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EPOK – Centre for Organic Food & Farming

ORGANIC FOOD
– food quality and potential health effects

A review of current knowledge, and a discussion of uncertainties

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Preface

There is a lively public debate whether or not organic food is healthier than conventional food. Research does not provide a clear answer. EPOK has initiated the work leading to the present report with the aim to summarize existing scientific evidence and identify knowledge gaps.

There is also an ambition to show how diverging perceptions among the public are linked to and have their origin in existing research. At some points, namely in the discussions of statistical issues in the comparison of crop nutrient contents, of gaps in today's risk assessment of pesticides, and of the potential relevance of epidemiological studies of pesticide effects for public health, we aim at presenting and interpreting research in order to advance the scientific or public debates.

The report touches agricultural, chemical, toxicological, nutritional and medical sciences. It is written with the intention that people who are not experts in these sciences can read most of it. The readers could be interested members of the public, researchers from other disciplines who want to get an overview over the area, or other societal stakeholders. At some points, however, it has been important to dig deeper with little chance to simplify.

Our ambition is not to present all studies that have been performed in the area. Where possible, we instead use systematic reviews and meta-analyses as starting points, and present selected original studies that we believe can illustrate or increase the understanding of specific issues.

Axel Mie is the main author of this report with Maria Wivstad as co-author. The report is not a scientific systematic review. The prioritization of themes and the selection of studies have been done with care, but without claims of being exhaustive. Some examples are chosen with a Swedish and European perspective in mind. Discussions of political and societal implications can for the most part not be found in the scientific literature; these represent personal analyses of the authors.

Uppsala, January 2015

Maria Wivstad
Director, EPOK

Contents

Summary and outlook

In this report, we try to approach the question "Is organic food healthier than conventional food?" from a scientific perspective. We can conclude that science does not provide a clear answer to this question. A small number of animal studies and epidemiological studies on health effects from the consumption of organic vs. conventional feed/ food have been performed. These studies indicate that the production system of the food has some influence on the immune system of the consuming animal or human. However, such effects are not easily interpreted as positive or negative for health. The chemical composition of plants is affected by the production system; however, the relevance for human health is unclear, and when one focuses on single compounds such as vitamins, the picture is diffuse with small differences between production systems but large variations between studies. The composition of dairy products is definitely influenced by the organic vs. conventional husbandry systems due to different feeding regimes in these systems. From today's knowledge of the functions of fatty acids, the composition of organic milk is more favorable for humans than the composition of conventional milk, due to a higher content of omega-3 fatty acids. However, less is known about other animal products, and dairy fats contribute little to the population's intake of polyunsaturated fatty acids, so the importance for human health is small. For pesticides, organic food consumption substantially lowers pesticide exposure. According to European governmental bodies, pesticide residues in food are unlikely to have long-term effects on the health of consumers. There are however some important epidemiological studies, and uncertainties in pesticide regulation that may justify a precautionary approach for vulnerable population groups.

All the small pieces of evidence collected in this report justify more attention being paid to conducting epidemiological studies on the preference for organic vs. conventional food. From animal studies (namely on chicken health), from functional knowledge of fatty acids, and from epidemiological studies of pesticide effects, it would be possible to formulate interesting research hypotheses that could be tested in long-term studies of humans, dedicated to investigating potential health effects of conventional vs. organic food. ■

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Introduction

Often, if a food has a high vitamin content, it is regarded as healthy. This is true in situations where the consumer of the food is facing vitamin deficiency. The discovery of vitamins and their functions and deficiency symptoms have historically brought great benefit to humankind. Nonetheless, vitamins are not the same as health. For example, a high intake of beta-carotene and vitamin E via food supplements is associated with a higher mortality rate (deaths per year per 1 000 people)[1]. In contrast, a high intake of vegetables is associated with a lower mortality[2]. That is, vitamin contents alone do not tell the whole truth about whether a food is healthy or not: "Food, not nutrients, is the fundamental unit in nutrition", as one nutritionist puts it[3].

Many people have an opinion on whether organic food is more (or equally or less) healthy compared to conventional food. It may be surprising to know that only a very small number of scientific studies have addressed this question directly. There are, however, numerous studies that compare the vitamin, mineral, antioxidant contents of organic and conventional fruits and vegetables, or the fatty acid composition of organic and conventional milk.

The reason is that it is far easier to measure the vitamin content of organic and conventional fruit, than to measure if either one is healthier. In order to measure healthiness, one would need to have a group of humans eating only organic and another one eating only conventional food, and then after a while compare which group is healthier (such studies are discussed in more detail further below). However, humans are difficult to control and participants in such a study may, for example, not report their food intake correctly. Even more importantly: there is no accepted way of measuring if a person is "healthy". The World Health Organisation (WHO) definition since 1946 is that "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[4]. More recently, scientists have suggested defining "Health as the ability to adapt and to self manage"[5]. None of these definitions are operational in the sense that they can be easily used to measure if or to what degree a person is healthy.

One can, however, define specific health outcomes of interest. It would for example be possible to test if organic food consumption is associated with a lower or higher risk of developing cancer. Such a study would take a long time to perform, because normally cancer develops many years after an initial cause.

In this report, first and most importantly, a small number of animal and human studies of health effects in relation to organic vs. conventional feed/food consumption are presented. After this, a substantial part of this report examines and discusses research on the nutrient content of organic and conventional food of plant and animal origin, bearing in mind that a more favourable content of a few nutrients is not necessarily equivalent to healthier food. However, a lot of research has been done on this topic, and some important insights can be gained. Also, the exposure of consumers to pesticides, potential adverse health effects from pesticides, and gaps in today's pesticide risk assessment are covered. Other food qualities, such as taste, appearance, food additives, food processing, and also cadmium content and antibiotic-resistant bacteria are not or only briefly mentioned. Further aspects of organic farming such as biodiversity and ecosystem services, as well as the effect of the production on climate and food security are covered by other publications from EPOK (in Swedish language)[6, 7].

■

Studies of health effects

How to measure health

Medical sciences know two ways of studying health effects of dietary choices in human populations: observational studies and intervention studies.

In observational studies, a study group is observed and relevant data are collected, but care is taken not to influence the normal behaviour of study subjects. For example, researchers could record food preferences (organic, conventional), dietary patterns, and health parameters in a study population. This can be done at one occasion (cross-sectional study) or several times (longitudinal study).


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In intervention studies, researchers control certain parameters. They could, for example, exchange conventional food for organic food in one study group, but not in a control group, and record health parameters before, during, and after the intervention.

Both types of studies have their limitations: observational studies do not normally allow conclusions on causal relationships. And long-term intervention studies are expensive and difficult to design.

It is easier to study health effects of organic food in laboratory animals. Most environmental factors in animal studies can be controlled, and it is also possible to conduct studies over several generations. It is not always straightforward, though, to draw conclusions for humans. Also, the animals in animal studies do not represent a natural human population with a variety of lifestyles.

Animal feeding trials

Animal feeding studies are performed because it is much easier to control the food intake of animals than of humans over long periods. A recent important study in this area compares chicken that were fed organic or conventional feed over two generations[8]. Three chicken lines, bread for different immune responsiveness, were used in this study. Two batches of feed were identically composed of ingredients obtained from organic and conventional pairs of neighbouring farms, and the feeds were comprehensively analysed for nutrients in order to avoid nutrient deficiencies. However, the feeds differed to some extent in their nutritional content. For example, the amount of proteins was about 10 percent higher in the conventional compared to the organic feed. No pesticide residues were detected in any of the feed ingredients.

A variety of health parameters, many related to the development of the immune system, were measured in the chickens of the second generation. The most important observations, in the breeding line representing the general population, were:

1. chickens on conventional feed grew faster,
2. chickens on organic feed showed a higher immune responsiveness, as measured by the production of antibodies in response to a vaccine, and
3. after an immune challenge, induced by the injection of a protein foreign to the body, the growth rate of all chickens was reduced, but chickens on organic feed recovered their growth rate more quickly.

The authors summarize: "The animals on organic feed showed an enhanced immune reactivity, a stronger reaction to the immune challenge as well as a slightly stronger 'catch-up growth' after the challenge." Even other parameters such as feed intake, body weight and growth rate, as well as several immunological and physiological parameters differed between the groups on organic and conventional feed. These differences are not easily divided into positive or negative for the organism. Nonetheless, they cannot be explained by the small differences in organic and conventional feed composition that the authors found. Overall, the enhanced "catch-up growth" in chicken on organic feed is interpreted as a sign of health[9].

Generally, in all organisms prioritization of resource allocation takes place all the time. The observations of the chicken study can be interpreted such that the source of feed (organic, conventional) affects prioritization towards growth (conventional feed) or immune system development (organic feed). To date, this has not been subject to any long-term study in humans.

Human studies

In hundreds of studies, long-term health effects of pesticide exposure have been investigated (see chapter "Public health effects of low-level pesticide exposure"), but few studies directly address the health effects of the consumption of organic food.

In the cross-sectional PARSIFAL study with 14 000 children from 5 European countries, children aged 5-13 years in families with an anthroposophic lifestyle, which comprises the preference of organic (or biodynamic) food, had fewer allergies than other children[10]. This is in line with other studies[11, 12] of the anthroposophic lifestyle and allergies in children, but the allergy-protective effect of lifestyle cannot be attributed to the organic food consumption.

