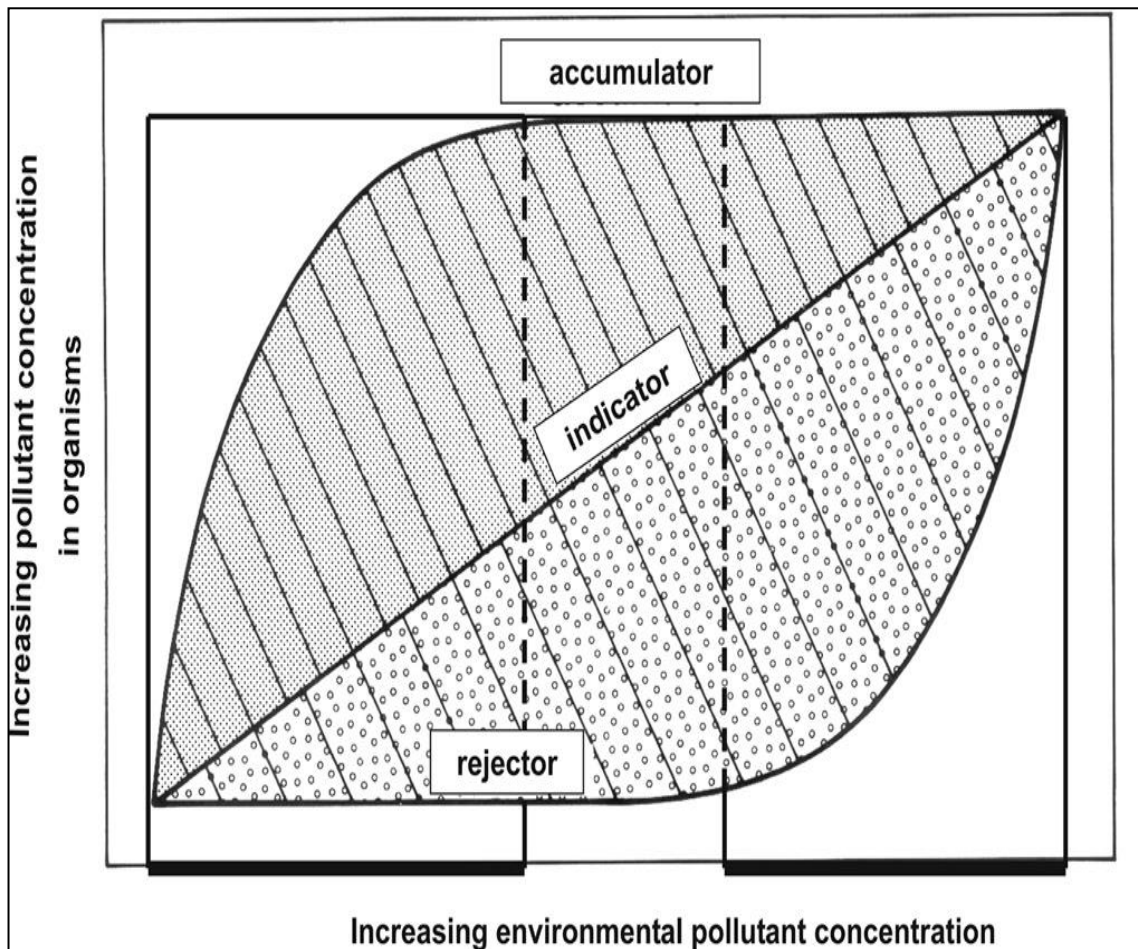
We speak of **active** bioindication (biomonitoring) when bioindicators (biomonitors) bred in laboratories

are exposed in a standardized form in the field for a defined period. At the end of this exposure time the reactions provoked are recorded or the xenobiotics taken up by the organism are analyzed. In the case of **passive** biomonitoring, organisms already occurring naturally in the ecosystem are examined for their reactions. This classification of organisms (or communities of these) is according to their "origin".

For further definitions and explanation of terms related to the above...as accumulation, effect, or impact indicators /monitors; biomagnifications, bioconcentration, biomarkers, biosensors, tolerance, resistance, sensitivity please have a look into Markert et al. [26, 27].

Because of unfavourable location, many plant species have developed the ability to enrich high concentrations of individual elements, often regardless of whether these elements are physiologically useful or not. These plants are called accumulators. With respect to biomonitoring there should be a correlation between the environmental concentration of a pollutant to be observed and the content in the organism proper. A linear, indicative interrelation of both measure values has not been found so far for any organism. The concentration ranges which might be interesting for bioindication and biomonitoring showed very small 'measuring ranges' (black bars) in accumulator and excluder organisms (fig. 5).

**2.2 Using plant species as bioindicators/biomonitors:**



**Figure 5:** Differing uptake activities in living organisms as a function of the substrate concentration [68, 69].

For example, regardless of the amount of element in the soil, some Ericaceae have a high concentration of manganese, and beeches have a high amount of zinc. The accumulative behaviour, which may have genetically predetermined origins rather than ones determined by locations, makes it possible to chemically fingerprint a very wide variety of plant types. In the future, this might lead to the chemical characterization, and therefore to the systematization, of individual plant types, which could provide information about evolutionary connections on a phytosociological level. A rejection, or reduced uptake of individual elements, occurs less frequently than does an accumulation of elements, but rejection behaviour has been demonstrated for numerous plant species. In plants the so-called checkpoints were described as control points in uptake and translocation of some heavy metals resulting in control of transport processes from the soil to the inner tissues [70]. These checkpoints result in generally lower heavy metal content in the shoot compared with the root and in protection of generative organs from excess of these elements. The reduction in concentration of an element in an organism can be the result of a complete or a partial exclusion. For example, bacteria, algae, and higher plants contain populations which are resistant to metal(loid) excess and which can reduce considerably their uptake by excreting mucilaginous substances or by changing their cell walls.

In addition to microorganisms, fungi, algae, mosses, lichens, ferns, and higher plants (examples are f.e. described in [26]), animals can be used as bioindicators and biomonitors. In comparison to

plants animals have generally developed a wider arsenal of stress-coping mechanisms; also in relation to the ease of exchange of genetic determinants (e.g. operons) encoding for the physiological resistance mechanisms, which are generally located on genetically mobile elements. In addition, nonsessile animals can avoid a certain number of threatening environmental or anthropogenic stressors by virtue of their mobility or motility [71]. Owing to the generally higher sensitivity of aquatic animals to xenobiotics in comparison to that of terrestrial organisms they play a major role in acute, sub chronic and chronic tests. Under field conditions inquiries into distribution patterns and the different for organotropic accumulation of xenobiotics are the major fields of interest in various bioindicative/biomonitoric approaches [71]. Some animal groups representing indicative qualities are given in [62]. The possible integrative relation of atmospheric element pollution, soil samples, stomach content and tissue and organs of rats in a specific study area is given by [72, 73]. The results of bioindicative studies of humans is manifold. Results on the relation of chemical elements to nutritional intake, human milk and transfer of the milk to babies clearly demonstrated that human milk cannot be used as bioindicator / biomonitor for the metal(loid) pollution status of the environment [74, 75]. Other stimulating examples of bioindication and biomonitoring studies for controlling organic pollutants are given amongst others in [76]. In addition, some requirements of an "acceptable" bioindicator/biomonitor are given in Fig. 6.

**Common paradigm**

- high abundance (frequency)
  - widespread (global)
  - easy identifiability
  - easy availability
  - analytical ability
- accumulation of pollutants

**As an example, mosses**

- primitive morphology
  - without cuticula
  - without roots
- without water conducting system
- accumulation of pollutants
  - wide distribution
  - easy to collect

**Figure 6:** “Simple” requirements for bioindicators/biomonitor.

In Fig. 6 the requirements for a bioindicator will be called “simple”. But each location in the world is characterized by specific conditions of climate and living conditions at all. Therefore, it is extremely difficult to find species or groups of species which are working in the common sense of a bioindicator or biomonitor given in the requirements of Fig. 6 on a global level. They seem still today not available. Therefore, for each region, each selected indicator must be handled with care and experience of the scientists. A comparison of instrumental measurements and the use of bioindicators with respect to harmonisation and quality control has been made in [26].

**2.3 Mosses as bioindicators/biomonitor for controlling the atmospheric deposition of chemical elements:** Mosses are suited for corresponding work as they lack a cuticula interface. In higher plants, the cuticula limits evaporation, protecting plants against drought. On the other hand, cuticula puts an obstacle

to uptake of water and salts dissolved in it via the surface of a plant. Because there is no cuticula, mosses can directly take up water and minerals required for growth via their leaf surfaces and thus do need neither “genuine” (i.e., mineral-absorbing) roots nor a water conduction organ system. Thus the “primitive” structure of mosses as compared to different plants exactly becomes an advantage in pollutant level observations, with the pollutants likewise taken up directly through the surface unprotected by a cuticula [26].

In addition to lacking a cuticula, mosses are distinguished by a rather large resistance towards enhanced levels of various anthropogenic air pollutants, permitting their use also in polluted areas. With many species being far spread (living in quite different regions), larger regions can be monitored using a given species. Owing to their large surface-volume ratio, mosses will readily accumulate elements. When transferred into the plant, pollutants

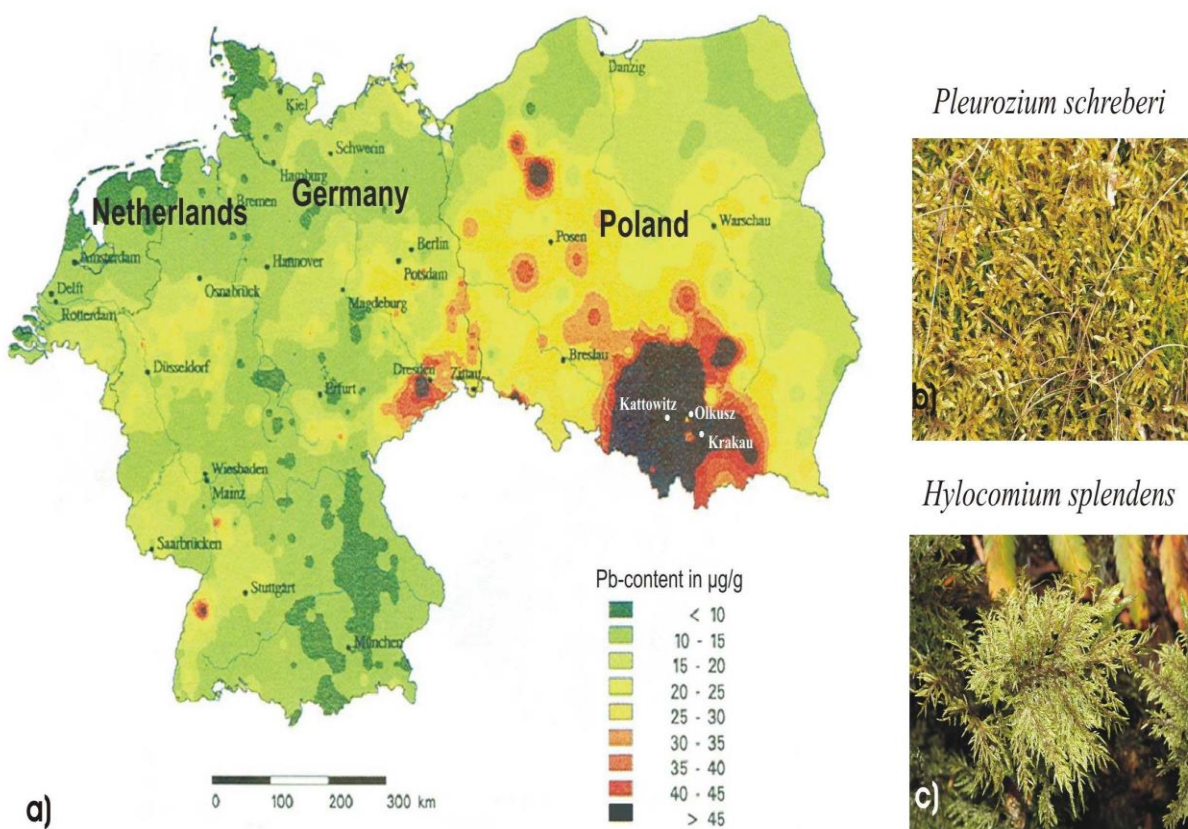
get bound to cell walls. Thus, mosses accumulate substances throughout the entire period of vegetation growth, providing information on an averaged pollution situation integrated along the period of growth. Thus, mosses are perfectly suited for monitoring pollution which is due to atmospheric deposition [26].

Results from chemical analysis are converted into multi-color maps of pollution using geographic information systems (GIS), providing maps such as that for lead (moss samples were taken from 1990-1992, fig. 7 a, b, c).

Meanwhile the moss monitoring program is done by different European nations and give excellent

results for the development of different trace elements, ozone and other chemical substances [77, 78].

