

GDCh-Advisory Committee
on Existing Chemicals (BUA)

**Biological Impact of Synthetic
and Natural Endocrine Active
Substances — Effects on
Human Health**

**Update and Supplementation
of BUA Report 212**

BUA Report 228



S. Hirzel

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**GDCh-Beratergremium
für Altstoffe (BUA)**



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Preface

The Advisory Committee on Existing Chemicals of Environmental Relevance, BUA for short, was established in May 1982 to help the German federal government cope with the large task of dealing with existing chemicals. In an agreement between federal government, scientific community, and the chemical industry, it was associated with the German Chemical Society (GDCh-Gesellschaft Deutscher Chemiker) to ensure objective work, carried out in accordance with scientific principles.

At the end of 1997, the Committee was renamed 'GDCh Advisory Committee on Existing Chemicals' (abbreviation 'BUA' as before) and the statutes were revised to include EU level aspects of occupational safety for the handling of existing chemicals from then on. The collaboration with the Employment Accident Insurance Fund of the Chemical Industry (BG-Chemie), with its knowledge on workplace exposure and the toxicologic properties of chemicals, is a valuable addition to the BUA's know-how.

The cooperation between authorities, industry, and the scientific community, upon which the BUA is based, has proven worthwhile. No other national or international body has dealt with the ecological and health-related effects of so many existing chemicals as the BUA. On the national level, the BUA has produced comprehensive reports on about 300 substances and carried out preliminary evaluation and classification (priority-setting) for approximately 200 more, as of 1997. Publication of the process leading to priority-setting, in addition to the BUA Reports, lends transparency to the Committee's work.

Since the EU presently considers only those substances with a production volume of more than 1000 tonnes/year, the BUA began an additional national project in 1997, which also selects and assesses existing chemicals with a lower production volume in the range of 100 - 1000 tonnes/ year. The chemical industry presents about 50 databases for substances each year, for which the BUA sets the priority. Comprehensive reports are published on chemicals suspected of having a hazardous potential. If the data available for substance assessment are insufficient, the gaps in knowledge are documented and, if necessary, investigations recommended.

The BUA, as expert committee, increasingly addresses broad scientific questions and problems, such as 'endocrine disruptors', selection criteria for 'persistent organic pollutants' (POPs), 'risk assessment for soils and sediments', 'assessment criteria for the marine sector', and 'safety factors within the framework of toxicologic risk assessment'. The state of scientific knowledge on these subjects is researched, documented, and published as 'BUA Reports'. Through such scientific projects is a basis for an evaluation laid. The aim is to develop assessment approaches for the German federal government, determine gaps in knowledge, identify necessary research, and, last but not least, reduce information deficits in the general population. The present BUA report on the phytoestrogen Genistein is the result of intensive investigations and discussions on the theme of endocrine substances in the environment.

Munich, in February 2001

Helmut Greim
BUA Chairman

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List of Abbreviations

bw	body weight
DDE	dichlorodiphenyldichloroethene
p,p'-DDE	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
DDT	dichlorodiphenyltrichloroethane
DES	diethylstilbestrol
DHT	dihydrotestosterone
EDSTAC	Endocrine Disruptor Screening and Testing Committee of the US EPA (American environmental agency)
Genistein	4',5,7-trihydroxyisoflavone
i.p.	intraperitoneal
Linuron	3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea
n	number of samples
OECD	Organization of Economic Cooperation and Development
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzo furans
T3	triiodothyronine
T4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TSH	thyreotropin
Vinclozolin	3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-oxadolidine-2,4-dione

Biological Impact of Synthetic and Natural Endocrine Active Substances—Effects on Human Health

Summary and Conclusions

This BUA report supplements and updates BUA Report 212 “Biological Impact of Synthetic and Natural Endocrine Active Substances—Effects on Human Health”, which appeared in 1999. A supplement became necessary after such a short time, due partly to the constantly growing amount of published data on this topic, particularly on epidemiological findings in humans, but also because other aspects have been brought into the discussion concerning chemicals affecting the hormone system. These include anti-estrogenic, androgenic, and anti-androgenic influences, as well as effects on the thyroid system through environmental chemicals and their impact on human health. Moreover, in some studies with in utero or early postnatal exposure, effects were described in unexpectedly low dose ranges, the relevance of which is now a matter of controversy (the so-called low-dose hypothesis).

An evaluation of recent scientific literature on the above aspects by the BUA led to the following results:

Insights from Recent Epidemiological Investigations

The postulated connection between an environmental or food-related exposure to chemicals affecting the hormone system and various hormone-dependent changes described in humans has not been confirmed with certainty.