In the longitudinal KOALA study, which followed about 2 700 babies through childhood, an association was found between the consumption of organic dairy products during pregnancy and infancy and a lower risk for eczema at 2 years of age. This was possibly mediated via a higher content of some ruminant fatty acids in organic milk (see chapter "Composition of animal foods" below)[13].

The Nutrinet-Sainté study is a French-Belgian study on the relation between nutrition and health in a large population. In one sub-study with about 54 000 adult participants, researchers characterized sub-populations of consumers who did or did not prefer organic food with respect to food habits, socioeconomic factors, and body mass index (BMI). Regular consumers of organic food had a substantially lower risk of being overweight (women 28 and men 27 percent decreased risk) or obese (41 and 57 percent decreased risk) compared to the control group of consumers who were not interested in organic food.

This association holds even after adjustment for age, physical activity, education, smoking status, energy intake, restrictive diet, and adherence to public nutritional guidelines. Also, participants with a strong preference of organic food did not differ in average household income from the group of participants who were not interested in organic food. Due to the nature of the study (observational, cross-sectional), it was not possible to draw conclusions on what caused the lower observed risk for overweight and obesity among people preferring organic food. The authors speculate, however, that long-term low-level exposure to pesticides could be the cause[14].

One recent study follows over 600 000 middle-aged women in the UK over 9.3 years and investigates associations between the intake of organic food (never, sometimes, usually/always) and the incidence of cancer. For all cancers, there was no association between the preference of organic food and cancer. There were, however, weak associations between organic food preference and non-Hodgkin lymphoma (21 percent decreased risk for consumers of organic compared to conventional food) and between organic food preference and breast cancer (9 percent increased risk for organic consumers)[116].

A small number of short-term dietary intervention studies with conventional and organic food have also been performed[15], but with limited scope and without any conclusive differential health effects reported. ■

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Composition of plant foods

Biology

By practice and by regulation, fertilization differs between organic and conventional agriculture. Typically, in conventional agriculture, the soil is fertilized with mineral fertilizer containing the plant nutrients nitrogen (nitrate and ammonia), phosphate and potassium (among other minerals). In contrast, in organic agriculture, these nutrients are supplied to the soil mainly in the forms of farm manure, green manure, or other organic materials, while e.g. synthetic nitrogen mineral fertilizers are not allowed. Generally, mineral nutrients are water-soluble and readily available to the plant, while a large portion of the nutrients in organic fertilizers first needs to be decomposed (mineralized), before the nutrients are available to the plant.

Furthermore, the total amounts of these nutrients used for fertilization per hectare per year are on average higher in conventional than in organic agriculture, by regulation and in practice. Accordingly, plants in conventional agriculture receive higher amounts of important plant nutrients in a more easily available form, compared to plants in organic agriculture.

Are differences in plant nutrient amounts and availability of the fertilizer reflected in differences in the composition of the crops? This is what the theory says:

PRO: Biologists sometimes break down plant metabolism into primary and secondary metabolism. Primary metabolism is responsible for basic plant functions such as growth and reproduction, while secondary metabolism is responsible for plant functional diversification, such as defence or appearance. Both the primary and the secondary metabolism are active at all times. Although the classification into primary and secondary metabolism is not clear-cut and represents a simplification, generally associated with primary metabolism are compounds like sugars, carbohydrates, lipids, and many vitamins. Secondary plant metabolites include compounds like phenols, flavonoids, and glucosinolates, among others.

The abundance of plant nutrients (nitrogen, phosphorus, potassium) can influence the balance between primary and secondary metabolism; higher plant nutrient abundance generally causes a shift towards the primary metabolism (sometimes referred to as growth-differentiation balance hypothesis[16]). This is one reason why conventional and organic crops can be expected to be different in their composition.

CONTRA: Plants (as all living organisms) are homeostatic, i.e. they are able to maintain their functions over a range of environmental conditions. Both conventional and organic farmers strive for optimum growth and health in their crops, and within the range of environmental conditions (here: different fertilization regimes), plants develop equally in both production systems. This is one theoretical argument why conventional and organic crops can be expected to be similar or identical in their composition.

Scientific experiments comparing organic and conventional crops are needed in order to test this reasoning.

Comparative studies: types

Three kinds of study designs are used in order to compare the composition of organic and conventional crops:

1. Field trials

On one field site, the crop of interest is grown in several field plots with different agricultural practices. Often, there are randomized replicate plots in such field trials. The researchers have control over all agricultural practices used in the experiment, which is very valuable. However, such a field site does not necessarily reflect the diversity of realistic production conditions on farms.

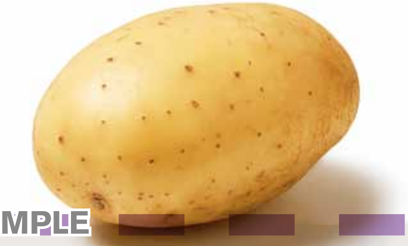
2. Farm-pairing studies

In a farm-pairing study, neighbouring farm pairs, one organic and the other one conventional but both producing the same crop, are identified. It is usually left to the farmers to make all necessary decisions during cultivation, e.g. when weeds should be controlled, if irrigation should be used, and so on. Sometimes, farmers are supplied with seeds; otherwise the choice of cultivar is left to the farmer. Such a study is more realistic than a field trial, but it is also more difficult to ensure that the comparisons are valid. If organic farms for example tend to use another cultivar than conventional farms, any observed differences in nutrient contents or other characteristics could be due to different farming practices or differences between cultivars.

3. Market-basket studies

Here, samples of fresh produce or processed foods are taken at the consumer end of the distribution chain, for example at markets or supermarkets. In field trials and farm-pairing studies, normally some kind of "best practice" of agricultural management is ensured. In contrast, the range of products offered at a supermarket represents the actual agricultural practice and the distribution chain. This is a relevant perspective for the consumer, but it is very difficult to ensure the general validity of findings. For example, any changes in the supply chain (different farms of origin, changed means of transport, changed storage) may affect the final composition of the products, and are very difficult to control. Thus, the results need to be interpreted with caution.

None of these three kinds of studies are able to provide the final answer to the question of the effect a production system has on crop composition. Moreover, depending on the details of the study design, they could lead to different answers to a similar research question. However, dramatic differences in crop composition due to the production system are likely to manifest themselves irrespective of the kind of study design.



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EXAMPLE

A study could be designed to test the hypothesis "organic potatoes contain more vitamin C than conventional potatoes" in Sweden. A controlled field trial would compare potatoes of the same variety in one or several typical potato production areas under conventional and organic conditions, thereby directly measuring the influence of organic and conventional production regimes on this specific variety's vitamin C content under the given climatic and soil conditions.

However, in Sweden, the most popular table potato variety is King Edward VII. King Edward VII is susceptible to the disease late blight (*Phytophthora infestans*) and therefore receives fungicide treatment frequently during the growing season. Consequently, King Edward is not well suited for organic cultivation in Sweden. Therefore, a farm-pairing study would most likely collect a different mix of potato varieties from the conventional and from the organic farms. A comparison of vitamin C contents would then measure a mix of the influences of production system and variety on the vitamin C level.

This may be more relevant to the consumer than a field trial, because the farm study ideally reflects the potato varieties available on the market. On the other hand, the popularity of potato varieties changes over time, and differs between countries and even regionally, so care needs to be taken when generalizing such results. Accordingly, the same question, answered using different study designs, may have different answers.

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Comparative studies: overview

Minerals, vitamins, antioxidants* are all frequently compared in their concentrations in organic and conventional foods. Macronutrients (protein, total fat, carbohydrates) have generally attracted less interest in this context.

In excess of 150 studies have been published that investigate the content of various nutrients in a wide range of food crops in response to conventional and organic production. The results diverge between studies and it is not easy to draw straightforward conclusions of general validity such as "crops from production system A contain *xy* percent more of a certain vitamin". Rather, careful statistical analysis is needed when summarizing all available data, in order to find consistent trends. Several review articles have been published in recent years, summarizing original research. Here, three such reviews are discussed (rather than discussing individual studies) in order to summarize the state of the science in this subject. Further below, the sources of variation between studies are discussed in more detail.

For each nutrient, the reviews report an effect size (i.e. a measure of the magnitude of the difference between production systems) and a statistical significance (i.e. the probability that the observed difference is due to chance).

Organic food crops are more nutritious

Brandt and co-workers published in 2011[17] a meta-analysis of all 102 available studies since 1992 comparing the content of seven (groups of) vitamins and secondary metabolites in organic and conventional food crops: Total phenolics, phenolic acids, other defence compounds (three groups of plant defense related compounds), as well as carotenoids, flavones and flavonols, other non-defense compounds, and vitamin C (four groups of not plant defence related compounds). According to Brandt's analysis, plant defense related compounds were on average present in 16 percent higher concentrations in organic crops. Vitamin C was six percent higher, flavones and flavonols were eleven percent higher, and other non-defense compounds were eight percent higher in organic crops. There was no significant difference in carotenoid content between organic and conventional crops. The overall conclusion of the authors was that on average, organic crops contained twelve percent more vitamins and secondary metabolites than conventional crops.