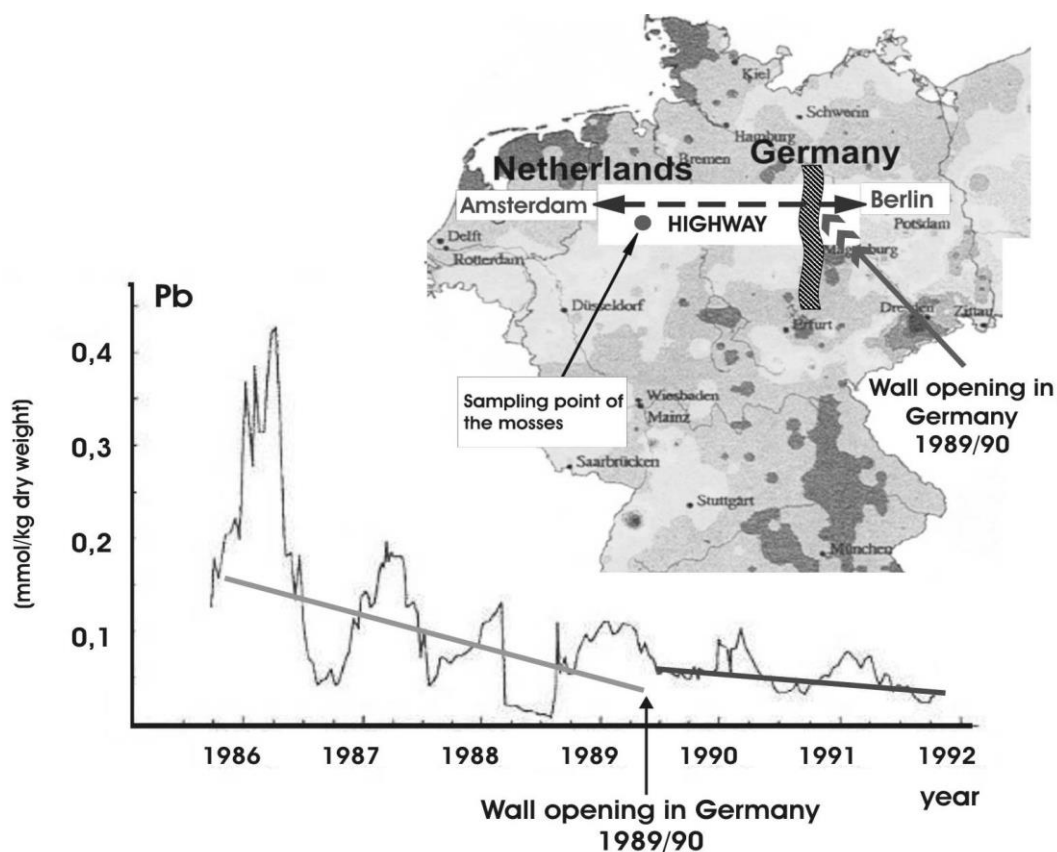
As a final output of above investigations bioindication results compare relative (analytical) data of (element) concentrations given by bioindicator species (mosses). In this example the mosses are represented by different locations around Middle Europe. Same can be done by using bioindicator to get an impression on the behavior of chemicals by time. An example is given for Pb in mosses (*Polytrichum formosum*) collected over some years.



**Figure 7a, b, c.** a) This map gives Pb contents in moss species from different countries (Netherlands, Germany and Poland). The moss samples were taken from 1990-1992 [79]; b,c) Mosses (only two moss species of totally four of the overall European program are shown as examples, *Hylocomium splendens* (b) and *Pleurozium schreberi* (c) as bioindicators / biomonitors for controlling the atmospheric deposition of different chemical elements. Courtesy of the photographs b and c: Wikipedia.

The characterization of typical summer/winter oscillations of Pb (and other elements given in [80, 81] can be explained by a dilution effect during biomass production during spring and summer month, which clearly explains the maximum concentrations of lead found in the winter month and lowest concentrations found in the summer month (graph in fig. 8). As a result of lower emission rates, the concentrations for lead decreased from 1985 to 1992. This ranged from 0.2 to 0.005 mmol/kg, i.e. a 4-fold decrease of the original value. In addition, a reduction of the yearly amplitude can be manifested. The minimum Pb values in fig. 8 should be noted. The lowest value was 0.01 mmol/kg, a figure which then (summer 1988) has not yet been reached. The reason for this was probably the opening of the Berlin Wall in 1989

(Germany), as the biomonitor study site was no more than 200 m away from the highway. Consequently, these increased Pb concentrations were a result of automobile emissions. After the fall of the wall in 1989/1990 the ex-East Germans bought (cheap) cars which required leaded petrol. Thus, the amount of leaded petrol used increased and hence also the emission of lead. These emissions are directly correlated with the much frequented (by “eastern” cars) traffic routes as represented by the Autobahn 2 and Autobahn 30 in between Berlin and Amsterdam (Markert and Weckert 1994). From a statistical point of view (fig. 8) the slopes of Pb concentrations before and after November 1989 increased from -0.0442 to -0.017, which can be explained by the higher lead input during this period.



**Figure 8:** Decrease in Pb concentration in the moss *Polytrichum formosum* near Osnabrück (Germany) after regular sampling (two weeks intervals) close to the highway in between Berlin and Amsterdam. The seasonal variations can be explained by the dilution effect during biomass production of *Polytrichum formosum* at the beginning of the vegetation period [80, 81].

Different research has already given the proof that seasonal variations are already known to all different forms of mosses, independent if they are ectohydric or endohydric mosses. Therefore, it is important to have a clear-cut sampling period during the European moss survey; for instance, sampling should be performed during August. The sampling period should not extend to several month during the year, because seasonal variations might influence the biological concentration of trace elements in the moss so far that the results are not comparable to each other.

For **quantitative results** for transferring bioindicative into biomonitoring data the values can be converted into quantitative deposition rates for chemical elements found in mosses using the formula

$$D = c \cdot \frac{A}{E_x}$$

Where D = estimated deposition, c = measured concentration in moss, A = biomass increase/year according to Zechmeister (1997), and E = efficiency factor of uptake by [82]. The unit of D is given in  $\mu\text{g} \cdot \text{m}^{-2} \cdot \text{a}^{-1}$ . [83] examines the deposition of different elements via mosses in the Euroregion Neisse (ERN, East Germany, a cross bordering region in between Czech Republic, Germany and Poland) in the years 1995 and 1996 as well in Austria.

**2.4 Conclusion/outlook: construction of a setup for preventive healthcare:** Fig. 9 is a diagram of a complete dynamic environmental monitoring system supported by bioindication. It can re-combine its measurement parameters according to the system to be monitored or the scientific frame of reference. The two main subjects of investigation – man and the environment – and the disciplines human toxicology and ecotoxicology derived from them are associated with various “toolboxes” and sets of tests (“tools”, e.g.

bioassays) for integrated environmental monitoring. The system shown in Fig. 9 consists of 6 toolboxes. The first two are derived mainly from environmental research: DAT (for data) and TRE (for trend). DAT contains, as a set, all the data available from the (eco-)system under investigation, i.e. including data acquired by purely instrumental means, for example from the meteorological sphere. DAT also contains maximum permissible concentrations of substances in drinking water, food or air at the workplace and the data for the relevant ADI (“acceptable daily intake”) and NO(A)EL (“no observed (adverse) effect level”). The toolbox TRE contains data on trends; these have been compiled mainly from years of investigations by national environmental sample banks, or information available from long-term national and international studies (e.g. 15, 84). Specific conclusions and trend forecasts can then be prepared using the subsequent toolboxes HSB (human specimen banking) and ESB (environmental specimen banking). The toolbox MED (medicine) contains all the usual methods employed in haematological and chemical clinical investigations of sub chronic and chronic toxicity, whereas ECO is largely made up of all the bioindicative testing systems and monitors relevant to ecosystems which may be combined to suit the particular situation to be monitored.

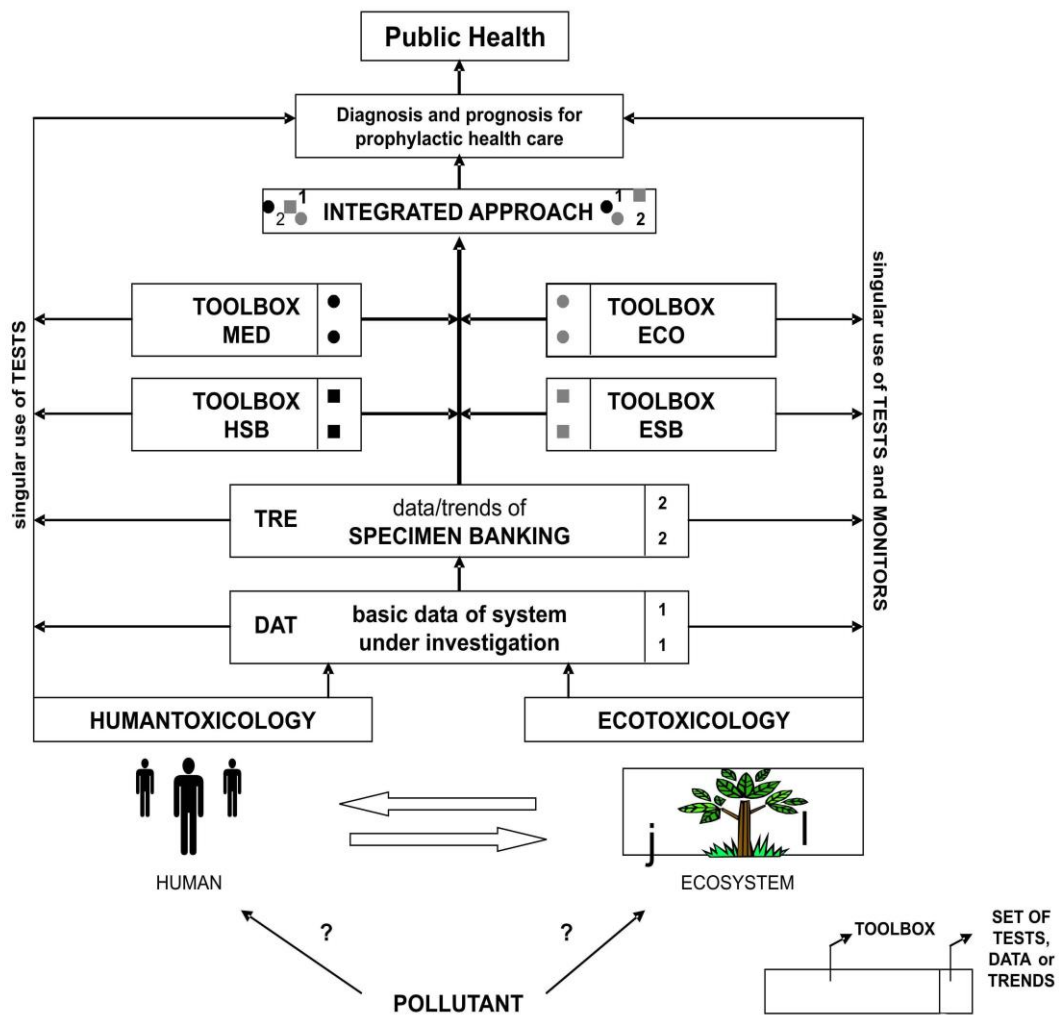
The data from all the toolboxes must interact with each other in such a way that it is possible to assess the average health risk for specific groups of the population or determine a future upper limit of risk from pollutants by forming networks. This risk assessment ultimately makes use of all the toxicological limits that take the nature of the effect and dose-effect relationships into account according to the status of scientific knowledge. Since toxicological experiments cannot be carried out on human beings, recourse must be made to experience at the workplace and cases of poisoning in order to permit an evaluation and risk assessment. Besides examining reports on individual cases, greater efforts must be made to reveal the effects of substances as a cause of disease by means of epidemiological surveys with exposed groups as



compared to a control group. The development and use of simulation models supported by information technology, taking all the data collected into account, will play an important role here, since a large number of parameters that do not interact directly have to be combined. They include various data from the field of epidemiology, from mutagenicity studies, toxicokinetics, metabolism research and structure-effect relationships.

[85] suggests what he calls "eco-medical" indicators. For the ecosystem medicine approach, efforts should be made to apply systematic diagnostic

protocols from human medicine to questions of ecosystem health. Beginning with the observation that medical practice has always relied on a suite of indicators for assessing human health, this broad approach is also required in screening ecosystems for possible pathologies. Further, in ecosystems, as in human health, no single indicator is likely to prove efficient as an early warning symptom, a diagnostic measure, and an integrated measure of the health of the entire system.



**Figure 9:** Possible hierarchical structure of a bioindicative toolbox model for integrative approaches in human- and ecotoxicology. The toolboxes MED and ECO contain single sets of tests that can be combined functionally to allow an integrated approach to the frame of reference or a specific scientific problem. The toolboxes HSB (human specimen banking) and ESB (environmental specimen banking) represent years of results from international environmental sample banks specializing in environmental and human toxicology; in addition to MED and ECO they provide important information on the ecotoxicological and human-toxicological behavior of environmental chemicals. In the integrated approach, all the results obtained singly are substantiated by existing basic data available from (eco-)systems research, toxicology, and environmental sample banks. The parameter constellations necessary for this are taken from the toolboxes TRE and DAT [26].

**3 Phytoremediation**[86]: Bioremediation (i.e., green technologies or phytotechnologies when relied upon plants) mainly deals with biological interventions aimed at environmental contamination assessment and alleviating pollution. Both industrialization and natural resource extraction resulted in the release of large amounts of toxic and waste compounds into the biosphere. These pollutants belong to two main classes: inorganic and organic ones. Due to transboundary effects of soil pollution 39 countries are surveyed by the European Environmental Agency (EEA) that estimated that soil contamination in EU concern 2.5 million of sites potentially contaminated by mineral oils and heavy metals [87], of which about 45 % have been identified. Currently, about 15% of the identified sites have already been remediated chiefly (33%) using excavation and off-site disposal, while *in-situ* and *ex-situ* remediation techniques for contaminated soil are equally applied [88]. According to EEA (European Environment Agency) estimates 1.4 million areas are contaminated [89].

Outside EU, only in India, there are about 20,000 abandoned mine sites covering about 60 different kinds of minerals. Globally, the OECD (2015) estimated that environmental pollution caused more than 7 million premature deaths every year (600,000 in Europe) imposing an economic cost to society of in the order of trillion of dollars, whereas specific estimates for soil pollution are not yet available. Biological interventions mediated by some wide array of biological species (none of which will be able to “remove everything”) can be used to remove

unwanted compounds from the biosphere, thus contribute significantly to the fate of toxic spills.