The available data indicate that the changes described by some authors for some of the parameters discussed (sperm density, malformation of male genitals, endometriosis, and endometrial cancer) are equivocal, as other authors determined decreases, increases, or no changes at all, depending on the region, race, and other not completely identified factors. In addition, the multitude of known factors contributing to these end points renders it practically impossible to identify the cause(s) of minor changes. This also applies to the end points which have, without doubt, increased over recent years (testicular cancer, prostate cancer, breast cancer). Thus, the so-called estrogen hypothesis, deduced mainly from human experiences with the estrogen analog diethylstilbestrol, which is highly potent and applied therapeutically

at high doses, as well as from findings in highly exposed animals, is not supported by epidemiological data.

Anti-Estrogenic Effects of Xenobiotics

Substance classes relevant to food and the environment, which have a proven anti-estrogenic effect *in vitro* and in animal experiments, are the PCDDs and PCDFs, coplanar congeners of PCBs, as well as some polycyclic aromatic hydrocarbons. Mechanistically, the anti-estrogenic potential of these compounds is attributed to binding to the cytosolic Ah receptor, which leads *i. a.* to a reduced expression of the estrogen receptor and an induction of estrogen-metabolizing enzymes. The extent to which the anti-estrogenic potential of these compounds can damage human health under actual exposure conditions has yet to be clarified. In animal experiments, anti-estrogenic doses of 2,3,7,8-TCDD, the substance best-studied in this respect, are orders of magnitude higher than those of actual human exposure.

Basically, depending on the test system and various methodical variables, anti-estrogenic effects can also be observed for various substances with proven estrogenic effects. The underlying assumption is that the effect of potent physiological estrogens can be reduced by substances with weaker estrogenic activity, when they competitively displace the more potent estrogen.

Androgenic and Anti-Androgenic Effects of Xenobiotics

No reports are available so far on human health damage which could be caused by androgenic or anti-androgenic effects of xenobiotics in the environment or diet. However, anti-androgenic effects have been described in *in vivo* and *in vitro* investigations of various chemicals, such as *p,p'*-DDE, linuron, vinclozolin, and di(*n*-butyl)phthalate. Although the *in vivo* investigations do not permit the deduction of NOAELs, effective doses are in a range that is orders of magnitude away from the actual exposure situation for man. Receptor-binding studies also indicate that chemicals tested so far have a relatively low androgenic or anti-androgenic potency, compared to the endogenous ligands testosterone or dihydrotestosterone, so that in general, disturbances of sexual development or other anti-androgenic adverse effects are not to be expected in man.

Effects of Xenobiotics on Thyroid Function

Various investigations suggest that a pre- or postnatal exposure to chemicals with effects on the hormone system, particularly PCBs, PCDDs, or PCDFs, even if it only amounts to background exposure, can influence the neurological development of children. These findings are controversial, especially since the mechanisms concerned and the causative factors have yet to be clearly explained. Since the neurological effects described partly resemble those occurring in newborns with hypothyroidism, it was also assumed that they could be due to an effect of environmental chemicals on thyroid gland function. An evaluation of the scientific literature showed, however, that a disturbance of the thyroid system is only of minor relevance, if at all, to the neurological deficiencies. Animal experiments and *in vitro* studies also indicate various targets outside the hormone system for the environmental chemicals investigated.

Animal Experiments With In utero or Postnatal Exposure to Substances Affecting the Hormone System and the Low-Dose Hypothesis

Some working groups have described effects at unexpectedly low doses when experimental animals are exposed *in utero* or during the early postnatal phase to various environmental chemicals affecting the hormone system. These findings and corresponding results from *in vitro* experiments supported the hypothesis that, under some circumstances, U-shaped or inverse U-shaped dose-effect relationships or a lack of threshold values could exist for hormones and substances affecting the hormone system, allowing effects to occur at doses far below previously known effective thresholds for these substances (the so-called low-dose hypothesis).

An evaluation of the scientific literature published so far has shown substantial doubts regarding the so-called low-dose hypothesis to be justified for the tested substances with effects on the hormone system. The study results that triggered this hypothesis could not be reproduced by various working groups using, at times, a higher methodological input. The causes of the discrepant findings have not been explained. Under discussion are the low expression of effects at high biological variability, species- and strain-specific differences, the type of statistical evaluation and sample composition (e.g. from one or more litters), and other unidentified interfering factors unrelated to the substance.

Present national and international research activities on substances with a possible effect on the hormone system continue to be considerable (e. g. Kavlock 1999), and various studies are also being carried out or planned on the aspects of the problem discussed in this report. This report shows, however, that a critical evaluation and assessment of defined questions is already possible on the basis of available information. Thus, results should continue to be regularly and critically examined and assessed by committees of specialists, with respect to the impact on human health, before new research activities are initiated.