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* A collective name for a diverse group of compounds that counteract oxidative damage in cells, including e.g. polyphenols

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Organic food crops are not more nutritious

In a systematic review from 2012[18], Smith-Spangler and co-workers summarized 153 studies comparing nutrient content in organic and conventional grains, fruits and vegetables. 14 nutrients were included in the comparison. Only phosphorus and total phenols concentrations were significantly higher in organic crops. For most nutrients, Smith-Spangler reports a high statistical heterogeneity, which means that results of the original studies are inconsistent. The authors also raise concern about reporting and publication bias (tendencies to report statistically non-significant results incompletely, or to prefer publishing studies with significant findings) in some cases. The authors report the effect sizes as Standardised Mean Differences (SMD), which is common in medical sciences but has no direct intuitive interpretation. The overall conclusion of Smith-Spangler *et al.* is that "The published literature lacks strong evidence that organic foods are significantly more nutritious than conventional foods."

Or are they?

In a review from 2014, Barański[19] and co-workers present the most comprehensive meta-analysis of compositional aspects of organic and conventional crops to date, comparing almost 120 nutrients, and other aspects of food quality from 343 original studies. The authors report a significantly higher content of a range of (groups of) antioxidants in organic food, ranging between 19 and 69 percent for phenolic acids and flavanones.

Organic crops also had a lower content of amino acids and proteins. Many other compounds and groups of compounds did not significantly differ in concentration between the production systems.

The authors provide a structured analysis of the overall reliability of their findings: the findings with good reliability were a small increase in antioxidant activity (measured as Trolox equivalent antioxidant capacity, TEAC), a higher content of flavones and flavonols (sum), and a higher content of flavonols (including single compounds in that group) in organic products. Barański reports, similar to Smith Spangler, indications for the presence of publication bias in the meta-analyses of many compounds. Furthermore, Baranski includes all available peer-reviewed studies in the analyses without an evaluation of their quality, in contrast to Smith-Spangler and Brandt, who both apply (different) quality criteria for studies to be included. Data were analysed in two separate ways, in parallel to both Brandt's and Smith-Spangler's work, making a comparison with earlier meta-analyses easier.

Overall, this meta-analysis finds a higher systematic content of some groups of antioxidants and secondary metabolites as well as a lower protein, amino acid, nitrate, nitrite and total nitrogen content in organic crops. This is consistent with the principles discussed under "pro" in section "Biology" above, where a low nitrogen availability causes a shift towards the secondary metabolism. The data extracted from the 343 studies are freely available on the internet.

In summary, there is some evidence that organic crops contain higher amounts of vitamin C and some other beneficial compounds, but there is no final agreement. It is important to note that even if there was a systematically higher vitamin C content in organic fruits and vegetables, the difference due to the production system is small (6 percent higher in organic crops according to[17]), and the variation between cultivars, years, geographical growing locations, climatic conditions, ripeness at harvest etc. are much larger.

EXTENDED READING

The two reviews of Brandt and Smith-Spangler are in apparent contradiction to each other, although it should be noted that they cover somewhat different selections of nutrients. A closer look at the statistical procedures reveals, however, that Smith-Spangler has applied a statistical (Sidak) correction for the large number of comparisons (14 nutrients and 8 contaminants), while Brandt has not.

The "multiple testing problem" is a well-known problem in statistics: the more comparisons of nutrient levels that are made, the higher is the risk of false differences (i.e. differences due to chance alone) being found. A correction can be applied to decrease this risk. This, however, increases the risk of obscuring real differences. If Smith-Spangler *et al.* had not applied such a correction, they would have reported seven of the 14 compared nutrients (vitamin C, calcium, phosphorus, magnesium, quercetin, kaempferol, and total phenols, but not vitamins A and E, potassium, iron, protein, fibres, and total flavanols) in significantly higher concentrations in the organic crops, with the risk that approximately one of the detected differences was false.

Vitamin C is the only nutrient that both Brandt and Smith-Spangler report, and their divergent findings are here discussed in some detail. Brandt reports a statistically significant (p=0.006) six percent higher vitamin C content in organic crops, based on 86 comparisons from 30 published studies. Smith-Spangler reports no significant difference (p=0.48) after Sidak correction for multiple testing, but a significantly (p=0.029) higher vitamin C content in organic food without such a correction (calculated from data in[18]), based on 31 studies. The magnitude of the difference is reported as SMD (SMD=0.5), which is not easily translated into a percentage difference. The discussion as to whether organic crops contain more vitamin C than conventional crops appears thus to boil down to a discussion on statistics, i.e. whether it is appropriate or not to apply a multiple testing correction in a meta-analysis of a range of nutrients. There is no final answer to this question, as the appropriateness in part depends on what kind of decisions are to be based on the results.

However, the Cochrane Collaboration, which is renowned for their systematic reviews in medical sciences, state in their guidelines: "Adjustments for multiple tests are not routinely used in systematic reviews, and we do not recommend their use in general"[20]. It should also be noted that the two meta-analyses of Brandt and Smith-Spangler, and earlier ones, differ in a number of other methodological aspects, including the definition of what kind of data that constitute a data pair for the meta-analysis[21]. The recent review by Barański allows for a direct comparison of both Brandt's and Smith-Spangler's results.

Barański[19] finds a 29 percent (p=0.005) or 6 percent higher content of vitamin C in organic food, depending on if studies that have not reported the within-study variation of data are included or excluded. Barański also reports an SMD of 0.33 (p=0.018, without correction for multiple testing). This highlights that the recent meta-analyses indeed are to some extent consistent in their results, yet differences in the treatment of the multiple testing problem lead to different conclusions.

What is causing the variation between studies?

Different studies may find very different results when measuring the same nutrient in conventional and organic crops. For example, in 113 comparisons of vitamin C in various crops, 23 found more vitamin C in organic and 12 found more vitamin C in conventional crops, while in the remaining comparisons, no significant difference was found[18]. The reason for this variation between studies lies in the differing study designs, climatic conditions, soils, production years, crops, crop varieties, ripeness at harvest etc., all of which may influence the nutrient content of a plant.

As one illustrative example, quercetin is a plant compound of the flavonoid group. Quercetin has antioxidant properties and is generally desirable as a food component. Figure 1 illustrates how the production system (organic vs. conventional), the production year (2003, 2004, 2005) and the tomato variety (Burbank and Ropreco) all influence the quercetin content in tomatoes. From these data alone, no general trend is apparent as to whether organic or conventional tomatoes have a systematically higher content of quercetin. If the results of many different studies are analyzed together (meta-analysis), such a trend may appear, but it is important to keep in mind that other factors (like the variety) may be equally or more important.

Relevance of comparing nutrient contents

In recent years, it has been increasingly questioned whether it is adequate to describe a food's value by its content of vitamins, minerals and antioxidants in situations where malnutrition does not generally occur; as one researcher puts it: "Food, not nutrients, is the fundamental unit in nutrition"[3]. Fo-

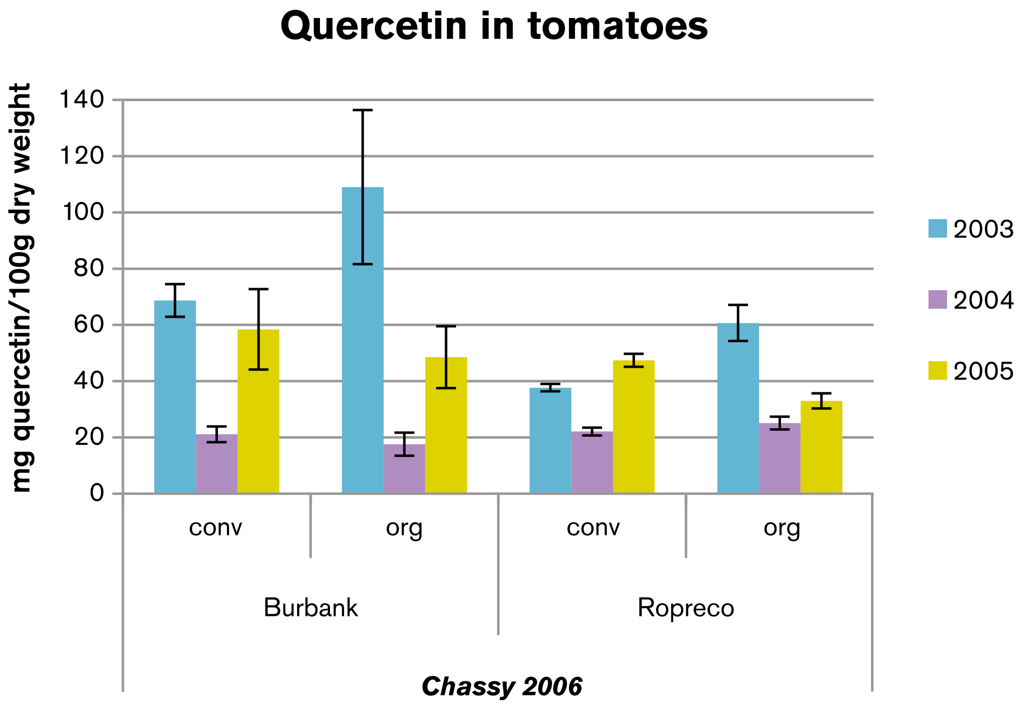

Figure 1. Quercetin concentrations in 2 tomato varieties in organic and conventional production from a 3-year study. Means ± standard deviation of 3 samples are displayed. This figure is based on data from Chassy 2006[22].

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cusing on a few compounds neglects the "matrix" they exist in, the fact that any fruit or vegetable is composed of maybe 10 000 small compounds, most of them probably with some interaction with the organism that eats it, and/or with other nutrients.