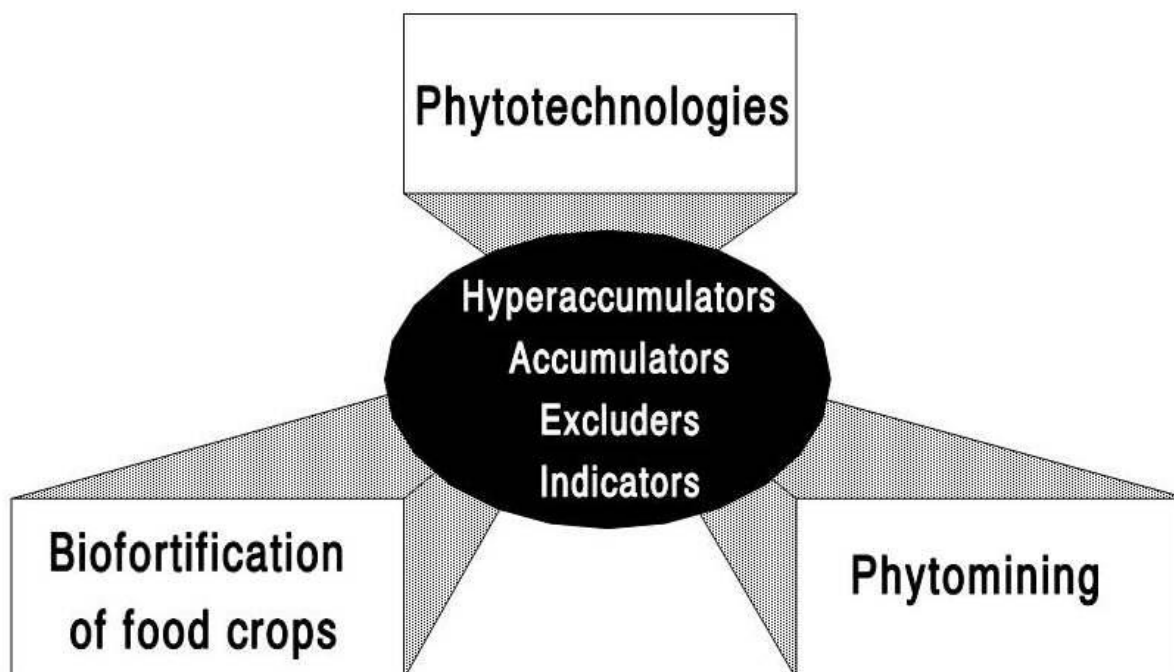
Phytotechnologies deal with the use of plants in pollution control and removal as well as on aspects related to plants from polluted environments as a source of food, fodder, fuel, and fertilizer. Plants can indicate, exclude, accumulate, hyperaccumulate or metabolise toxic inorganic or organic substances. Thereby they contribute significantly to the fate of chemicals, and they can be used to remove unwanted compounds from the biosphere. On the other hand, chemicals can enter the food chain via plants, which cause unwanted/causing harmful effects [90].

Phytoremediation is the use of certain plants to clean up soil and water contaminated with metals and/or organic contaminants such as solvents [91, 92, 93], crude oil, and polyaromatic hydrocarbons (PAHs). Phytoremediation conducted with metal tolerating or accumulating ornamental plants is also aesthetically pleasing, solar-energy driven, passive technique that can be used along with-or, in some cases, in place of-mechanical clean-up methods at sites with shallow, low-to-moderate levels of contamination that can be suitable options for the management of contaminated soil, water and air, with positive effects on crucial ecosystem services, and providing value and benefits to otherwise simply degraded land. These sustainability aspects of phytomanagement will gain increasing attention in the future, also considering that the [88] reported that 42% of the total expenditure for the management of contaminated sites comes from public budget.

Thus, the current phytomanagement options for contaminated soils offers an environmentally friendly, cost effective, and carbon neutral approach for the

clean-up of toxic pollutants in the environment [94-99].

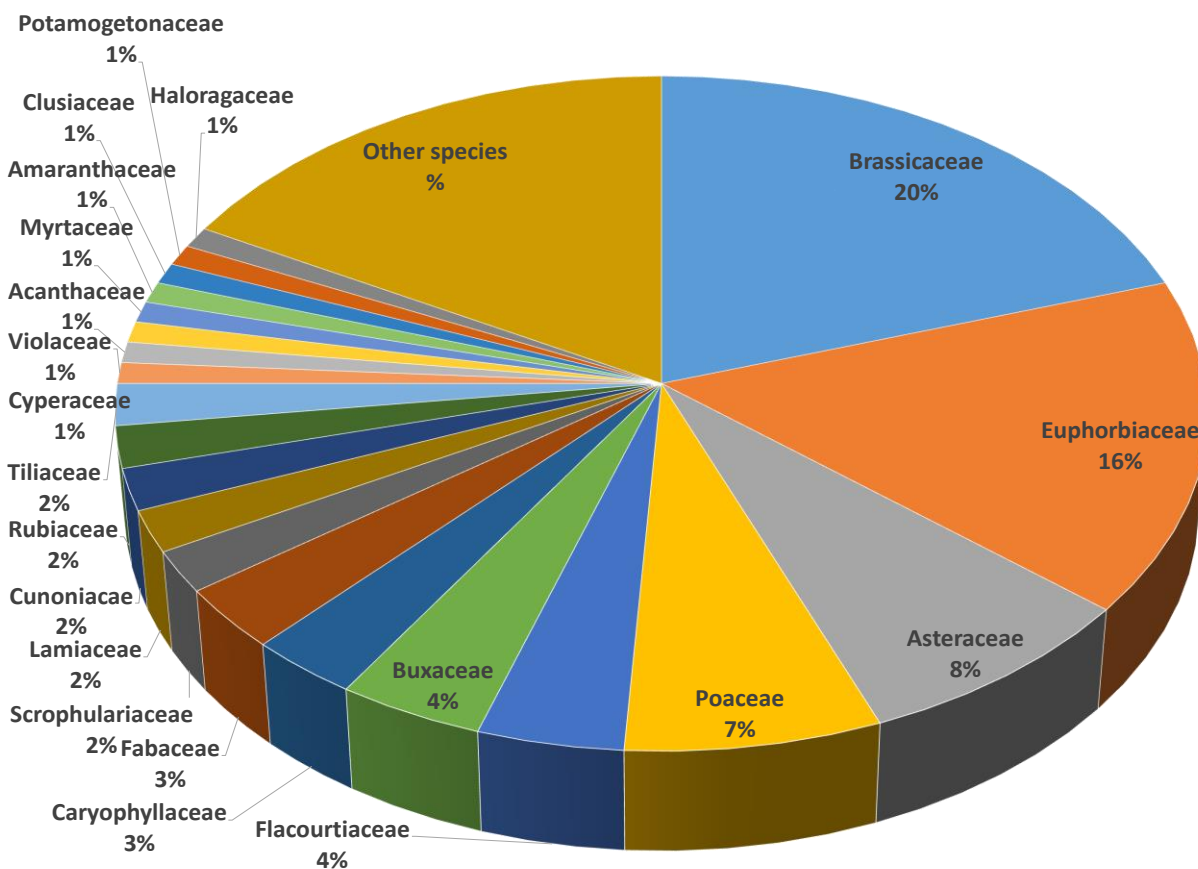
Plants with abilities to hyperaccumulate, accumulate, exclude, and indicate heavy metals are important in environmental remediation (fig. 10).



**Figure 10:** Beneficial use of plant metal interactions: a) Phytoremediation, b) Biofortification of food crops, and c) Phytomining. The desirable traits are high tolerance to contaminants, hyperaccumulation, wide ecological amplitude, easy management, economics and value additives, fast-growing and high biomass producing plants, such as *Salix* and *Populus* spp. *Indicator*: Plants in which uptake and translocation reflect soil metal concentration and exhibit toxic symptoms. *Accumulator*: Plants in which uptake and translocation reflect soil metal concentration without showing toxic symptoms. *Excluder*: Restricted uptake of toxic metals over a wide range of soil metal concentration. *Hyperaccumulator*: Plants in which metal concentration is up to 1% dry matter (this is metal dependent, most often Ni or Zn, see fig. 5 [69, 100].

Selection of plants utilizable for phytoremediation purposes is focused in several directions. One of them are fast-growing and high biomass producing plants, such as *Salix* and *Populus* spp. (e.g. 89, 101, 102], the other are hyperaccumulating species [103]. Hyperaccumulator species are spread among the plant kingdom irregularly and some families (e.g. Brassicaceae) are represented by a high number of hyperaccumulating species (Fig. 11). Except for mining areas, a common limiting factor in

phytomanagement of contaminated sites is that often the sites are relatively small areas and in specific contexts (e.g. agricultural, industrial, urban peri-urban) which hardly fulfil the minimum criteria for the establishment of biological successions and ecological interactions. In all these cases, the best phytomanagement options can be those providing economic or societal services in terms of site re-use for urban reconnection, recreational activities and landscaping.



**Figure 11.** Distribution of hyperaccumulating species in different families [104, modified].

#### 4 Effects of Chemical Elements to living Organisms<sup>1</sup>

The biogeochemical cycles of elements are the mechanisms maintaining the life on earth. Most of the biotic elemental transformation are carried out by oxidoreductases enzymes that release metabolic utilizable energy during the electron-transfer reactions within the cells of living organisms and through the global food web. More than 50% of oxidoreductases enzymes require metallic elements for their catalytic activities. By also considering the occurrence and importance of other non-enzymatic metalloproteins in living organisms, the availability of biochemically active metals appears as a main factor

conditioning the energy flow in nature. This sentence becomes very clear when for example we examine the essential role of Fe, V and Mo in the active site of the nitrogenase, the enzymes catalyzing the first step of the N biological fixation and the fundamental dependence of living organism from reduced N.

The metal availability in nature strongly depend on the habitat physico-chemical properties and is subjected to natural fluctuations over highly variable timespans. During the evolution, cell metabolisms has increased the number of metals requested for correct metabolism, from mainly Fe, Cu and Mn of bacteria up to many elements, systematized by [106] in the

<sup>1</sup>Related to [105]

Biological System of Elements. This increase observed in all higher animal and plant organisms is also due to the presence of chemical vicariance, that allow some enzyme efficiently function with different metallic co-factors, like in the case of Mo and W in various enzymes. The evolution of the vicariance phenomenon could likely depend on variations of metal availability in time a space.

Differently for transition metals, alkaline metals are not directly involved in redox reactions within the biological systems, possibly due to their lower binding stability constant with biological molecules, as compared to transition metals, but their presence is often essential in the maintenance of redox potential of fundamental biological molecules, like in the case of Mg coordination in the chlorophyll porphyrin rings. The essential role of transition elements in the evolution of the biological systems is confirmed by both the genetic inheritance of metal-absorbing physiological mechanisms and the presence of metal tolerance/acquisition mechanisms present on genetic mobile elements that allow the spread of metal-trafficking capacity through living organisms, with some metallic elements (e.g. Fe, Mn, Ni, Zn) being ubiquitous among biological taxa.

#### **4.1 The Biological System of the Chemical Elements (BSCE) and the Role of Lithium for Mental Health Care**

**4.1.1 An Introduction into the Biological System of the Chemical Elements (BSCE):** The position and classification of the chemical elements in the Periodic System of the Elements (PSE) according to [107] does not allow any statement to be made about their

functional essentiality or their acute or chronic toxicity for living organisms. The PSE is based on purely physiochemical aspects [10].

Mendeleev wrote about the Periodic Table in the first volume of the Journal of the Russian Chemical Society in 1869. While working independently, Dimitri Mendeleev and Lothar Meyer developed the basis for this periodic table. Mendeleev published his work as "The dependency the chemical properties of the elements of atomic weight." In the process, 63 elements were grouped in ascending order according to the atomic mass in seven groups with similar properties. The same principle was also established through Meyer. However, Mendeleev could have better represented his work by following his system predictions about missing elements and their properties. His system found worldwide recognition [107-109].

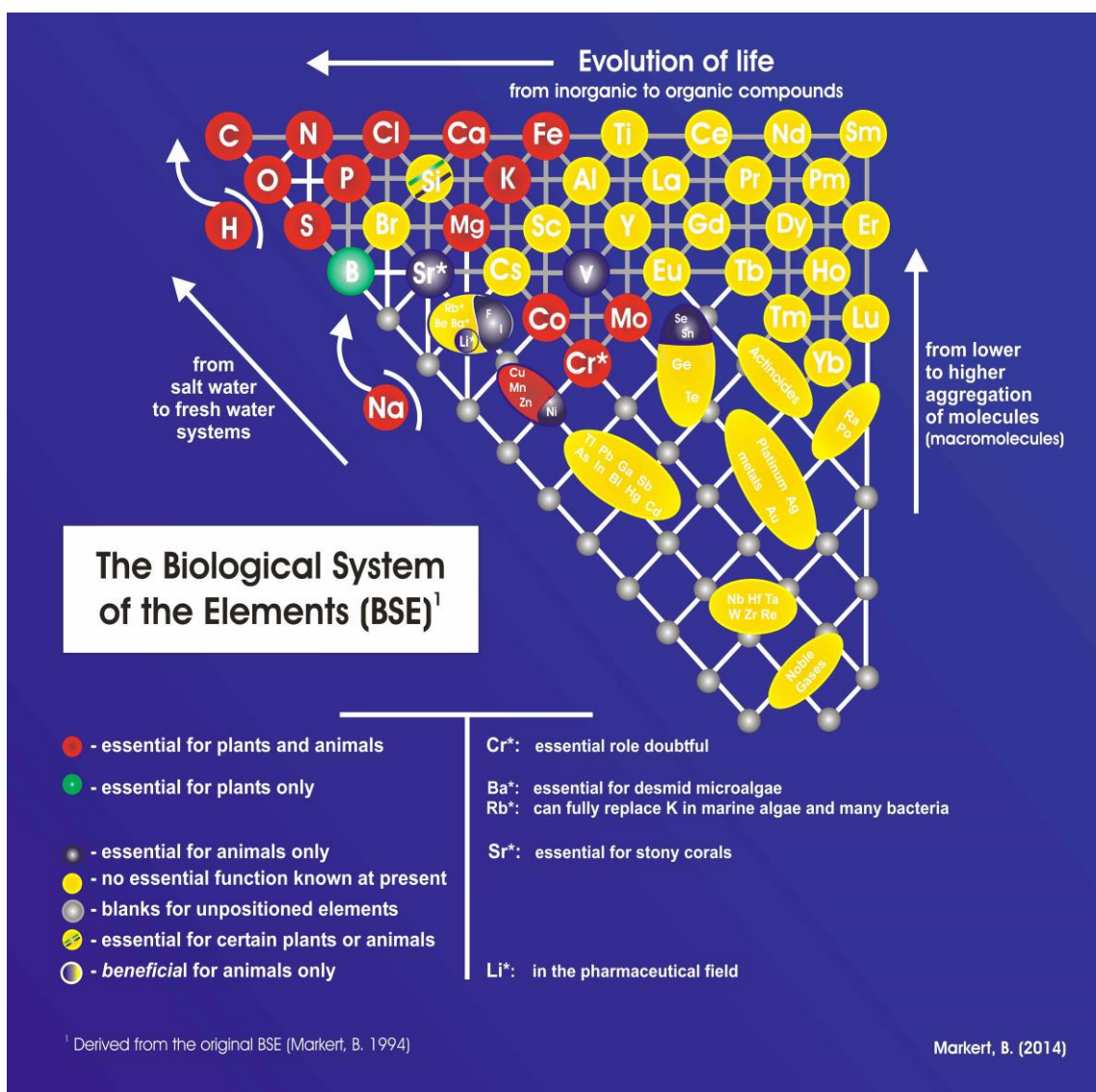
Therefore, the attempt has been made to develop a Biological System of Elements (BSE), with preliminary consideration of the aspects of basic biochemical and physiological research. Due to the inadequate chemical description of biological and medical relationships in the Periodical System, the Biological System of the Elements (BSE) was first established in 1994 (Fig. 12). Since 2018, the BSE or the Biological System of the Elements has been referred to as the Biological System of the Chemical Elements (BSCE). The main factors for establishing this first "intuitive" system have been accurate and precise multielement data including representative sampling procedures, interelement relationships, physiological function of elements, uptake mechanisms, and evolutionary aspects [106].