As an illustrative example, in a recent meta-analysis of 78 scientific studies of vitamins A, C, E, beta-carotene and selenium antioxidant supplements with in total 297 000 participants, beta-carotene and vitamin E supplementation seem to slightly increase the mortality rate (number of deaths per 1 000 individuals per year) compared to supplementation with a placebo, or no supplementation[1]. In contrast, there is strong evidence that a high consumption of fruits and vegetables has positive health effects including a lower mortality rate[2]. This is a quite drastic example of the fact that vitamins outside their natural matrix (i.e. our food) are not necessarily "good". In this example, people received comparatively high doses of isolated vitamins, and it is unlikely that vitamins in their natural concentrations in food would have such an effect. Yet, it is questionable whether the vitamin content of a fruit or vegetable alone is a good indicator of food quality, especially in a setting where vitamin deficiencies are generally rare (such as Western Europe).

In the absence of drastic differences, it is therefore questionable if differences in, for example, vitamin contents between products from different production systems can be directly translated into health claims. As a fruit or vegetable is composed of thousands of compounds, studies of actual health effects are to be preferred over studies of a few nutrients and an extrapolation to health effects.

Overall plant composition

Some scientists have measured the influence of the production system on the entire set of expressed genes, proteins, or metabolites, approaches known as "Omics" (transcriptomics, proteomics, metabolomics). Generally these studies have shown that the production system has some effect on the overall plant composition (e.g. [23–25]), but there is no easy way of judging whether, or how, the observed effects are of relevance for human nutrition.

For example, in one study, researchers measured approximately 1 600 metabolites (small plant compounds) in organic and conventional white cabbage samples from two years from a controlled field trial[26]. The production system left a measurable imprint in the cabbage composition that was retained between production years. This imprint was successfully used to predict the production system of samples from one year using data of samples from the other year. However, at present no knowledge about which production system yields the healthier crops can be directly gained from such measurements, because it is difficult to chemically identify so many compounds, and because nutritional science is far from understanding the interplay of so many compounds with the human body.

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Significance for adherence to dietary guidelines

In Sweden, the National Food Agency has adopted the Nordic Nutrition Recommendations[27] as guidance for the intake of various nutrients in the general population. Recommendations include suggested intakes for macronutrients (carbohydrates, fats, proteins) and a number of vitamins and minerals. Of the ten vitamins and nine minerals for which a recommended intake is specified in the Nordic Nutrition Recommendations, the recent review by Barański[19] presents comparisons of three vitamins (B1, C, E) and six minerals (Ca, Mg, Fe, Zn, Se, Cu) in organic and conventional foods. For vitamin B1, no differences were detected. For vitamin C, the content was as mentioned earlier higher in organic crops. Vitamin E, in contrast, was nine or 15 percent higher in conventional crops. Regarding the small potential systematic differences in nutrient composition, and the uncertainty in the meta-analyses ("overall reliability" for vitamin C and E is moderate), these potential differences do not clearly speak in favour of either organic or conventional crops, with respect to meeting dietary recommendations. For both magnesium (Mg) and zinc (Zn), a slightly (less than five percent) higher content in organic crops was found. Although a higher intake of these minerals is generally desirable, the authors argue that these differences are probably not important. For the other minerals, no differences were detected in the meta-analyses of this paper.

It is sometimes discussed that a higher intake of secondary metabolites (such as many antioxidants) in organic produce would increase the "effective intake" of fruit and vegetables, making it easier to meet or exceed the recommendation of eating five portions of fruit or vegetables per day with organic choices. This assumes that the content of secondary metabolites or antioxidants is responsible for the beneficial health effects of a high fruit and vegetable consumption.

However, as discussed above, there is still no general agreement that organic fruits and vegetables have systematically higher contents of such compounds. Also, the Nordic Nutrition Recom-

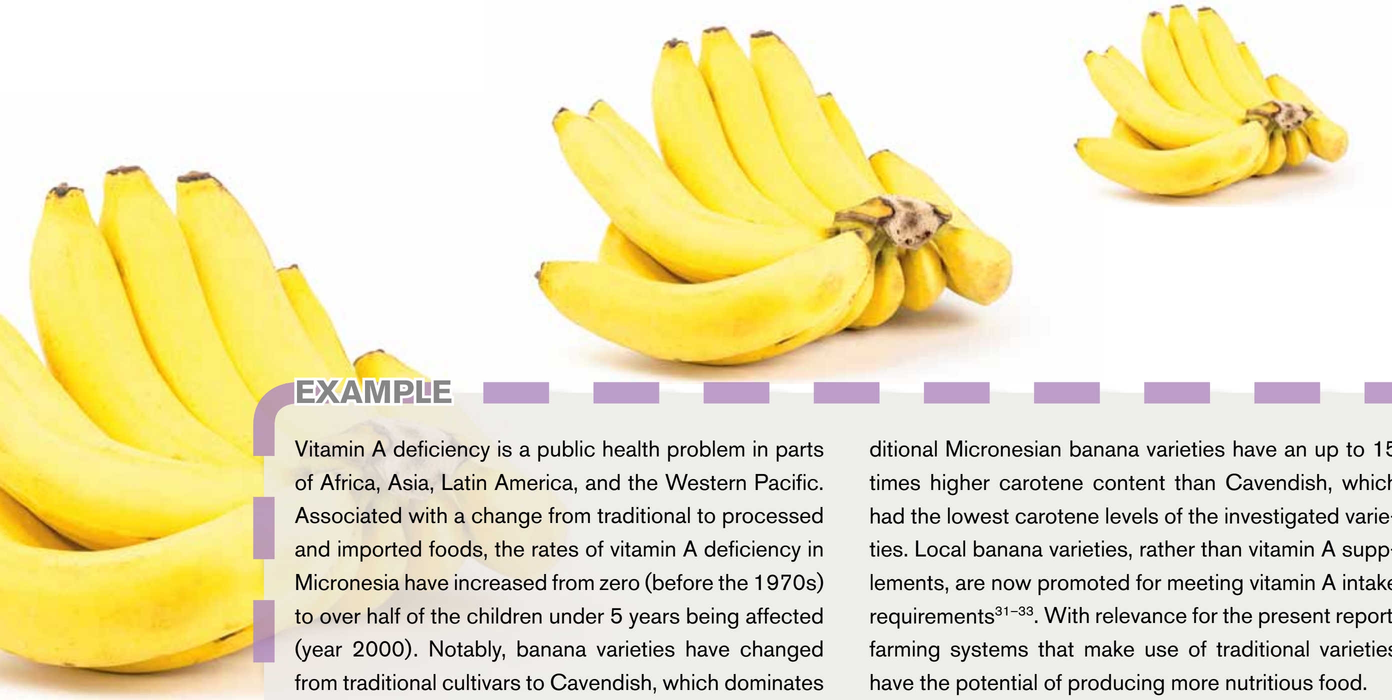
mendations conclude that, apart from the general advice on fruit and vegetable intake, at present no recommendations towards antioxidant-rich fruits and vegetables (e.g. some berries) can be made[27]. That is, according to present knowledge, health benefits come with fruit and vegetable consumption, and not specifically with antioxidant-rich fruit and vegetable consumption.

Trends of plant food composition

A large number of studies have been performed that compare the content of a range of nutrients in a range of crops under a range of conventional and organic management practices. Summarizing these findings, if conventional and organic crops differ in the content of specific nutrients, then these differences are small. Sometimes, the belief is expressed that organic fruits or vegetables are "full of healthy stuff", while conventional food is "empty". There is no scientific base for this belief. If large differences existed under present farming practices, they would have been found by now.

One aspect that has received little attention so far is the choice of crop varieties (with their individual characteristics with respect to disease resistance and yield, and their individual ability of taking up trace minerals, or forming some phytochemicals) in the different farming systems. There is substantial evidence that the development of high-yielding varieties during the past half century has had an impact on the mineral content of crops (e.g. 20–30 percent lower concentrations of zinc, iron, copper and magnesium in high-yielding semi-dwarf wheat varieties compared to old varieties in a 160 year experiment, irrespective of fertilizing regime[28]). Generally, a too strong focus on yield may lead to a breeding of less nutritive varieties[29, 30].

However, under current market conditions and facing a global population of 9 billion people in 2050, high crop yields are an important priority. One potential way of combining a high nutritive value and yield is the development of intercropping systems. Another potential way forward is the development of "nutritional yield" concepts[30] and their introduction in plant breeding. ■



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EXAMPLE

Vitamin A deficiency is a public health problem in parts of Africa, Asia, Latin America, and the Western Pacific. Associated with a change from traditional to processed and imported foods, the rates of vitamin A deficiency in Micronesia have increased from zero (before the 1970s) to over half of the children under 5 years being affected (year 2000). Notably, banana varieties have changed from traditional cultivars to Cavendish, which dominates the global banana trade. Research has shown that traditional Micronesian banana varieties have an up to 15 times higher carotene content than Cavendish, which had the lowest carotene levels of the investigated varieties. Local banana varieties, rather than vitamin A supplements, are now promoted for meeting vitamin A intake requirements[31–33]. With relevance for the present report, farming systems that make use of traditional varieties have the potential of producing more nutritious food.

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Composition of animal foods

Fatty acids in the diet

For the comparison of organic and conventional animal-derived foods, the fatty acid composition of fresh milk and dairy products is the best studied quality parameter. The fatty acid composition is a nutritionally important parameter of dietary fats. Fatty acids are often grouped into saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids. Each of these groups comprises a large number of individual fatty acids. PUFAs include omega-3 and omega-6 fatty acids.

The fatty acid composition is of relevance for various states of disease. As the probably most well-studied example, many Western diets have a relatively high share of SFA of total fat. Replacing SFA-rich foods by PUFA-rich foods has been shown to decrease the risk of cardiovascular diseases[34, 35]. The dietary fatty acid composition may also be of importance for other diseases, e.g. metabolic syndrome/type II diabetes, and development of the immune system, but a review of this matter is beyond the scope of this report. It should be noted that not all aspects of how the fatty acid composition of the diet affects human health are well understood. Also, fatty acids in the diet always come as mixtures.

Two fatty acids, linoleic acid (C18:2 omega-6, LA) and α-linolenic acid (C18:3 omega-3, ALA), are essential to humans, as all other omega-3 and omega-6 fatty acids can be formed by the human body from these two, while all SFAs as well as other unsaturated fatty acids can be formed from acetate by humans. LA and ALA are also the most abundant omega-6 and omega-3 fatty acids in the diet, respectively. The optimum intake is generally a matter of balance.

With relevance for this chapter, omega-3 fatty acids, especially the long-chain docosahexaenoic acid (DHA, C22:6 omega-3), play important roles in the body. DHA has for example an important role in brain development, and is an abundant constituent of the brain and of neurons. As LA and ALA compete for the same enzymes in forming longer and more highly unsaturated fatty acids, it is sometimes claimed that the LA:ALA ratio in the diet should not be too high. Sometimes, an optimal ratio of 2.3 is proposed, while the average diet in Sweden has a omega-6/omega-3 ratio of ca 3.4 (calculated from median intakes of omega-6 and omega-3 fatty acid intakes presented in[36]). In Sweden, there are no specific recommendations for the intake of long-chain omega-3 fatty acids (such as DHA), except for pregnant and lactating women (200 mg/day).

Fatty acids	**Recommended intake (energy-%)** (Nordic Nutrition recommendations[27])	**Actual intake (energy-%)** (Riksmaten 2010–11[36])	
		median	**5–95%**
Total fat	25-40	34	24.4–44.4
Saturated fatty acids	<10	12.9	8.2–18.4
cis-monounsaturated (MUFA)	10-25 *	12.6	8.7–17.4
cis-polyunsaturated (PUFA)	5-10 *	5.2	3.2–9.4
omega-3 fatty acids	>1	1.1	0.6–2.1
trans fatty acids (TFA)	As low as possible		

*Table 1. Current Swedish recommendations for fatty acid intake, as well as the actual intake in Swedish adults. As an additional recommendation trans fatty acids should be as low as possible *MUFA and PUFA together should make up at least 2/3 of total fatty acid intake.*

Importance of the feed for the fatty acid composition

Organic livestock husbandry requires that a large fraction of the feed should be locally produced. While soy, palm kernel cake, cereals, and maize silage are substantial feed fractions in many conventional livestock systems, they are less used ingredients in organic systems. On the other hand, grass-clover hay and other roughage make up a larger portion of the feed in organic than in conventional systems. There is a well-established link between the fatty acid composition of the feed, and the fatty acid composition in the product (milk, eggs, meat)[37]. Notably, soy, palm kernel cake, cereals and maize have a low content of omega-3, while grass and red clover are rich sources of omega-3 fatty acids.

Milk and dairy products

The composition of the feed determines to a large extent the fatty acid composition of the milk[38]. It is well established from studies in several countries and with a variety of study designs that the fatty acid composition is different in conventional compared to organic milk[39]. Organic milk consistently contains more omega-3 fatty acids than conventional milk, and the omega-6/omega-3 ratio is lower in organic milk. Also, many other fatty acids differ in their concentration between organic and conventional dairy products[39].

Over 400 different fatty acids have been detected in milk fat, but only about 15 occur in concentrations above one percent. Furthermore, in most studies only the major fatty acids are analysed. The focus here is on some major and potentially important differences between organic and conventional milk related to the occurrence of omega-3, ruminant and long-chain polyunsaturated fatty acids (see table 2).

Palupi and co-workers have summarized 13 individual studies from Europe and the USA[39] and found that, on average, there is a 64 percent higher content of omega-3 fatty acids in organic milk than in conventional milk. The ratio of omega-6/omega-3 fatty acids was 2.4 for organic and 4.3 for conventional milk. These numbers speak in favour of organic milk and dairy products.

For Sweden, it is sometimes stated in the public debate that the differences are less pronounced: Swedish cows, in contrast to cows in many other countries, have by law access to pasture during at least 2–4 months per year, depending on geographical latitude. The existing data only partly support such statements. For the outdoor season, two studies report the concentration of ALA, the most abundant omega-3 fatty acid in milk, and find 43 percent (central Sweden,[40]) and 67 percent (the region Scania in Southern Sweden,[41]) higher ALA in organic milk fat. For the indoor season, organic milk from south-eastern Sweden had 38 percent higher content of total omega-3 fatty acids compared to conventional milk[42], while organic milk from Scania (southern Sweden) had 87 percent higher ALA compared to conventional milk. Accordingly, differences in omega-3 content between organic and conventional milk in Scania appear to be in line with differences reported from other countries, while such differences are somewhat less pronounced, but still present, in milk from south-eastern and central Sweden.

A similar observation can be made regarding the omega-6/omega-3 ratio, where milk from Scania follows the international trend with a substantially higher ratio in conventional milk, while conventional indoor season milk from southeastern Sweden has a markedly low omega-6/omega-3 ratio but still higher than the organic milk. One explanation for these apparent regional differences is the fact that maize silage is a common feed component on conventional dairy farms in Scania, and in many other countries. In Sweden, maize is predominantly grown in Scania, and most of the crop is used for maize silage.

The season plays an important role in the fatty acid composition of milk. In both organic and conventional husbandry, the fraction of roughage is higher in summer than in winter, leading to a lower omega-6/omega-3 ratio in summer. The difference between the production systems is consistent in both summer and winter[39].

It is also established that organic milk has a higher content of conjugated linoleic acid (C18:2 cis-9 trans-11, CLA) and vaccenic acid (C18:1 trans-11, VA), compared to conventional milk. These fatty acids are collectively named ruminant fatty acids (see table 2 and [39]). According to the Nordic Nutrition Recommendations, the intake of trans-fatty acids should be as low as possible. However, negative effects are most often attributed to industrial trans-fatty acids, while there is some evidence that ruminant trans-fatty acids have a favourable effect on human health. At this point this is not conclusive[43]. Furthermore, the long-chain omega-3 trans-fatty acids EPA and DPA are consistently found in higher concentrations in organic milk (see table 2).

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study	**Palupi**		**Larsen**		**Fall**		**Von**		**Von**		**Benbrook**	
region	Europe + USA		Central Sweden (Dalarna, Gästrikland, and Hälsingland)		Southeastern Sweden (Uppland, Sörmland, Östergötland, and Småland)		Southern Sweden (Skåne)		Southern Sweden (Skåne)		USA	
sampling year	2008–2011		2004/2005		2005/2006		2008		2008		2011/2012	
season	indoor + outdoor		indoor + outdoor		indoor		indoor		outdoor		whole year	
number of farms					37		59		59			
	org	conv	org	conv	org	conv	org	conv	org	conv	org	conv
ALA	7.61	4.79	7.6	5.3	8.5	4.7	8.5	5.1	9.7	5.2	8.21	5.12
LA	21.6	27.26			24.9	19.9	17	18.3	17.1	16.8	20.6	27.6
CLA	8.38	6.59			6.3	4.8	6.4	5.9	9.7	5.8	7.31	6.18
EPA	0.64	0.37			0.79	0.59					1.06	0.81
DPA	1.04	0.66			0.96	0.77					1.42	1.19
total SFA	676	668			687	686	686	694	663	698	681	658
total MUFA	259	270			264	272	232	227	235	222	239	258
Total omega-3	9.2	5.61			14.4	10.4					10.3	6.38
total PUFA	45.39	43.89			41.9	32.2					33.4	36.9
omega-6/ omega-3	2.4	4.3			1.87	2.23	2.22	3.75	1.9	3.45	2.28	5.77

References for table: Palupi[39], Larsen[40], Fall[42] including unpublished data, Von[41], Benbrook[44]

Table 2. Fatty acid (FA) composition in milk and dairy products in several studies, expressed as g FA/kg total FA. The values are mean or median values, as reported by the studies. Studies may have different definitions of which FAs are added to groups such as total SFA, MUFA, PUFA, and total omega-3. (Palupi (2012) is a meta-analysis of 13 individual studies)

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Meat

Much less research has been done comparing the fatty acid composition of meat, and available studies are generally of highly varying design, and several of the studies are small. Also, meat is more difficult to sample at the farm level than milk. Apparently, as in the case of milk, the availability of clover-grass roughage, both as harvested feed and by grazing, leads to a higher omega-3 content of e.g. organic grass-fed beef[45]. By regulation and in practice, in Europe, organic cattle (and other animals) spend more time grazing than conventional cattle.

For example, in one study, sows grazed ca 2–2.5 kg clover and grass per day, corresponding to ca 50 percent of their energy intake[46]. Depending on the specific rules of certification, organic sows have access to pasture or grass-clover silage, while sows in conventional production are generally fed cereal-based concentrate feed.