As the BSE was first conceived in 1994, BSE diagrams have been translated into many languages including Chinese (Mandarin), French, German, Latvian, Lithuanian, Persian (Farsi), Polish, Spanish due to the support and discussion from many colleagues around the world. Arabic, Italian, Hindi, Russian, and other translations are being developed [122-128]. All translations can be found at [www.eisn-institute.de](http://www.eisn-institute.de).

Meanwhile, further research has shown there are exceptions to the role of certain elements to specific

bacteria, plants, animals, and humans [110]. Therefore, the original BSE was extended into a modified BSE (Fig. 13) where Cr, Ba, Rb, Sr, and Li will likely take the following role (more detailed information on the functionality of each chemical element can be read in [110]: The essential role of Cr is doubtful for plants and animals; Ba is essential for desmid microalgae; Rb can fully replace K in marine algae and many bacteria; Sr is essential for stony corals; Li has a beneficial effect to animals (humans) in the pharmaceutical field.



**Figure 13.** Extended Biological System of the Chemical Elements after [106] showing exceptions of the role of certain elements to specific bacteria, plants, animals and human [110]. Since 2018, the BSE or the Biological System of the Elements (BSE) has been referred to as the Biological System of Chemical Elements (BSCE).

#### 4.1.2 Beneficial Role and Function of Lithium for

**Mental Health Care:** Lithium (Li) is a silver-white, soft alkali metal and the lightest of all metals. Lithium was discovered in rocks in 1817. Lithium is called Lithos in Greek. A specific distribution pattern of Li in the environment is given in Part 2 of this publication series [105]. This metal is used in rubber production, the manufacturing of batteries, X-ray films, and for alloys with copper, lead, and nickel.

As a trace element, Li has been generally regarded as non-essential for humans. However, multiple therapeutic effects, especially on the psyche, using this metal have been demonstrated [129-146].

After studies by [147] and [148, 149], there has been no exactly known physiological function of Li in any living being. Accordingly, Li cannot be taken as an essential element. Regardless, lithium supply will still have a beneficial effect in certain circumstances. According to [150], Li depletion—induced in either rats or goats by corresponding food composition—will bring about problems concerning both metabolism and reproduction, which suggests there are conditions in which Li may also be important to humans. Li is well-known to be beneficial in bipolar depression (see below), which suggests lithium may be regularly involved in neurophysiology or CNS (Central Nervous System) brain function. In both whole-animal and tissue experiments, pharmacological doses of Li were shown to be active in biochemistry.

We have listed some of the effects of Li and Li compounds in animals and various cell lineages after [147]: Stimulation of hematopoiesis; altering activity of secondary messengers (adenyl cyclase ↓, phospholipase ↑); effect on inositol metabolism; effect on prostaglandin metabolism; suppression of

Na<sup>+</sup>/K<sup>+</sup>-ATPase; change of circadian rhythms; effect on neurotransmitter metabolism. We must acknowledge Li administration is highly dangerous if combined with antipsychotic drugs like haloperidol or fluphenazine, causing toxic encephalopathy and sometimes irreversible brain damage. In this case, compounds interact with the dopamine rather than the serotonin system; antibacterial and antiviral activities; effects on ion and water transport channels (due to extreme hydration, in addition to displaying some lipophily. Li<sup>+</sup> is even much bigger in aqueous media than either Na or Cs cations); neuroprotective effects; suppression of some enzymes involved metabolism, like phosphoglucomutase in glycogenolysis.

Studies have not confirmed whether these effects also apply to humans already exposed to levels of Li, which are common in and from nutrition [147].

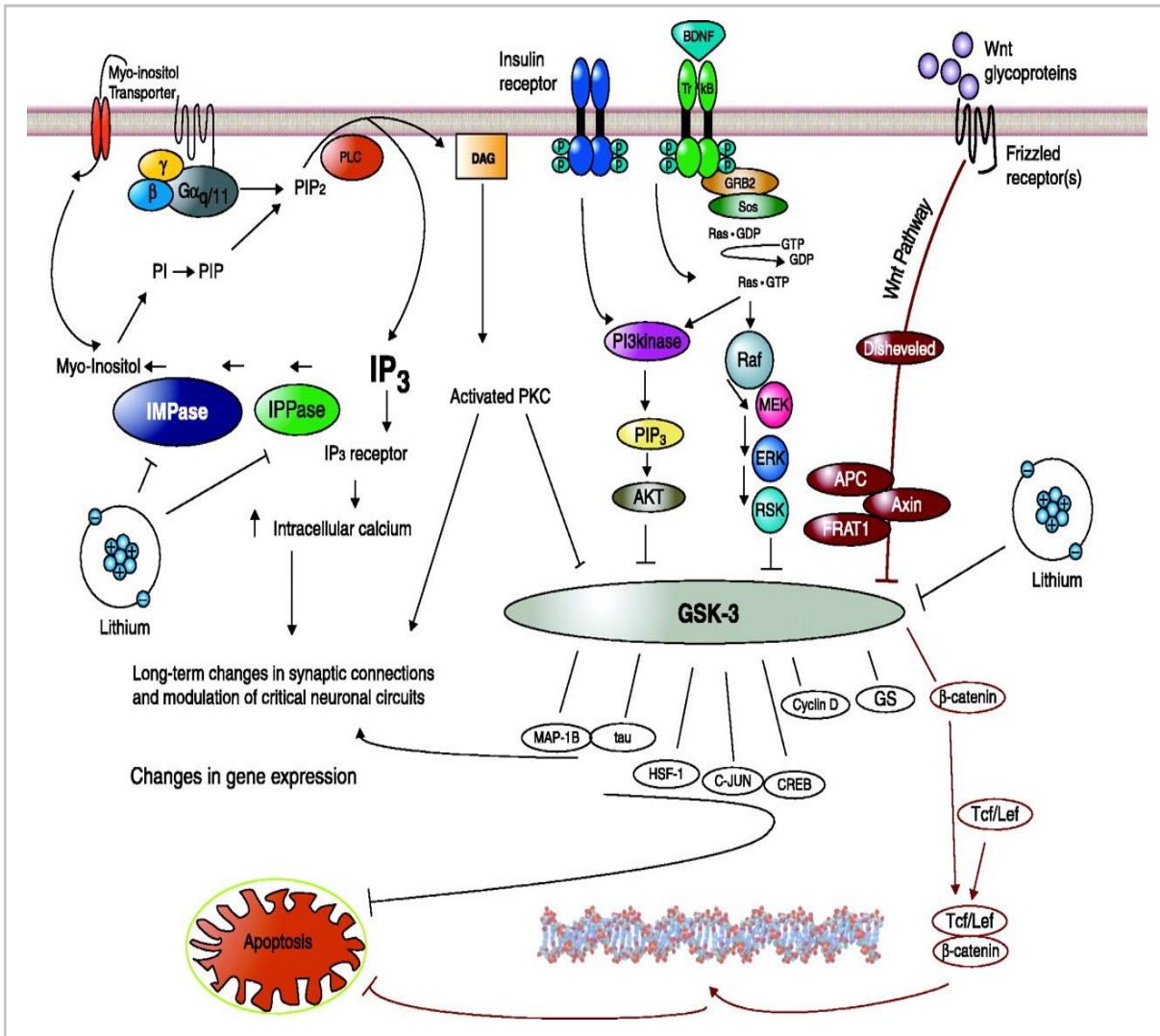
In 1949, Cade was the first to report positive effects on manic illness. This prompted numerous researchers to investigate the activity of Li in bipolar affective disorders (then called maniac depression). These researchers demonstrated how Li administration would inhibit further maniac or depressive episodes among most patients. This made Li salts the medication of choice in treating bipolar affective disorders for quite a period already [151]. However, more recent reports and studies have demonstrated Li therapy to be more efficient in precluding maniac recursions than for treating depressive components/phases. Until now, the way Li works in bipolar disorders is not completely clear. Regardless, Li does influence the activity of secondary messengers. According to [148,



149] the effect of Li on inositol metabolism seems to be pertinent (Fig. 14).

Inositol phospholipids are involved in various processes of information processing in the brain [152] (e.g. being important for receptor-mediated signal transduction). After G proteins and phospholipase C had been activated, 1,4,5-inositol triphosphate and

diacylglycerols form and initiate different kinds of intracellular reactions. These include Ca<sup>2+</sup> ion release and regulation of ion channels in addition to enzymes. An increased activity of this signal transduction system is likely to produce increased intra-CNS release of neurotransmitters like serotonin or dopamine.



**Figure 14.** Glycogen synthase kinase-3 (GSK-3) and inositol monophosphatase (IMPase) are direct targets of lithium [147].

The figure highlights relevant interactions among intracellular pathways related to lithium’s action. GSK-3 functions as an intermediary in several

signaling pathways including neurotrophic signaling pathways, the insulin–phosphatidylinositol 3 kinase (PI3K) pathway, and the Wnt pathway. The activation

of these pathways inhibits GSK-3. The upper left portion of the figure depicts lithium's actions on the PI signaling pathway. Activation of some G proteins induces phospholipase C hydrolysis of phosphoinositide-4,5-bisphosphate (PIP<sub>2</sub>) to diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP<sub>3</sub>). DAG activates protein kinase C (PKC). IP<sub>3</sub> binds to the IP<sub>3</sub> receptor while also functioning as a calcium channel in the cell. IP<sub>3</sub> is recycled back to PIP<sub>2</sub> by IMPase and inositol polyphosphate phosphatase (IPPase), both of which are inhibited by Li [153]. The inositol depletion hypothesis suggests that Li exerts its therapeutic actions by depleting free inositol, which thereby dampens the activation of downstream signaling pathways in neurons [130]. The figure and text were reproduced with permission from H. Manji (one of the authors of 154).

Li has a variety of effects on the central nervous system. Studies have not yet fully clarified which specific effect is ultimately responsible for effectiveness, especially in the case of bipolar disease. The effectiveness may be the result of various effects. Li is not only effective in bipolarity but also for many other diseases which are likely to be caused by mental or central nervous mechanisms [155]:

1. Inactivation of ion channels: Li acts similarly to anticonvulsants (medicines against epilepsy) in the cellular Na K stream and may reduce the central excitability of the brain.
2. Effect on second messenger-systems: All functions of life take place at the smallest cell level. Among the main executive instruments are enzymes and proteins. By interfering with such enzyme chains (Fig. 14: Inositol monophosphatase inhibition), Li leads to a reduction of certain enzyme products and their secondary products (Fig. 14: Inositol-phosphatidylinositol). The inhibition of these (and other) products leads to a decrease in the Ca concentration in the cells. This is exactly what is required in the case of bipolar

disease since intracellular Ca concentration is typically increased in the case of bipolar disease.

3. Release of GABA: GABA (*gamma*-Aminobutyric acid) is a messenger substance in the brain, which is directly linked to mood, like other messengers. Li increases the release of GABA.
4. Serotonin increase: Li leads to an increased release of the "mood transmitter" serotonin and simultaneously inhibits its degradation.

Major depressive disorder (MDD) affects millions of patients [133, 144]. However, the pathophysiology is not well understood. Rodent models have been developed using chronic mild stress or unavoidable punishment (learned helplessness) to induce features of depression such as general inactivity and anhedonia [133, 144]. A three-day vibration-stress protocol for *Drosophila* which reduces voluntary behavioral activity was reported [144]. As in many MDD patients, lithium-chloride treatment can suppress this depression-like state in flies. The behavioral changes correlate with reduced serotonin (5-HT) release at the mushroom body (MB) and can be relieved by feeding the antidepressant 5-hydroxy-L-tryptophan or sucrose, which results in elevated 5-HT levels in the brain. This relief is mediated by 5-HT-1A receptors in the  $\alpha$ -/ $\beta$ -lobes of the MB, while 5-HT-1B receptors in the  $\gamma$ -lobes control behavioral inactivity. The central role of serotonin in modulating stress responses in flies and mammals indicates evolutionary conserved pathways can provide targets for treatment and strategies to induce resilience [144].

Highly impressive findings have discovered Li must have a positive influence in reducing the suicide rates [135-137, 141]. In Japan, the suicide rate is particularly high. About 30,000 Japanese people have ended their lives every year since 1998. According to the WHO, in 2006 there were 29,921 people who no longer wanted to live, two-thirds of whom were men: about 100 people a day took their lives. Based on

these statistics, the rate is 23.7 per 100,000 people (male: 34.8). In 2007, more than 33,000 people lost their lives. In 2008 there was a slight decrease back to 32,249. However, in January 2009 2,645 people killed themselves, which is 15 percent higher compared to that of January 2008. One possible factor was the recession. In Japan, this is called a suicide epidemic [156, 157]. Lithuania still beats Japan with 38.6 suicides per 100,000 inhabitants. The suicide rate in Russia is also very high (32.2). In Germany, which occupies a medium position, 13 out of 100,000 people die, and the trend is falling. But in Germany there are far more men than women who take their lives. However, in Germany most people who commit suicide are over 65. People 75 years and older in Germany, 45-54 year-olds and those over 75 years of age in Russia, and 55-64 year-olds in Japan are the most at risk (i. e. when working life ends and retirement begins or is in prospect) [156, 157].