In direct parallel to milk, and bearing in mind the known[37] importance of the feed fatty acid composition for the meat fatty acid composition, organic meat has the potential of having a more preferable fatty acid composition than conventional meat, e.g. higher omega-3 content and a lower omega-6/omega-3 ratio. Indeed, several studies on beef[47], pork[48], lamb[49], chicken[50, 51], rabbit[52] have shown such trends, although some exception exist[53, 54].

To date, however, no formal meta-analysis of these and other studies has been performed, and the high variability in study designs and feeding regimes in the studies comparing organic and conventional meat composition hampers definite conclusions. However, it is likely that findings on the difference between organic and conventional milk composition are paralleled by similar differences in meat, because a high intake of fresh forage and roughage, with a known beneficial effect on meat fatty acid composition, is guaranteed in most organic systems.

Eggs

Few studies on the fatty acid composition of organic and conventional eggs have been published. One study reports higher omega-3 fatty acid con-

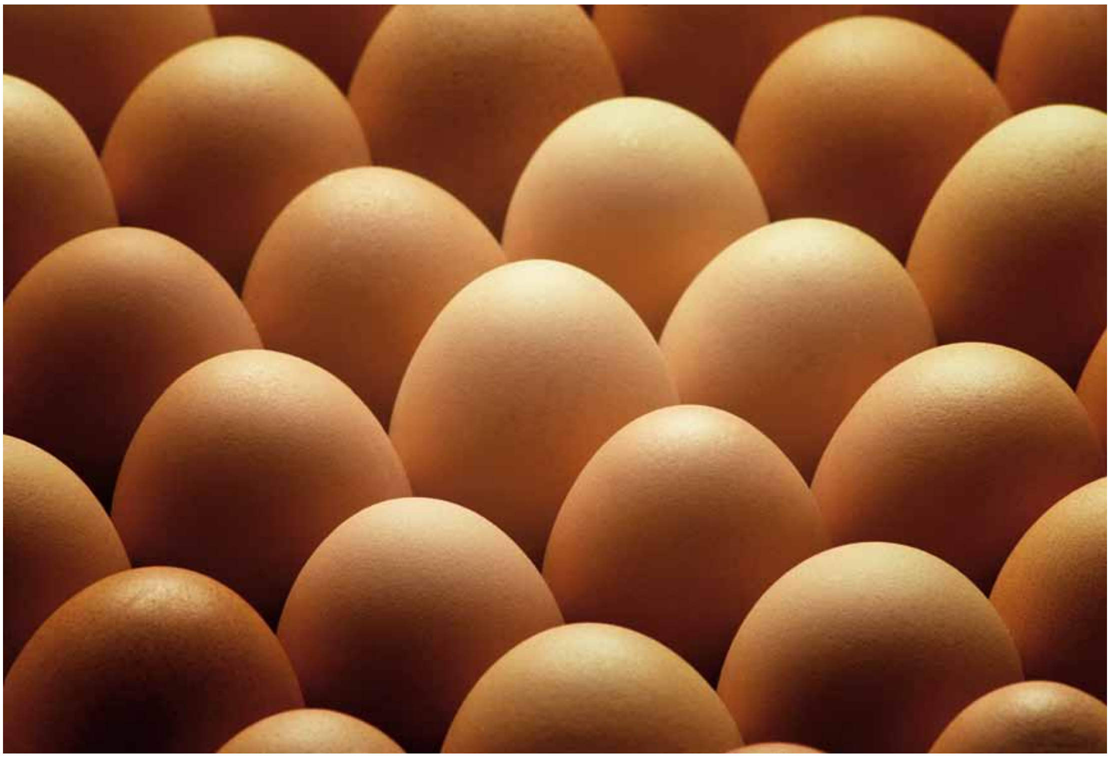


PHOTO: ISTOCKPHOTO © BALEFIRE9

tent and a lower omega-6/omega-3 ratio in organic eggs, especially when pasture was widely available[55]. Hens were kept indoors in a standard housing system ("control"), with access to 4 m^2 of pasture per hen ("organic"), in line with current requirements for organic laying hens, or with access to 10 m^2 of pasture ("organic plus").

For example, the annual average of DHA was 88 mg/100g egg yolk for control chicken, 110 mg/100g for organic chicken, and 321 mg/100g for "organic plus" chicken. This underlines the importance of hens having access to grass pasture for egg fatty acid quality. In the EU, laying hens and broilers in organic production have access to at least 4 m^2 of pasture per animal by regulation, while conventional laying hens typically do not have access to pasture.

Other qualities

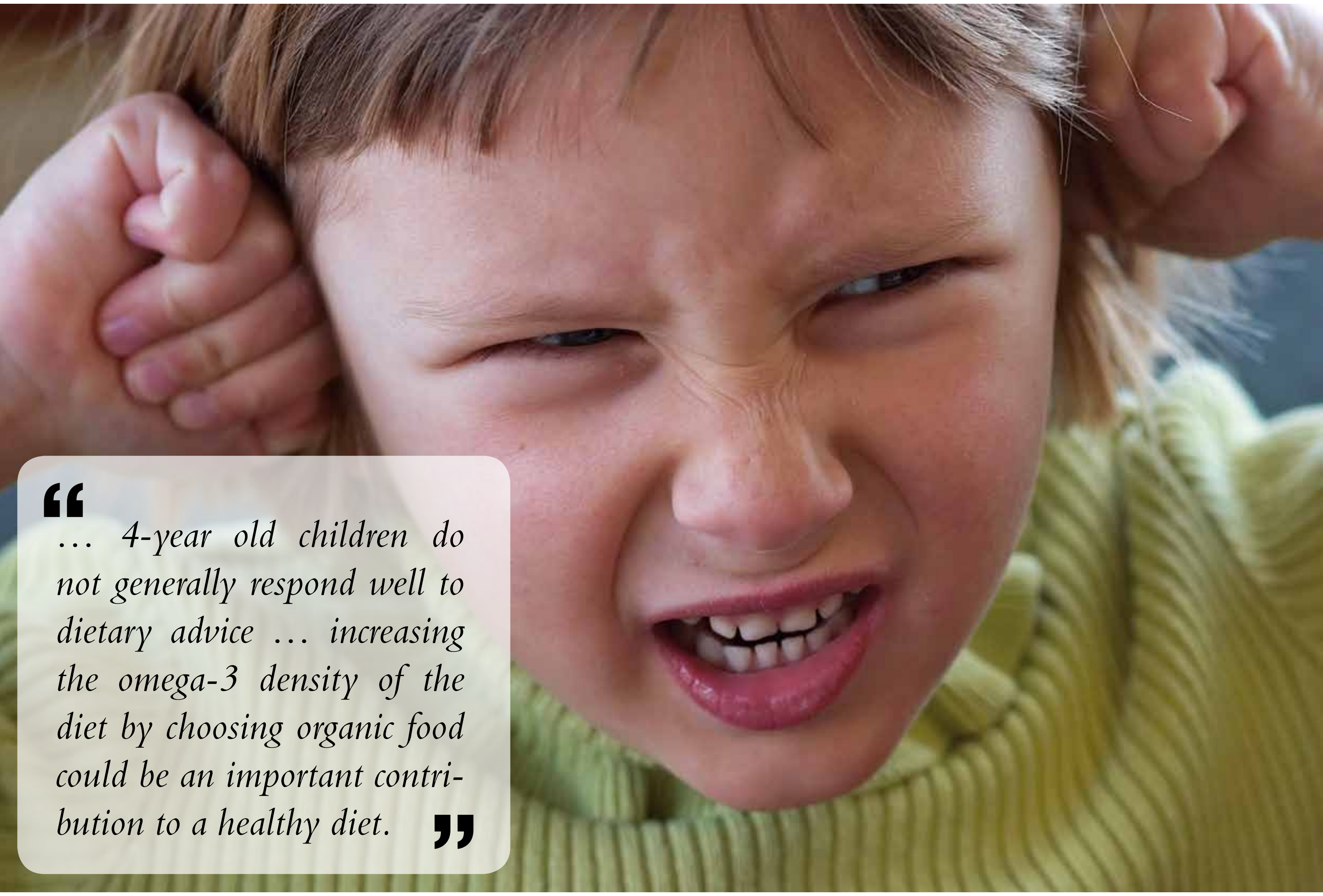
The fatty acid composition is of course not the only quality trait of milk, dairy products, meat, and eggs. The focus is here put on the fatty acid composition because they constitute an important and well-researched group of nutrients. There are indications that other beneficial feed components can end up in the food, and can therefore be modulated by the agricultural system. For example, a high access to pasture for laying hens appears to cause a high content of flavonoids in eggs[55].

Significance for health

Little research on health effects of a differential dietary fatty acid composition as a consequence of organic vs. conventional food preferences has been performed. In the Dutch KOALA cohort study mentioned earlier (page 9), it has been shown that the breast milk of lactating women with a strong preference for organic meat and dairy products had a similar omega-3 fatty content but a 36 percent higher CLA and a 23 percent higher vaccenic acid (VA) content, compared to women preferring conventional food[56]. In the KOALA study, it has also been shown that a high content of ruminant fatty acids (CLA + VA) and long-chain omega-3 fatty acids (EPA + DPA + DHA) were associated with lower incidences of parent-reported eczema until two years of age, atopic dermatitis at two years of age, and allergic sensitisation in the children at one year of age but not at 2 years[57]. This suggests a mild allergy-protective effect of some fatty acids that are present in higher concentrations in organic animal-derived products than in conventional products.