As reported in the British Journal of Psychiatry, Japanese psychologists, and psychiatrists from the universities of Oita and Hiroshima have discovered that even small amounts of Li can reduce the propensity to suicide [156]. For their study, they examined the drinking water of the 18 communities of the prefecture of Oita on the island of Kyushu for the naturally occurring Li concentrations. The different values, which varied considerably and ranged from 0.7 to 59 micrograms per liter, was compared with suicide rates in the communities. The result between the years 2002 to 2006 was the following: the communities with the highest Li levels in drinking water had the lowest suicide rates. Even if the concentration was very low, scientists suspect that the constant intake could have a cumulative effect [156].

[137] confirmed for Austria that there is a negative correlation between suicide incidence levels and Li concentrations in drinking waters which had been noticed before on other continents. Yet there are no viable conclusions concerning a causal relationship between the values. Accordingly, there

are no implications for conducting suicide prevention by adding low amounts of Li to food or water.

According to [157], Li has been used as a mood-stabilizing drug in people with mood disorders. Previous studies have shown that natural levels of Li in drinking water may protect against suicide. The study conducted by [157] evaluated the association between Li levels in tap water and the suicide standardized mortality ratio (SMR) in 40 municipalities of Aomori prefecture, which has the highest levels of suicide mortality rate in Japan. Li levels in the tap water supplies of each municipality were measured using inductively coupled plasma-mass spectrometry. After adjusting for confounders, a statistical trend toward significance was found for the relationship between Li levels and average SMR among females [157]. These findings indicate that natural levels of Li in drinking water might have a protective effect on the risk of suicide among females [157]. Future research is warranted to confirm this association.

Typical groups for a surplus of Li: In chronic bipolar and partly in unipolar depression [142] in the case of mental instability, especially in the case of aggressive behavior; in gout and uric acid stones; for the purpose of immunostimulation, especially with the accompanying treatment of cancer diseases; in alcoholism; possibly also for external use in herpes, fungi, and eczema (Li-containing ointments and water).

Li preparations contain a much higher dose of Li than one could ever consume over the normal diet: concentrations of about 200 milligrams (mg) of Li per day are common in a therapy. In contrast, on average only 0.8 mg of Li per day is observed.

The use of Li as a medicament is only recommended under medical supervision. In clinical psychiatry, Li is used primarily for the treatment of affective disorders, as well as for headache attacks in the context of migraine or cluster headaches. The side effects of Li therapy, as with all drug treatments, are primarily dependent on the specific sensitivity of the patient to Li. Pure Li gifts - not the often-used

combination gift with other psychopharmaceuticals - are relatively rare. Only very occasionally massive symptoms of poisoning occur [105, 158-162].

If the patient is well adjusted and observed during therapy, signs of side effects can usually be detected at an early stage. The side effects usually depend on the dose. Common side effects are for example [163]: increase in weight; frequent urination; thirst; nausea, diarrhea, vomiting.

In the area of neurological side effects (nerve and muscle function) the following phenomena can occur in relatively rare cases when taking Li [163]: muscle weakness; muscle tremor; movement disorders; reduced nerve conduction velocity; interference with reflexes; Nystagmus; visual field failure; disturbances of memory and concentration.

**4.1.3 Lithium in Practice:** "I don't believe in God, but I believe in lithium" is the title of an article from the New York Times magazine in 2015 where American journalist Jaime Lowe described her twenty years of struggle with bipolar suffering [164-167]. She revealed what happened when she tried to cope without the medicine. After seven years of therapy, Lowe stopped using the drug at the age of 24. Afterwards, Lowe wore hundreds of necklaces at once, spent a fortune on butternut pumpkin, growled and yelled instead of talking, and wanted to challenge President George Bush to a speech duel [167].

The potential of Li not only to protect against mania but also possibly against dementia has also been demonstrated in animal experiments [167]. If rats were mixed with trace elements in food, their memory increased. Bipolar patients also seemed to benefit; with Li therapy, the memory functioned in the long term better than without. In 2011, Brazilian physicians tested the drug with 45 seniors with first slight memory weaknesses and were able to slow down mental decline. High doses were not even necessary for these effects, which was demonstrated by colleagues with only one five hundredths of the crowd [167].

The result shocked Danish physician Lars Kessing at the psychiatric center of Copenhagen University [167]. The concentrations to which every human being is exposed in everyday life were obvious. Li is practically everywhere, within drinking water, milk, meat, eggs, and vegetables [1167] "And this day in and day out," says Kessing, who took care of the Danish population register in order to find a possible influence on the risk of dementia with very high Li concentrations in drinking water. People suffer less from Alzheimer's disease, as Kessing [167] reported in the JAMA Psychiatry trade journal in summer 2017 [167]. However, the risk of dementia did not increase correspondingly at low concentrations, as would be expected in a causal connection. While these remain unproven [168]. Kessing believes "it is quite possible that the active ingredient could play a role in the prevention of dementia" [167].

#### **4.1.4 Outlook: Meeting functional Food Philosophy:**

To address the functional food philosophy (Danik Martirosyan) of using the intake of microbes, plants, or animals for health care benefits, the relationship of Li to neurological diseases will be discussed.

According to the high (positive) influence which is given by Li pharmaceutical intake to bipolar disorders and the effect the given by Li to lower suicide attempts found in Japan, Austria, and Texas, a suggestion was to use Li accumulating plants to balance Li distribution in human body. Suggested plants include those from the plant family of Solanacea (i.e. tomato, potato, and paprika), which are well known for accumulating Li under specific conditions.

For example, [155] described the occurrence of Li in the environment of the Jordan Valley and its transfer into the food chain. The study was conducted to investigate the concentration and distribution of water-soluble Li in solid of the Jordan Valley and its concentration in citrus trees and some important food crops in view of the significant implications of Li for human health. The concentration of soluble Li was measured in 180 soil sample collected at two depths

(0-20 and 20-40 cm), while its content was determined in fully expanded leaves collected from citrus and different vegetable crops [155]. Concentrations of soluble Li in soils vary from 0.95 to 1.04 mg/l in topsoil and from 1.06 to 2.68 mg/l in subsoil, while Li concentration in leaves ranged from 2 to 27 mg/kg DM (Fig. 15). Li concentration of the same family or different families vary with location in the valley (e.g. they decreased from north to south). Soluble Li in soils and the plant family did not solely affect Li transfer in the food chain. Furthermore, soil EC, Ca, Mg, and Cl, which increased from north to south might adversely affect plant Li uptake. The current study has demonstrated how consuming 200-300 g FW of spinach per day and per person is recommended to provide consumers with their daily Li requirement for significant health and societal benefits [155].

Scientific findings to date, some of which have been described above, suggest how Functional Food Therapy (FFT) using plants that accumulate high Li

concentrations in the form of "green pills" should be discussed and potentially produced from plants which accumulate high levels of Li. In the second part of our lithium series, we will describe the distribution of the Li in different environmental compartments and present a model that allows us to describe the Li requirement for mental phase stabilization, which would also be combined with a positive mood stabilization [105]. It is important to keep the absorption of Li well below the toxicologically effective Li concentrations. The accumulated Li in foods such as French fries, potatoes, tomatoes, ketchup, paprika, gypsy sauce and more will move in areas containing only about 500 to 1000 times the concentration of Li, which would be toxicologically effective.

Further intensive scientific studies on Li metabolism, its genetic predetermination, and its biochemical and molecular-biological detectable dose effect curves in humans should be considered.

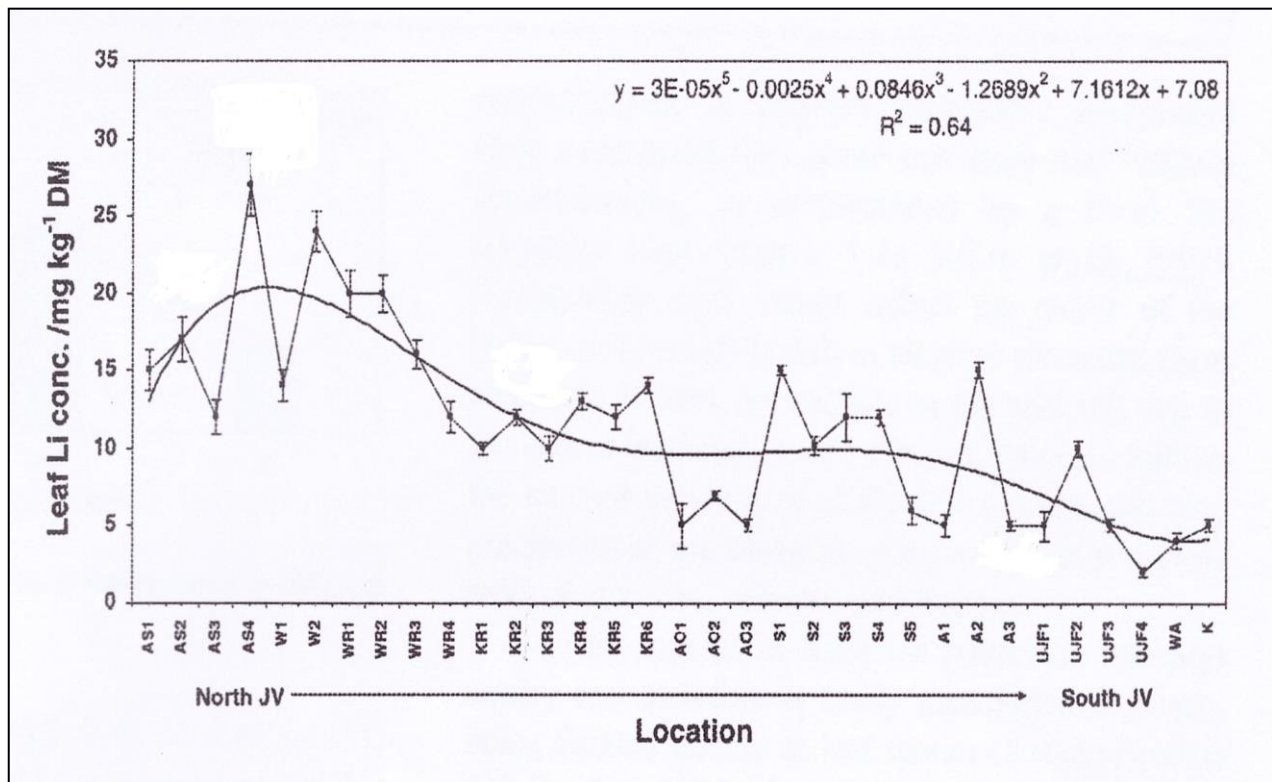


Figure 15. Leaf Li concentration of various common (food) crops grown in different locations of the Jordan Valley [155].

#### 4.1.4 Consequences for Phytoremediation and B & B Technologies

##### 1. From analytical point of view

Ecological reference information should be used to define restoration goals of a contaminated site. Nevertheless, it was estimated that during soil remediation interventions, on average 81% of expenditures are for remediation measures and only 15% for site investigations (EEA 2010). While this is thought to be in line with the clean-up objectives of the site owners and the other stakeholders, it highlights the relatively poor attention of the phytoremediation actors to the site monitoring, which is essential to determine the restoration potential of the sites, and evaluate the success of the restoration interventions in terms of requested stewardship and self-sustaining behaviour.

Selection of appropriate B & B approaches should rely on their potential to provide 'ecological information' from phytomanaged sites without, often without the possibility of a direct comparison with 'reference sites', with limited possibilities to gain direct picture of the actual site conditions in terms of soil properties and hydrological processes, soil microbial genetic diversity and functional activity plant successional stage. In selecting the B & B it is important that they do not only provide the current situation but also allow to hypothesize the site evolution in terms of both ecosystem processes, impact on human health and on society. From this point of view, time is a key factor because phytomanaged sites can be considered as ecosystem under nonstationary state, and all the experimental results indicate that the site responses are generally nonlinear, with rapid positive responses in short times after intervention with relatively limited information on the evolution of the ecological and environmental parameters on the long term. The lack of information prevents the set-up of models for

phytomanagement, allowing scientists and stakeholders to extrapolate the current site conditions in the midterm.

##### 2. From environmental monitoring point of view

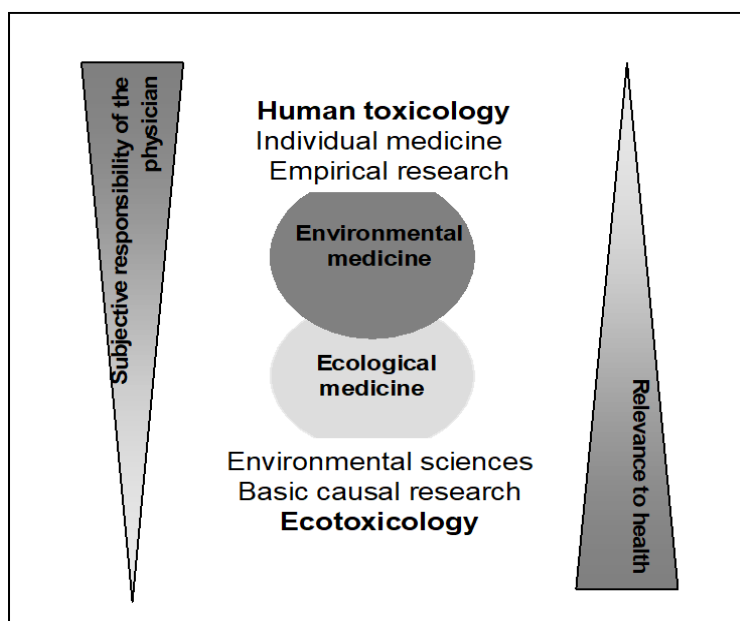
Contaminated sites though under phytomanagement underlies to natural conditions, and if so, a basic question would be: how precise a site restoration can be under a phytomanagement option? In other words, can we determine with an acceptable approximation the degree of restoration of a phytomanaged site? These key questions, not shared in case of 'hard' site remediation interventions, constitute usually tacit objectives during the appraisal of the different phytomanagement options, particularly when phytomanagement is conducted with energy crops. In other cases, when a more ecological approach is adopted, like on the case of the Aznacollar mine spill accident (Spain) or the revegetation of various mining sites all over the world, the future trend of the restored ecosystems is drawn to develop a more stable and resilient ecosystem, as compared to the same sites with no intervention. This is usually achieved when biodiversity is increased, and species dominance and relative abundance of rare species are established. In this context, the natural attenuation of the contamination in terms of total concentrations and bioavailability is the premise for the site colonization by organisms with narrow contaminant tolerance.

The use of the large body of evidence in the scientific literature is fundamental for a practical and successful phytomanagement of contaminated sites. It is important to underline that although phytomanaged sites are man-built environments, they still follow the natural processes that can be described with ecological laws. Relying on these assumptions, due to the lack of a 'natural reference',

phytomanagement requires the development of specific tests sensitive to the dynamics of contaminants in their ecological context, and integrate it into models capable of accounting for the natural variation of the remediated sites in terms of contaminant changes in concentration and geochemical species, biological diversity, complexity of ecological interactions, ecosystem resistance and resilience, and human wellness also in relation with the restored ecosystem services. The practical experience suggests that, for several reasons, all this is currently done informally, with poor integration of the scientific evidence in planning of contaminated sites management. We restate that such a scientific based approach should be used in a top-down mode, i.e. when setting the site-specific restoration goals

and the explicitly admit the possibility to develop the phytomanaged sites towards a range of possible future states and uses, depending on the needs of human societies through the decades.

Finally, we must ask ourselves about the consequences of specific environmental burdens for man, i.e. we need to search for interactions between human beings and the environment in the pathogenic sense [169]. Recent medical history has seen the development of environmental medicine and ecological medicine. Environmental medicine and its methods tend to take the form of an individual approach (involving empirical research), whereas ecological medicine has more to do with basic research into causes together with the environmental sciences (Fig. 16).



**Figure 16:** Differentiation between the terms “environmental medicine” and “ecological medicine” in respect of objectives and content. Definitions in the text (adapted from 169).

According to [169], environmental medicine is that branch of medicine that is concerned with identifying, investigating, diagnosing and preventing impairment of health and well-being

and with identifying, investigating, assessing and minimizing risks caused by definable spheres of interaction between man and the environment. The definable spheres of interaction between

man and the environment are direct and indirect anthropogenic influences of a physical, chemical, biological, socio- psychological, and perceptive nature. “Environment” is the totality of all processes and areas in which interaction between nature and civilisation takes place. In the context of this definition, environmental medicine deals with impairment of health and risks caused by definable anthropogenic influences on the environment. It therefore constitutes the link between health (as a state of equilibrium and adequate stability of essential measurements and values) and the environment (as processes and areas of interaction between civilisation and nature).

Ecological medicine is really an extension of environmental medicine, which centres on the patient, to supra-individual factors relating to health or superordinate risks resulting from interaction between man and the environment or between civilisation and nature [169]. There is no sharp dividing line between environmental medicine and ecological medicine, but environmental medicine takes a chiefly anthropocentric view of effects and risks from the environment, whereas ecological medicine analyses the characteristics of systems – i.e. biological, sociological and ecological factors – underlying these effects and risks. So, whereas environmental medicine reflects the medical effects of interaction between man and the environment, ecological medicine is concerned with the causes. Following the ecosystem approach, ecological medicine constitutes a link between observations of the environment (as

processes and areas of interaction between civilisation and nature) and health (as a state of equilibrium and stability of essential measurements and values) [169].

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**List of Abbreviations:** B&B: Bioindication and Biomonitoring, BSE: Biological System of Elements, BSCE: Biological System of Chemical Elements, DEP: Dialogue Education Process, DM: Dry Matter, EEA: European Environment Agency, FW: Fresh Weight, OECD: Organization for Economic Co-operation and Development: Ba: Barium, Br: Bromine, C: Carbon, Cl: Chlorine, Cr: Chromium, Li: Lithium, Mg: Magnesium, N: Nitrogen, Ni: Nickel, O: Oxygen, Pb: Lead, Rb: Rubidium, Sr: Strontium, Zn: Zinc

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#### REFERENCES:

1. Roots EF: Environmental information – autobahn or maize. In: Schroeder W, Fraenzle O, Keune H, Mandy P (eds.): Global monitoring of terrestrial ecosystems. Ernst und Sohn Verlag für Architektur und technische



- Wissenschaften, Berlin; 1992, 3-31, Does not looks as if it is formatted correctly
2. Menke-Glückert P: Working paper, 'Eco-Commandments for World Citizens' presented at UNESCO conference 'Man and Biosphere', March 9 in 1968, Paris.
  3. Markert B, Kanschak, R (eds.): Mögliche Wege zu einem gesellschaftsfähigen Ethik-Konsens. Was können Hochschulen leisten? Peter Lang Verlag, Frankfurt/M; 2003.
  4. Arias A, Marcovecchio J : Marine Pollution and Climate Change. Tylor and Francis; 2017.
  5. Badran A (ed.): At the Crossroads: Education in the Middle-East, PWPA Book, Paragon House, N.Y.; 1989.
  6. Baydoun E: Arabic Encyclopaedia on Knowledge for Sustainable Development, Volume 2 (Environmental Dimension). 573pp. UNESCO; 2006.
  7. Jayasundara J, Jayasekara R, Ratnayake R: Liquid organic fertilizers for growth enhancement of *Abelmoschus esculentus* (L.) Moench and *Alternanthera sessilis* (L.) DC.. Tropical Plant Research; 2016, 3(2): 336-340.
  8. Kang H, Kim C, Kim E: Human influence, regeneration, and conservation of the Gotjawal forests in Jeju Island, Korea; 2013. DOI: 10.1016/j.imic.2013.11.003
  9. Leskova A, Fabiano R, Giehl H, Hartmann A, Fargasová A, Wirén N: Heavy metals induce iron-deficiency responses at different hierarchic and regulatory levels; 2017. DOI: <https://doi.org/10.1104/pp.16.01916>
  10. Markert B, Fränzle S, Hosang M: Vorzeichenwechsel. Wie Gesellschaft sich verändern kann. Peter Lang, Frankfurt a.M.; 2005.
  11. Mench M et al.: Intensify production, transform biomass to energy and novel goods and protect soils in Europe, INTENSE Newsletter #5, NEWS MONTHLY N°5 April 2018. DOI: 10.13140/RG.2.2.30866.15043
  12. Pacyna J, Pacyna E (eds): Environmental Determinants of Human Health. Springer International Publishing; 2017.
  13. Tiessen H, Brklacich M, Breulmann G, Menenezes R (eds): Communicating global change science to society: an assessment and case studies. SCOPE 68, Island press, London; 2007.
  14. Jantsch E: Die Selbstorganisation des Universums. Vom Urknall zum menschlichen Geist. Hanser; 1992.
  15. Ellenberg H, Mayer R, Schauermann J: Ökosystemforschung. Ergebnisse des Solling Projektes. Ulmer, Stuttgart; 1986.
  16. Haber W: Nachhaltige Entwicklung unter human-ökologischen Perspektiven im globalen Wandel. Erste Hans Carl von Carlowitz-Vorlesung des Rats für Nachhaltige Entwicklung anlässlich seiner 9. Jahreskonferenz am 23. November 2009 in Berlin; 2009.
  17. Zhu Y, Jones K: Urbanisation and health in China. Lancet; 2010, 376, 232-233.
  18. Adriano D (ed): Biogeochemistry of Trace Metals, Lewis, Boca Raton; 1992.
  19. Baker A, Brooks R: Terrestrial higher plants which hyperaccumulate metallic elements – A review of their distribution, ecology and phytochemistry. Biorecovery; 1989, 1, 86-126.
  20. França E, De Nadai Fernandes E, Bacchi M, Tagliaferro F, Saiki M: Soil-leaf transfer of chemical elements for the Atlantic Forest. Radioanalytical and Nuclear Chemistry; 2007, 271, 2, 405-411.
  21. Kashulina G, de Caritat P, Reimann C: Acidity status mobility of Al in podzols near SO<sub>2</sub> emission sources on the Kola Peninsula, NW Russia. Applied Geochemistry; 1998, 13, 391-402.
  22. Rauch S: Platinum group elements in urban environments. Poster at the Urban Environmental Pollution Conference, June 20-23, 2010, Boston, US.
  23. Reimann C, Halleraker J, Kashulina G, Bogatyrev I: Comparison of plant and precipitation chemistry in catchments with different levels of pollution on the Kola Peninsula, Russia, Science of the Total Environment; 1999, 243, 244, 169-191.
  24. Schull M, Hauck M: Extraction methods for assessing the availability of cations for epiphytic lichens from bark, Environmental and Experimental Botany; 2003, 49, 273-283.
  25. Wang M, Markert B, Shen W, Chen W, Peng C, Ouyang Z: Microbial biomass carbon and enzyme activities of urban soils in Beijing. Environmental Sciences and Pollution Research; 2011, 18, 958-967.
  26. Markert B, Breure T, Zechmeister H (eds.): Bioindicators & Biomonitors. Principles, Concepts and Applications. Elsevier, Amsterdam; 2003.
  27. Markert B, Breure T, Zechmeister H: Definitions, strategies and principles for bioindication / biomonitoring of the environment. In: Markert B, Breure T, Zechmeister H. eds. Bioindicators & Biomonitors. Principles, Concepts and Applications. Elsevier; 2003, Amsterdam, 3-39.
  28. Nriagu J, Pacyna J: Quantitative assessment of worldwide contamination of air, water and soils by trace metals. Nature; 1988, 333, 134-139. <https://doi.org/10.1038/333134a0>
  29. Nriagu J, Pacyna J: Quantitative assessment of worldwide contamination of air, water and soils by trace metals. Nature; 1988, 333, 134-139. <https://doi.org/10.1038/333134a0>
  30. Baltrėnaitė E, Lietuvninkas A, Baltrėnas P: Biogeochemical and engineered barriers for preventing spread of contaminants. Environmental Science and Pollution Research; 2018, 25(6), 5254-5268.
  31. Bargagli R, Monaci F, Borghini F, Bravi F, Agnorelli C: Mosses and lichens as biomonitors of trace metals. A comparison study on *Hypnum cupressiforme* and *Parmelia caperata* in a former mining district in Italy. Environmental Pollution; 2002, 116, 279-287.
  32. Carreras H, Gudino G, Pignata M: Comparative biomonitoring of atmospheric quality in five zones of Cordoba city (Argentina) employing the transplanted lichen *Usnea* sp.. Environmental Pollution; 1998, 103, 317.
  33. Chettri M, Sawidis T, Zachariadis G, Stratis J: Uptake of heavy metals by living and dead *Cladonia thalli*, Environmental and Experimental Botany; 1997, 37, 39-52.
  34. Chiarenzelli J, Aspler L, Dunn C, Cousens B, Ozarko D, Powis K: Multi-element and rare earth element composition of lichens, mosses, and vascular plants from the Central Barrenlands, Nunavut, Canada. Applied Geochemistry; 2001, 16, 245-270.
  35. Chudzinska E, AleksandraWojnicka-Połtorak, Wiesław Prus-Głowacki, Konrad Celinski, Jean B. Diatta, Leszek D: Adaptation Mechanisms of *Pinus sylvestris* L. in Industrial Areas. I. Sherameti I, Varma A (eds.): Heavy