There is a lively ongoing scientific debate on the importance and effect of various dietary fatty acids on human health. Nonetheless, from a fatty acid perspective, most nutritionists would probably prefer organic milk over conventional milk due to the higher content of very-long-chain PUFA in organic milk, due to the higher content of long-chain omega-3 fatty acids, or due the lower omega-6/omega-3 ratio in organic milk.

It should be kept in mind that animal-derived foods are not the only source of fat for humans. The choice of what plant oil to use in cooking, or if butter or plant-based margarine are used as bread spreads, will generally outweigh the choice of conventional or organic animal products for the overall fatty acid composition of a diet. On the other hand, fat from animal sources (excluding fish) accounts for approximately 40 percent of the total fat intake in the Swedish adult population[36]. Accordingly, changes in the fatty acid composition in our food from animal origin will have an effect on our overall fatty acid intake.



> *“… 4-year old children do not generally respond well to dietary advice … increasing the omega-3 density of the diet by choosing organic food could be an important contribution to a healthy diet.”*

PHOTO: ISTOCKPHOTO © IZANOZA

Significance for adherence to dietary guidelines

According to a Swedish dietary survey[36], approximately 40–45 percent of the adult population has a dietary intake of total omega-3 fatty acids (ALA, EPA, DHA, DPA) below the recommended one energy-percent (E-%) (see table 1); the median intake of DHA is 0.4 g/day.

For children, the median omega-3 fatty acid intake was 0.6 E-% for children aged 4, 8 and 11 years, with a median DHA intake of 60, 80 and 70 mg/day for these age groups[58]. Over 90 percent of the children had a lower than recommended intake of omega-3 fatty acids.

There are several dietary changes available to achieve the recommended omega-3 fatty acid intake, namely an increased consumption of fatty fish or certain plant oils. However, for young children, some dietary changes (e.g. fatty fish) may not be viable, because 4-year old children do not generally respond well to dietary advice. In such cases, increasing the omega-3 density of the diet by choosing organic food could be an important contribution to a healthy diet.

The intake of PUFA from milk and dairy products (including butter and cheese) amounts to about eight percent of the total PUFA intake in the Swedish adult population. The intake of PUFA from eggs and meat make up another 19 percent of total PUFA intake. This amounts to five percent (from milk) and twelve percent (eggs and meat) of omega-3 intake[36, 59].

To our knowledge, no one has so far calculated how many people would meet the recommended intake of omega-3 fatty acids if all intake was from conventional vs. organic production, although data from extensive surveys such as Riksmaten[36] would relatively easily allow for such estimates. Assuming an approximately 50 percent higher omega-3 fatty acid content in organic milk fat and a five percent contribution by milk fat to the total omega-3 fatty acid intake of the Swedish population, a rough estimate is that on average an individual would increase the omega-3 fatty acid intake by 2.5 percent by switching from conventional to organic milk and dairy products. This is a small but conclusive difference (in contrast to e.g. differences in vitamin C intake due to organic and conventional fruit and vegetables).


PHOTO: ISTOCKPHOTO © ANNELEVEN

Should future work confirm that even organic eggs and meat have a similar advantage over their conventional counterparts with respect to omega-3 content, then this difference may be relevant for meeting the recommendation for omega-3 fatty acid intake for a substantial part of the population, most notably children.

For 4-year-old children, dairy products (including butter) account for about six percent of the PUFA intake, and meat and eggs for 21 percent[58, 60], similar to adults.

In summary, a higher omega-3 content in organic dairy products leads to a higher intake for a consumer who prefers organic over conventional dairy products. The increase is small (about 2.5 percent on average) but definitive and desirable, because a substantial fraction of the population does not reach the recommended omega-3 intake. The increase may also be larger and more important for population groups with a high intake of animal-derived fats. ■

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Pesticide regulation

Basics of regulation in the EU

In the European Union and other countries, extensive risk assessment is performed before pesticides for agricultural use are approved. The process of approval is very complex, and only a rough overview with a focus on the EU is given here. Companies that seek approval for a new pesticide compound ("active substance") have to perform a substantial amount of studies, investigating potential adverse effects for humans (using *in vitro* and animal studies) and the environment. Based on these data, one national regulatory authority carries out a risk assessment on behalf of the European Food Safety Authority (EFSA). This risk assessment is then reviewed by the other EU member states' national authorities. Finally, EFSA issues a "Conclusion on the peer review of the pesticide risk assessment", on which the European Commission bases its decision of approval or non-approval ("Review report").

This process is regulated in EU regulation 1107/2009[61]. The stated purpose of this regulation is "… to ensure a high level of protection of both human and animal health and the environment and to improve the functioning of the internal market through the harmonisation of the rules on the placing on the market of plant protection products, while improving agricultural production."

Safe levels of exposure

It is the company seeking approval that has to provide the EU with data of the toxicology and ecotoxicology of the active substance. For example, companies have to present studies regarding acute toxicity, genotoxicity, carcinogenicity, reproductive toxicology, delayed neurotoxicity in mammals (often rats) and/or in cell assays, data on the behaviour and degradation of the active substance in the environment. Effects on bees, earthworms, and fish have to be assessed, along with many other aspects of toxicology and environmental fate. The current data requirements are detailed in EU regulation 283/2013[62]. Commonly, safe levels of exposure (no observed adverse effect level – NOAEL) measured in animal studies are translated into safe levels for humans by the application of a safety factor (often a factor of 100) to account for variation in susceptibility between species and between individuals. The active substance will be approved when it is established by the risk assessment that its use does not cause harm to human or animal health or to groundwater, and it does not pose unacceptable risks for the environment.

Furthermore, the substance should be effective for its purpose, and not cause unnecessary suffering on vertebrates to be controlled, and not cause unacceptable effects on plants. An active substance may have toxic properties but will still be approved if its proper use does not lead to an exposure (via exposure at work or via residues in food) that poses a risk. An exception are the cut-off criteria for mutagenic, carcinogenic, and endocrine disrupting properties and reproductive toxicity, detailed in Annex II of EU regulation 1107/2009[61]. Active substances which with high confidence have such properties cannot be approved (with some exceptions).

This extensive risk assessment is justified by the facts that pesticides comprise the only group of commercially available chemicals that are designed to kill organisms, and that they are sprayed outdoors implying a risk of spreading into the environment. There are also risks for effects on non-target organisms in the agricultural landscape.*

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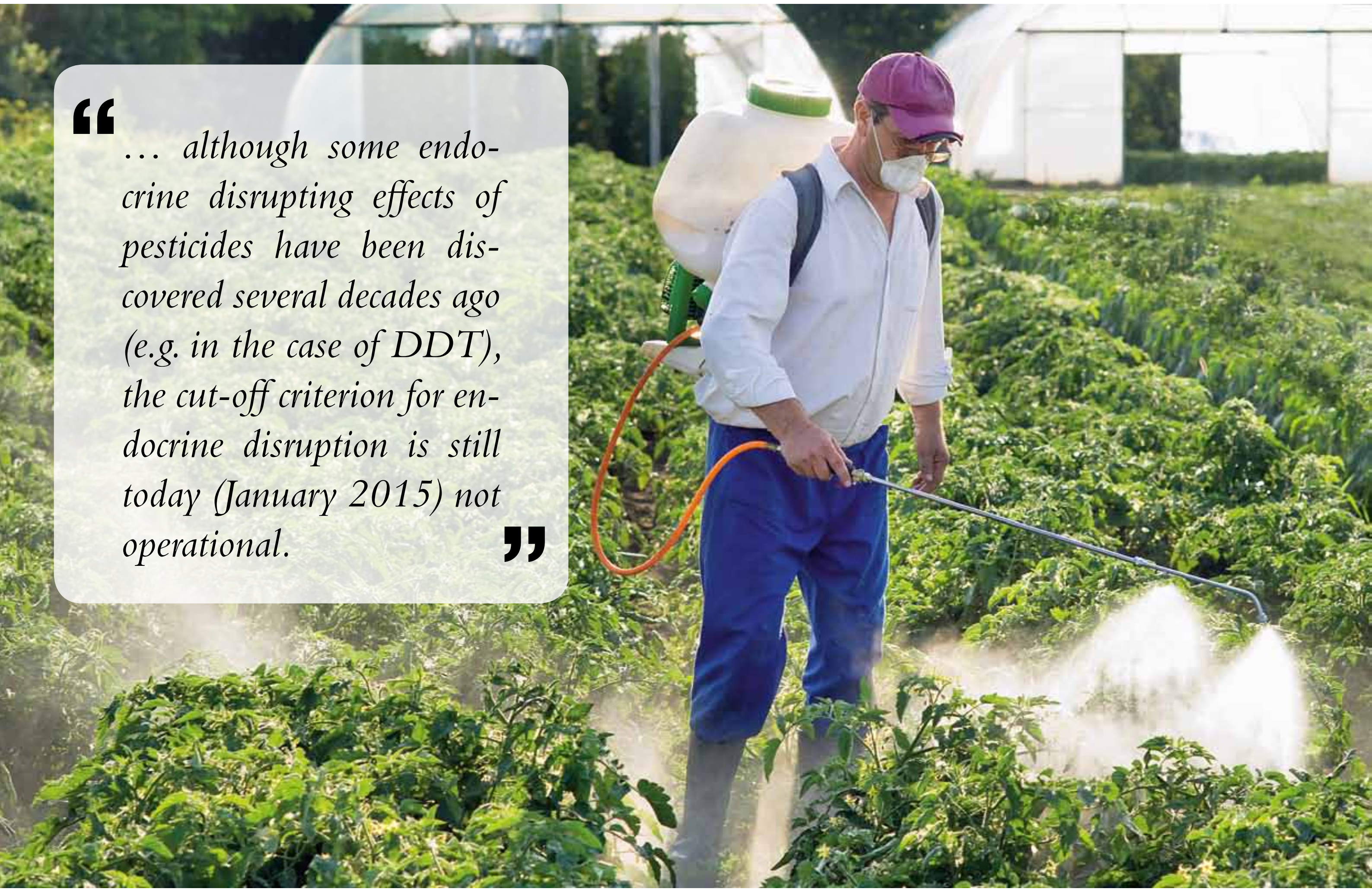
* A stronger risk evaluation, however only for effects on human health and not for environmental effects, is only required for pharmaceutical drugs, which are designed to interfere with the body's functions and intended to be ingested.