- Metal Contamination of Soils, *Soil Biology* 44, Chapter 11. Springer International Publishing Switzerland; 2015, DOI 10.1007/978-3-319-14526-6\_11, pp. 195-213.
36. Conti M, Cecchetti G: Biological monitoring: lichens as bioindicators of air pollution assessment – a review. *Environmental Pollution*; 2001, 114, 471-492.
  37. Culicov O, Yurukova L: Comparison of element accumulation of different moss- and lichen-bags, exposed in the city of Sofia (Bulgaria). *Journal of Atmospheric Chemistry*, 2006, 55, 1-12.
  38. Djingova R, Kuleff I: Instrumental techniques for trace analysis. In: Markert, B., Friese, K. (eds) *Trace elements, their distribution and effects in the environment*. Elsevier, Amsterdam, 2000, pp 137–185.
  39. Figueiredo A, Nogueira C, Markert B, Heidenreich H, Fraenzle S, Liepelt G, Saiki M, Domingos M, Millian F, Herpin U: The use of an epiphytic (*Tillandsia usneoides* L.) as bioindicator of heavy metal pollution in Sao Paulo, Brazil. In: Morrison G, Rauch S (eds) *Highway and urban environment. Proceedings of the 8th Highway and Urban Symposium*, Springer; 2007, pp 249–257.
  40. Frontasyeva M, Steinnes E, Harmens H: Monitoring long-term and large-scale deposition of air pollutants based on moss analysis. In: Aničić Urošević M, Vuković G, Tomašević M (eds.): *Biomonitoring of air pollution using mosses and lichens: a passive and active approach: state of the art research and perspectives*. Hauppauge, New York, Nova Science Publishers; 2016, 1-20.
  41. Gałuszka A: The chemistry of soils, rocks and plant bioindicators in three ecosystems of the Holy Cross Mountains, Poland. *Environmental Monitoring and Assessment*; 2005, 110, 55–70.
  42. Haas J, Bailey E, Purvis O: Bioaccumulation of metals by lichens: Uptake of aqueous uranium by *Peltigera membranacea* as a function of time and pH, *American Mineralogist*; 1998, 83, 1494-1502.
  43. Golan-Goldhirsh A: Bridging the gap between ethnobotany and biotechnology of *Pistacia*. *Isr. J. Pl. Sc.*; 2009, 57, 65-78.
  44. Hempel M, Botte S, Negrin V, Nedda Chiarello M, Marcovecchio J: The role of the smooth cordgrass *Spartina alterniflora* and associated sediments in the heavy metal biogeochemical cycle within Bahia Blanca estuary salt marshes. *J. Soils Sediments*; 2008, 8, 289-297.
  45. Hooda P (ed.): *Trace elements in soil*. Wiley and Sons, New York, 2010.
  46. Lee J, Tallis J: Regional and historical aspects of lead pollution in Britain. *Nature*; 1973, 245:216 – 218.
  47. Klos A, Rajfur M, Waclawek M, Waclawek W, Wuenschmann S, Markert B: Quantitative relations between different concentrations of micro- and macroelements in mosses and lichens: the region of Opole (Poland) as an environmental interface in between Eastern and Western Europe, *Int. J. Environment and Health*; 2010, Vol. 4, No. 2/3, 98-119.
  48. Kwaansa-Ansah E, Adimado A, Nriagu J, Basu N: Comparison of Three Analytical Methods for the Quantitation of Mercury in Environmental Samples from the Volta Lake, Ghana. *Bulletin of Environmental Contamination and Toxicology*, 2016. PMID 27660189 DOI: 10.1007/s00128-016-1920-6
  49. Loppi S, Giomarelli N, Bargagli R: Lichens and mosses as biomonitors of trace elements in a geothermal area (Mt. Amiata, central Italy), *Cryptogamic Mycologie*; 1999, 20, 119-126.
  50. Loppi S, Bonini I: Lichens and mosses as biomonitors of trace elements in areas with thermal springs and fumarole activity (Mt Amiata, Central Italy). *Chemosphere*; 2000, 41, 1333-1338.
  51. Marcovecchio J, Ferrer L: Distribution and geochemical partitioning of heavy metals in sediments of the Bahia Blanca estuary, Argentina. *Journal of Coastal Research*; 2005, 21 (4), 826-834.
  52. Ozturk M, Yucel E, Gucel S, Serdal S, Aksoy A: Plants as biomonitors of trace elements pollution in soil. In: Prasad, M.N.V., ed., *Trace elements – Nutritional Benefits, Environmental Contamination, and Health Implications*. Wiley; 2008, 721-742.
  53. Pesch R, Schmidt G, Schroeder W: Changing Plant Phytology in Germany. Lecture given at the 5th International Workshop on Biomonitoring of Atmospheric Pollution (BIOMAP); 2009, 20-24 Sept. 2009, Buenos Aires, Argentina.
  54. Pignata M, Gudifio G, Wannaz E, Pla R, Gonzalez C, Carreras H, Orellana L: Atmospheric quality and distribution of heavy metals in Argentina employing *Tillandsia capillaries* as a biomonitor. *Environ. Pollution*; 2002, 120, 59-68.
  55. Saiki M, Horimoto L, Vasconcellos M, Marcelli M: Substrate influence on elemental composition of *canoparmelia texana* lichenized fungi, in *Proc. of the International Workshop in Biomonitoring of Atmospheric Pollution – BioMAP II*, Vienna; 2003, pp. 271-277.
  56. Seaward M: Biomonitors of environmental pollution: an appraisal of their effectiveness. *Ecological Chemistry and Engineering*; 2006, 13(3-4), 193-199.
  57. Senhou A, Chouak A, Cherkaoui R, Moutia Z, Lferde M, Elyahyaoui A, El Khoukhi T, Bounakhla M, Embarche K, Gaudry A, Ayrault S, Moskura M: Sensitivity of biomonitors and local variations of element concentrations in air pollution biomonitoring. *Journal of Radioanalytical and Nuclear Chemistry*; 2002, 254(2), 343-349.
  58. Smodis B, Pignata ML, Saiki M, Cortes E, Bangfa N, Markert B, Nyarko B, Arunchalan J, Garty J, Vutchkov M, Wolterbeek H, Steiness E, Freitas N, Lucaciu A, Frontasyeva: Validation and application of plants as biomonitors of trace atmospheric pollution – a coordinated effort in 14 countries, *Journal of Atmospheric Chemistry*; 2004, Vol., 49, 3-13.
  59. Szczepaniak K, Biziuk M: Aspects of the biomonitoring studies using mosses and lichens as indicators of metal pollution. *Environmental Research*; 2003, 93, 221-230.
  60. Tabors G, Lapina L: Growth dynamics of the *Hylocomium splendens* moss. In: Nriagu, J, Pacyn, J, Szefer P, Markert B, Wünschmann S, Namiensnik J (eds.): *Heavy metals in the Environment*. Maralthe Publisher, Leiden; 2012, 311-321.
  61. Zechmeister H, Hagendorfer H, Hohenwallner D, Hanus-Ilmar A, Riss A: Analyses of platinum group elements in mosses as indicators of road traffic emissions in Austria. *Atmospheric Environment*; 2006, 40, 7720-7732.
  62. Vutchkov M: Biomonitoring of air pollution in Jamaica through trace-element analysis of epiphytic plants using nuclear and related analytical techniques. In: Coordinated research project on validation and

- application of plants as biomonitors of trace element atmospheric pollution, analyzed by nuclear and related techniques. IAEA, NAHRES-63, Vienna; 2001.
63. Wolterbeek H, Garty J, Reis M, Freitas M: Biomonitors in use: lichens and metal air pollution. In: Markert B, Breure A, Zechmeister H (eds.): Bioindicators and Biomonitors, Principles, Concepts and Applications, Elsevier; 2003, 377-419.
  64. Wolterbeek B, Sarmiento S, Verburg T: Is there a future for biomonitoring of element air pollution? A review focused on a larger-scaled health-related (epidemiological) context. *J. Radioanal. Nucl. Chem.*; 2010. DOI 10.1007/s10967-010-0637-y.
  65. Schairer L, Van't Hof J, Hayes C, Burton R, de Serres F: Exploratory monitoring of air pollutants for mutagenicity activity with the *Tradescantia* stamen hair system. *Environ. Health Perspect*; 1978, 27: 51-60.
  66. Misik M, Solenska M, Micieta K, Misikova K, Knasmüller S: In situ monitoring of clastogenicity of ambient air in Bratislava, Slovakia using the *Tradescantia* micronucleus assay and pollen abortion assays. *Mutat. Res.*; 2006, 605, 1-6
  67. Markert B, Wünschmann S, Fränzle S, Wappelhorst O, Weckert V, Breulmann G, Djingova R, Herpin U, Lieth H, Schroeder W, Siewers U, Steiness E, Wolterbeek B, Zechmeister H: On the road from environmental biomonitoring to human health aspects: monitoring atmospheric heavy metal deposition by epiphytic/epigeic plants: present status and future needs. *Int J Environ Pollut*; 2008, 32(4):486-498.
  68. Markert B, Oehlmann J, Roth M: Biomonitoring von Schwermetallen – eine kritische Bestandsaufnahme. *Z. Ökologie u. Naturschutz*; 1997, 6, 1-8.
  69. Baker A: Accumulators and excluders-strategies in the response of plants to heavy metals. *J. Plant. Nutr.*; 1981, 3, 643-654.
  70. Martinka M, Vaculík M, Lux A: Plant cell responses to cadmium and zinc. In: Nick, P., Opatrný, Z. *Applied Plant Cell Biology: Cellular Tools and Approaches for Plant Biotechnology. Plant Cell Monographs*; 2014, 22. Springer. pp 209-246.
  71. Fränzle O: Bioindicators and environmental stress assessment. In: Markert B, Breure T, Zechmeister H: Bioindicators and Biomonitors. Elsevier; 2003, 41-84.
  72. Wünschmann S, Oehlmann J, Delakowitz B, Markert B: Untersuchungen zur Eignung wildlebender Wanderratten (*Rattus norvegicus*) als Indikatoren der Schwermetallbelastung, Teil 1. *UWSF-Z Umweltchem Ökotox*; 2001, 13 (5), 259-265.
  73. Wünschmann S, Oehlmann J, Delakowitz B, Markert B: Untersuchungen zur Eignung wildlebender Wanderratten (*Rattus norvegicus*) als Indikatoren der Schwermetallbelastung, Teil 2. *UWSF-Z Umweltchem Ökotox*; 2002, 14 (2), 96-103.
  74. Wünschmann S, Fränzle S, Markert B: Transfer von Elementen in die Muttermilch. Methoden, Modellierungen, Empfehlungen. *Ecomed-Medizin Verlagsgesellschaft / Springer, Landsberg*; 2004.
  75. Wünschmann S, Fränzle S, Markert B, Zechmeister H: Input and transfer of trace metals from food via mothermilk to the child – an international study in Middle Europe. In: Prasad M: Trace Elements, Nutritional Benefits, Environmental Contamination, and Health Implications. Wiley & Sons; 2008, 555-592.
  76. Schwarz O, Jonas W: Bioaccumulation of xenobiotic organic chemicals by terrestrial plants, Chapter 14. In: Wang W, Gorsuch J, Hughes J (eds): Plants for environmental studies. CRC Press, Boca Raton; 1997, pp 417-449
  77. Harmens H, Mills G, Hayes F, Sharps K, Frontasyeva M: Air pollution and vegetation: ICP Vegetation annual report 2015/2016.
  78. Frontasyeva M, Smirnov I, Steinnes E, Lyapunov S, Cherkintsev V: Heavy metal atmospheric deposition study in the South Ural Mountains. *Journal of Radioanalytical and Nuclear Chemistry*; 2004, Vol. 259, No. 1, 2004, p. 19-26.
  79. Herpin U, Berlekamp J, Markert B, Wolterbeek B, Grodzinska K, Siewers U, Lieth H, Weckert V: The distribution of heavy metals in a transect of the three states the Netherlands, Germany and Poland, determined with the aid of moss monitoring. *The Science of the Total Environment*; 1996, 187, 185-198.
  80. Markert B, Weckert V: Time-and-site integrated long-term biomonitoring of chemical elements by means of mosses. *Toxicological and Environmental Chemistry*; 1993, 40, 43-56.
  81. Markert B, Weckert V: Higher lead concentrations in the environment of former West Germany after fall of the "Berlin Wall", *The Science of the Total Environment*; 1994, 158, 93-96.
  82. Berg T, Røyset O, Steinnes E: Moss (*Hylocomium splendens*) used as biomonitor of atmospheric trace element deposition: estimation of uptake efficiencies. *Atmospheric Environment*; 1995, 29 (3), 353-360.
  83. Wappelhorst O: Charakterisierung atmosphärischer Depositionen in der Euroregion Neißer durch ein terrestrisches Biomonitoring. Dissertation, Internationales Hochschulinstitut Zittau; 1999.
  84. Likens G, Bormann F, Pierce R, Eaton J, Johnson N: Biogeochemistry of a forested ecosystem. Springer, Berlin; 1977.
  85. Rapport D: Evolution of indicators of ecosystem health. In: McKencie D, Hyatt D, McDONALS V eds. *Ecological Indicators, Vol 1. Elsevier Applied Science*; 1992.
  86. Prasad M, Freitas H, Markert B, Fränzle S, Wünschmann S: Knowledge explosion in phytotechnologies for environmental solutions. *Environmental Pollution*; 2010, 158, 18-23
  87. Panagos P, Borelli P, Meusburger K, van der Zanden E, Poesen J, Alewell C: Modelling the effect of support practices (P-factor) on the reduction of soil erosion by water at European scale. *Environmental Science and Policy*; 2015, V 51, pp 23-34.
  88. European Environment Agency (EEA): Annual Report 2010 and Environmental Statement; 2011.
  89. Puschenreiter M, Türktaş M, Sommer P, Wieshammer G, Laaha G, Wenzel W, Hauser M: Differentiation of metalliculous and non-metalliculous *Salix caprea* populations based on phenotypic characteristics and nuclear microsatellite (SSR) markers. *Plant Cell Environ*; 2010, 33(10):1641-1655.
  90. Schroeder P, Schwitzguébel J: New Cost Action Launched: Phytotechnologies to promote sustainable land use and improve food safety. *J Soils & Sediments*; 2004, 4 (3), 205.
  91. Salt, D.E., M. Blaylock, N.P.B.A. Kumar, V. Dushenkov, B.D. Ensley, I. Chet, and I. Raskin. (1995). Phytoremediation: a novel strategy for the removal of

- toxic metals from the environment using plants. *Biotechnology* 13: 468-474.
92. Vangronsveld J, Herzig R, Weyens N, Boulet J, Adriaenssens K, Ruttens A, Thewys T, Vassilev A, Meers E, Nehnevajova E, van der Lelie D, Mench M: Phytoremediation of contaminated soils and groundwater: lessons from the field. *Environ Sci Pollut Res Int.*; 2009, 16:765-94.
  93. Schwitzguébel J, Comino E, Plata N, Khalvati M: Is phytoremediation a sustainable and reliable approach to clean-up contaminated water and soil in Alpine areas? *Environmental Science and Pollution Research*; 2011, V. 18, No. 6, 842-856.
  94. Diatta J, Chudzinska E, Drobek L, Wojcicka-Pottorak A, Markert B, Wünschmann S: Multiple-Phase Evaluation of Copper Geochemistry. In: Sherameti, Varma A (eds.): *Heavy Metal Contamination of Soils, Soil Biology* 44, Chapter 3. Springer International Publishing Switzerland; 2015, pp. 43-79.
  95. Kennen K, Kirkwood N: *Phyto*. Taylor & Francis Ltd.; 2015.
  96. Mench M, Vangronsveld J, Beckx C, Ruttens A: Progress in assisted natural remediation of an arsenic contaminated agricultural soil. *Environ Pollut.*; 2006, 144(1):51-61.
  97. Rizwan M, Ali S, Zia ur Rehman M, Rinklebe, Tsang D, Bashir A, Maqbool A, Tack F, Ok Y: Cadmium phytoremediation potential of Brassica crop species: a review. *Science of the Total Environment*; 2018, 631-632. p.1175-1191
  98. Rinklebe J, Du Laing G: Factors controlling the dynamics of trace metals in frequently flooded soils. CRC Press. Taylor & Francis Group. *Dynamics and Bioavailability of Heavy Metals in the Root Zone*. Edited by: Magdi Selim H; 2011, 245-270.
  99. Quintela-Sabarís C, Marchand L, Kidd PS, Friesl-Hanl W, Puschenreiter M, Kumpiene J, Müller I, Neu S, Janssen J, Vangronsveld J, Dimitriou I, Siebielec G, Gałzka R, Bert V, Herzig R, Cundy AB, Oustrière N, Kolbas A, Galland W, Mench M: Assessing phytotoxicity of trace element-contaminated soils phytomanaged with gentle remediation options at ten European field trials. *Sci Total Environ.*; 2017. Dec 1;599-600:1388-1398.
  100. Markert B: Instrumental element and multielement analysis of plant samples – methods and applications. Wiley Publisher; 1996.
  101. Greger M, Landberg T: Use of willow in phytoextraction. *International Journal of Phytoremediation*; 1999, 1: 115-123.
  102. Lux A, Šottníková A, Opatrná J, Greger M: Differences in structure of adventitious roots in *Salix* clones with contrasting characteristics of cadmium accumulation and sensitivity. *Physiol Plant.*; 2004, 120:537-545
  103. Baker A, McGrath S, Reeves R, Smith J: Metal hyperaccumulator plants: a review of the ecology and physiology of a biological resource for phytoremediation of metal-polluted soils. In: Terry N, Banuelos G (eds.): *Phytoremediation of Contaminated Soil and Water*. Boca Raton (FL), Lewis Publishers; 2000, pp. 85-107.
  104. Vaculík M: *Basic Principles of Phytoremediations*. (in Slovak language) Comenius University in Bratislava Publisher; 2018, pp. 90, ISBN 978-80-223-4541-9
  105. Markert B, Ammari T, Wünschmann S, Fränzle S, Rinklebe J: The Distribution of Lithium in the Environment, its Natural Accumulation in Different Solanaceae [Tomatoes, Potatoes, and others] under Arid Climatic Conditions and the Preparation of Functional Food and “Green Pills”, 2018, in prep.
  106. Markert B: The Biological System of the Elements (BSE) for terrestrial plants (glycophytes). *Science of the Total Environment*; 1994, 155, 221-228.
  107. Mendelejew D: Über die Beziehungen der Eigenschaften zu den Atomgewichten der Elemente. *Zeitschrift für Chemie*; 1869, 12, 405-406.
  108. Mendelejew DI: Die periodische Gesetzmäßigkeit der chemischen Elemente *Annalen der Chemie und Pharmazie, Supplement*; 1871, 8,133-229.
  109. Meyer L: Die Natur der chemischen Elemente als Funktion ihrer Atomgewichte. *Annalen der Chemie und Pharmazie*; 1870, 354-364.
  110. Markert B, Fränzle S, Wünschmann S: *Chemical Evolution – The Biological System of the Elements*. Springer; 2015.
  111. Bowen H: *Environmental Chemistry of the Elements* Academic Press, 1979.
  112. Markert B: Instrumental analysis of plants, in: Markert B (ed.) *Plants as biomonitors - Indicators for heavy metal pollution in the terrestrial environment*. VCH-Verlagsgesellschaft mbH; 1993, S.65-103.
  113. Nierboer E, Richardson D: A biologically and chemically significant classification of metal ions. *Environ Pollut.*; 1980, B1:3-26.
  114. Horovitz C: Is the major part of the periodic system really inessential for life? *J Trace Elem Electrolytes Health Dis.*; 1988, 2:135.
  115. Kabata-Pendias A, Pendias H: *Trace elements in soils and plants*. CRC Press, Boca Raton, 1984.
  116. Pais I: Criteria of essentiality, beneficiality, and toxicity. What is too little and too much? In: Pais I (ed) *Cycling of nutritive elements in geo- and biosphere*. Proceedings of the IGBPsymposium of the Hungarian academy of sciences, Budapest; 1991, 59-77.
  117. Markert B: Presence and significance of naturally occurring chemical elements of the periodic system in the plant organism. *Vegetatio*; 1992, 103:1-30.
  118. Streit B, Stumm W: Chemical properties of metals and the process of bioaccumulation in terrestrial plants. In: Markert B (ed) *Plants as Biomonitors – Indicators for Heavy Metals in the Terrestrial Environment*. VCH Weinheim, 1993.
  119. Fränzle S, Markert B, Wünschmann S: *Introduction to Environmental Engineering*, Wiley-VCH, Weinheim, 2012.
  120. Fränzle S: *Chemical Elements in Plant and Soil: Parameters Controlling Essentiality*. Task for Vegetation Sciences 45. Springer; 2010, 196 pp.
  121. Lieth H, Markert B (eds.): *Element concentration cadasters in ecosystems. Methods of assessment and evaluation*. VCH, 1990.
  122. Markert B, Wünschmann S, Herzig R, Quevauviller P: *Bioindicateurs et biomoniteurs : Définitions, stratégies et applications*, French Language. TechIng Paris; 2010, P4 170:1-16
  123. Markert B, Wünschmann S, Baltrėnaitė E: APLINKOS STEBĖJIMO NAUJOVĖS. BIOINDIKATORIAI IR BIOMONITORIAI: APIBRĖŽTYS, STRATEGIJOS IR TAIKYMAS, Lithuanian Language. *Journal of*

- Environmental Engineering and Landscape Management, 2012, 20:3, 221-239.
124. Markert B, Wünschmann S, Diatta J, Chudzirska E: Innowacyjna Obserwacja Środowiska: Bioindykatory i Biomonitoring: Definicje, Strategie i Zastosowania, Polish Language. Environmental Protection and Natural Resources; 2012, No. 53, 115-152.
  125. Markert B, Wünschmann S, Marcovecchio J, De Marco S: Bioindicadores y Biomonitores: Definiciones, Estrategias y Aplicaciones. In: Marcovecchio J, Freije R (eds): Procesos Químicos en Estuarios, 2013.
  126. Markert B, Wang M, Wünschmann S, Chen W: 生态环境生物指示与生物监测技术研究进展 (Bioindicators and Biomonitoring in Environmental Quality Assessment), (Mandarin) Language. Acta Ecologica Sinica, Elsevier China, 2013, Vol. 33, No 1, 33-44.
  127. Markert B, Wünschmann S, Ghaffari Z: شاخص-ها و فرآیندهای زیست-شناسی: تعاریف، راهبردها و کاربردهای ندمارکرتوسیمونوشمن Persian Language. Journal of Environmental Management and Planning; 2013, Vol. 2, No. 95-110.
  128. Markert B, Wünschmann S, Tabors G: Inovātie vides novērtējumi. Bioindikatoru un biomonitoringā: definīcijas, stratēģijas un programmas (Innovative Observation of the Environment: Bioindicators and Biomonitoring: Definitions, Strategies and Applications), Latvia Language. LATVIJAS UNIVERSITĀTES RAKSTI; 2014, 791. sēj. ZEMES UN VIDES ZINĀTNES, 17-49.
  129. Beliles R: Lithium. In: Clayton G, Clayton F (eds.): Patty's Industrial Hygiene and Toxicity (4th ed., Vol. II, Part C). New York: Wiley; 1995.
  130. Berridge M, Downes C, Hanley M: Neural and Developmental Actions of Lithium: A Unifying Hypothesis. Cell; 1989, 59: 411-419.
  131. Birch N: Lithium. In: Seiler H, Sigel H, Sigel A (eds.): Handbook on the Toxicity of Inorganic Compounds. New York, Marcel Dekker; 1988, 382-393.
  132. Cade J: Lithium Salts in the Treatment of Psychotic Excitement. In: Medical Journal of Australia; 1949, 2, 36, 3: 349-352.
  133. Castillo-Quan J, Li L, Kinghorn K, Ivanov D, Tain L, Slack C, Kerr F, Nespital T, Thornton J, Hardy J, Bjedov I, Partridge L: Lithium Promotes Longevity through GSK3/NRF2-dependent Hormesis. Cell Rep.; 2016, 15, 638-650.
  134. CentroSan B: Nährstoff-Lexikon, www. CentroSan.com, Managing Director Thomas Neumeyer, Jan Camperstraat 11A, 6416 SG Heerlen, The Netherlands, 2017.
  135. Cipriani A, Pretty H, Hawton K, Geddes J: Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: A systematic review of randomized trials. Am. J. Psychiatry; 2005, 162:1805-1819.
  136. Kabacs N, Memon A, Obinwa T, Stochl J, Perez J: Lithium in drinking water and suicide rates across the East of England. Br. J. Psychiatry; 2011, 198:406-407. doi: 10.1192/bjp.bp.110.088617.
  137. Kapusta N, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M, Praschak-Rieder N, Sonneck G, Leithner-Dziubas K: Lithium in Drinking Water and Suicide Mortality. Br. J. Psychiatry; 2011, 1, 198: 346-350. doi: 10.1192/bjp.bp.110.091041.
  138. Kasuya J, Kaas G, Kitamoto T: Effects of Lithium Chloride on the Gene Expression Profiles in Drosophila Heads. Neurosci.; 2009, 64: 413-420.
  139. Katsurada E, Sugihara Y: Gender-role Identity, Attitudes toward Marriage, and gender-segregated School Backgrounds. Sex Roles; 2002, 47: 249-258. doi: 10.1023/A:1021334710431.
  140. Lenox R, Hahn C: Overview of the Mechanism of Action of Lithium in the Brain: Fifty-Year Update. J. Clin. Psychiatr.; 2000, 61, (Suppl 9): 5-15.
  141. Logan R, McClung C: Animal Models of Bipolar Mania: The Past, Present and Future. Neuroscience; 2016, 321, 163-188.
  142. Pfennig A, Ritter P, Höfler M, Lieb R, Bauer M, Wittchen H, Beesdo-Baum K: Symptom Characteristics of Depressive Episodes prior to the Onset of Mania or Hypomania. Acta Psychiatr Scand; 2016, 133: 196-204.
  143. Ribas B: Lithium. In: Merian E (ed.) Metals and their Compounds in the Environment. Weinheim: VCH; 1991, 1014-1023.
  144. Ries A, Hermanns T, Poeck B, Strauss R: Serotonin Modulates a Depression-like State in Drosophila Responsive to Lithium Treatment. Nature Communications; 2017, 8, 15738, doi:10.1038/ncomms15738.
  145. Rybakowski J: Response to Lithium in Bipolar Disorder - Clinical and Genetic Findings. ACS Chem. Neurosci.; 2014, 5: 413-421.
  146. Schrauzer G, de Vroey E: Effects of Nutritional Lithium Supplementation on Mood. Biol. Trace Elem. Res.; 1994, 40: 89-101. doi: 10.1007/BF02916824.
  147. Ekmekcioglu C: Lithium (Li). In: Ekmekcioglu C, Markt W: Essenzielle Spurenelemente. Springer, 2006.
  148. Quiroz J, Gould T, Manji H: Molecular Effects of Lithium. Molecular Intervention; 2004, 4(5), 259-72.
  149. Quiroz J, Machado-Vieira R, Zarate A, Jr C, Manji H: Novel Insights into Lithium's Mechanism of Action: Neurotrophic and Neuroprotective Effects. Neuropsychology, Neuropsychobiology; 2010, 62(1): 50-60.
  150. Anke M: Lithium. In: Macrae R, Robinson R, Sadler M (Eds.): Encyclopedia of food science, food technology and nutrition Academic Press; 1993, pp. 2779-2782.
  151. Schou M: Forty Years of Lithium Treatment. Arch Gen Psychiatry; 1997, 54(1): 9-13; discussion 14-5.
  152. Fisher S, Heacock A, Agranoff B: Inositol Lipids and Signal Transduction in the Nervous System, an Update. J Neurochem; 1992, 58: 18-38.
  153. Majerus P: Nositol Phosphate Biochemistry. Annu Rev Biochem; 1992, 61: 225-250.
  154. Gould T, Quiroz J, Singh J, Zarate C, Manji H: Emerging Experimental Therapeutics for Bipolar Disorder: Insights from the Molecular and Cellular Actions of current Mood Stabilizers. Mol Psychiatry, 2004, 9: 734-755.
  155. Ammari T, Al'Zubi Y, Abu-Baker S, Dababneh B, Gnemat W, Tahboub A: The Occurrence of Lithium in the Environment of the Jordan Valley and its Transfer into the Food Chain. Environ. Geochem. Health; 2011, 33: 427-437.
  156. Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N: Lithium Levels in Drinking Water and Risk of Suicide. Br. J. Psychiatry 2009, 194: 464-465. doi:10.1192/bjp.bp.108.055798.

157. Sugawara N, Yasui-Furukori N, Ishii N, Iwata N, Terao T: Lithium in Tap Water and Suicide Mortality in Japan. *Int J Environ Res Public Health*; 2013, 10(11): 6044-6048.
158. Bradford G: Lithium toxicity. *California Agriculture*; 1961, 15: 14.
159. Gitlin M: Lithium Side Effects and Toxicity: Prevalence and Management Strategies. *Int. J. Bipolar Disorder*; 2016, 4y. 27.
160. Aral H, Vecchio-Sadus A: Toxicity of Lithium to Humans and the Environment – A Literature Review. *Ecotoxicology and Environmental Safety*; 2008, 70: 349-356.
161. Goodwin F, Fireman B, Simon, G., Hunkeler, E., Lee, J., Revicki, D. (2003). Suicide Risk in Bipolar Disorder during Treatment with Lithium and Divalproex. *J. Am. Med. Assoc*, 290: 1467–1473. doi: 10.1001/jama.290.11.1467.
162. Léonard A, Hantson P, Gerber G: Mutagenicity, Carcinogenicity Teratogenicity of Lithium Compounds. *Mutation Research/Reviews in Genetic Toxicology*; 1995, 339:131-137.
163. Gumpert N: Lithium, Medikamente gegen Depressionen, das medizinische Informationsportal, [www.dr.gumpert.de/lithium.html](http://www.dr.gumpert.de/lithium.html). accessed Jan. 2018.
164. Bauer M, Glenn T, Alda M, Sagduyu K, Marsh W, Grof P, Munoz R, Severus E, Ritter P, Whybrow P: Drug Treatment Patterns in Bipolar Disorder: Analysis of longterm self-reported Data. *Int J Bipolar Disorder*; 2013, 1: 1-8.
165. Bauer M, Glenn T, Pilhatsch M, Pfennig A, Whybrow P: Gender Differences in Thyroid System Function: Relevance to Bipolar Disorder and its Treatment. *Bipolar Disorder*; 2014, 16: 58-71.
166. Bauer R. et al.: Internet Use by Patients with Bipolar Disorder: Results from an International Multisite Survey. *Psychiatry Res*; 2016: 242: 388-394.
167. Brendler M: Das Rezept der Wüste. Lithium als Wirkstoff. *Frankfurter Allgemeine Zeitung*, updated November 25, 2017.
168. Kessing L, Gerds T, Knudsen N, Jorgenson L, Kristiansen A, Voutchkova D, Ernsten V, Schullehner J, Hansen B, Andersen P, Ersboll A, Kjær A: Association of Lithium in Drinking Water with the Incidence of Dementia. *JAMA Psychiatry*; 2017, 74 (10):1005-1010.
169. Mersch-Sundermann V (ed.): *Umweltmedizin, klinische Umweltmedizin, ökologische Medizin*. Georg Thieme Verlag, 1999.