PHOTO: ISTOCKPHOTO © FOTOKOSTIC



> “… *although some endocrine disrupting effects of pesticides have been discovered several decades ago (e.g. in the case of DDT), the cut-off criterion for endocrine disruption is still today (January 2015) not operational.*”

One result of the pesticide risk assessment is the establishment of an Acceptable Daily Intake (ADI, an amount of pesticide which may be ingested every day without estimated risks to human health) and an Acute Reference Dose (ARfD, an amount of pesticide which should not be exceeded at a single occasion).

In case of approval of the active substance by the EU Commission, the actual pesticide product (containing the active substance and other ingredients) has then to be assessed according to specific harmonized criteria in each EU member state where the company wants to market its product before it can be authorized for use. Approvals are normally valid for 10 years.

Gaps in risk assessment

One inherent weakness of this kind of risk assessment is that only those risks can be found that manifest themselves in the standardized tests, which are often years behind the development of science. For example, although some endocrine disrupting effects of pesticides have been discovered several decades ago (e.g. in the case of DDT), the cut-off criterion for endocrine disruption is still today (January 2015) not operational, because so far no scientific criteria and no technical guidelines are specified by the EU, that describe suitable tests for endocrine disruption. Some adverse endocrine effects could be discovered in certain studies, e.g. when studying the litter size of exposed and unexposed rats. But many more subtle effects of pesticides on the hormone system, which along with the neural system form the body's "communication system", may go undetected by today's risk assessment. The EU commission should have presented scientific criteria for the determination of endocrine disrupting properties by December 2013, but has not yet done so. The Swedish government has recently announced that it will take legal action against the European Commission on a similar issue: the same criteria for endocrine disruption are also missing for biocides, which is a group of pesticides for other than agricultural use, falling under different legislation.

Criteria for endocrine disruption are now expected to be specified in 2015 or 2016. Depending on the actual form of the final criteria (i.e. if such criteria can be tested using existing test guidelines), these may or may not be directly implemented. In any case, accepted test methods exist for effects mediated by the estrogen and androgen receptors, thyroid hormones, and for interference with steroidogenesis (i.e. the formation of steroids from cholesterol), but not for the other about 50 hormone systems in the human body[63]. For example, potential effects of pesticides on the corticosteroid system, with relevance for the development of diabetes, are unlikely to be detected in the risk assessment even when the endocrine effects are finally part of the assessment. It will take years or decades to develop tests for all human hormone systems.

> "*… effects on the hormone system are not part of the process of approval of pesticides in the EU.*"

The hormone system is sensitive

One reason why the EU commission has established a cut-off criterion for endocrine effects is the fact that dose-response relationships for hormones may be non-monotonous. For most other toxic effects, typically higher doses result in stronger effects, and in consequence, if one specific dose is shown to be safe, then all lower doses are also safe. For hormones, this is not necessarily true: in some cases, lower doses may produce effects that cannot be predicted from effects at higher doses, and dose-response curves may have all kinds of peculiar shapes[64]. In some cases of critical windows of exposure, the timing of exposure, rather than the dose, may be critical. Furthermore, in *in vitro*[*] studies, cases have been observed where the concentration of an endocrine disrupting compound was more than 100 times lower in human than in mouse and rat testis cells; in some other cases, endocrine effects found in mouse or rat cells were entirely absent in human testis cells. These inter-species variations are larger than in typical toxicological models, and raise concern about the use of animal models for estimating endocrine effects on humans[65].

As an illustrative example, one research group screened *in vitro* 37 pesticides that are commonly found as residues in food for their anti-androgenic potential, i.e. their potential to interfere with certain sex hormones[66]. Of those compounds 14 have previously been known to show anti-androgenic behaviour, which was confirmed in this study. Of nine further compounds, such an effect was demonstrated where previously unknown. Further seven compounds showed an androgenic effect (i.e. an "opposite" effect). It should be noted that this work addressed only one of approximately 50 hormone systems in humans.

Human fertility may be affected

The example illustrates that a number of the widely used pesticides may exhibit an effect on the endocrine system. This is possible because effects on the hormone system are not part of the process of approval of pesticides in the EU, as mentioned earlier. It is impossible today to judge whether the population's exposure to such pesticides via food represents an actual health risk or not, for example, the extent to which pesticides are responsible for observed declines in human fertility.

Also, even for tests accepted by the OECD (Organisation for Economic Co-operation and De-

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[*] Laboratory studies on simplified biological systems, for example on cells in a cell culture medium.

velopment), there is not always agreement among scientists that such tests accurately identify risks. For example, in an evaluation of a guideline for developmental neurotoxicity[67] (i.e. effects of chemicals on the development of the offspring's neural system during pregnancy or childhood), 16 studies of five evaluated chemicals have been summarized[68]. Of these, five studies were performed according to the OECD guideline TG 426, all but one found no sign of developmental neurotoxicity. In contrast, of the eleven studies not performed according to the guideline, all found evidence of developmental neurotoxicity. A more recent and extensive survey of studies investigating the potential developmental neurotoxicity of the compound Bisphenol A (BPA) suggests that studies performed according to guideline TG 426 may overlook sensitive effects of BPA, especially in female offspring. Especially anxiety-related, social and sexual behaviours, which are not tested according to TG 426, were found to be affected by BPA exposure during development[69]. One example of potential developmental neurotoxicity (chlorpyrifos) is discussed in some detail below, in section "In-depth example: Developmental neurotoxic effects of chlorpyrifos".

Cumulative effects

Another weakness is that (with few exceptions for chemically closely related compounds) the current risk assessment considers only one pesticide at a time, in spite of the obvious fact that we all are constantly exposed to a large number of pesticides simultaneously via our food. The reasons are (1) methodological difficulties in estimating the effects of exposure to multiple compounds, and (2) companies have the right to have their product assessed on its own merits, i.e. independent of which products their competitors sell.

Effects of several pesticides may add up to adverse effects. In animal studies, cases are known where mixtures of pesticide cause adverse effects at dose levels where the individual pesticides show no effect[70, 71] (so-called cumulative effects).

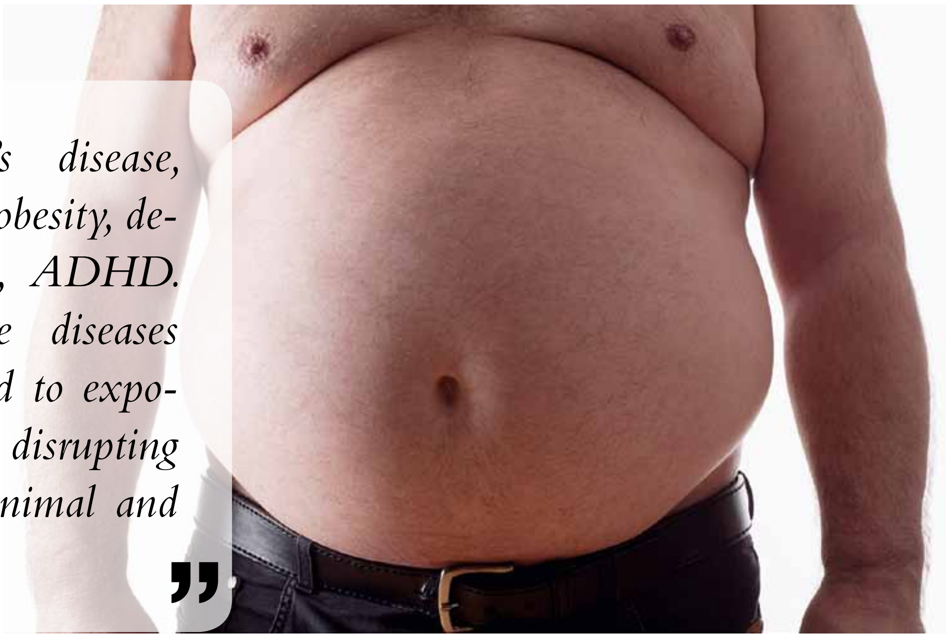
Independent science is disregarded

One weak point of the regulatory process of pesticide approval is the fact that independent science has a low impact on this process. Since Regulation 1107/2009[61] came into effect, independent science must be considered in the process of pesticide approval. However, an EFSA guidance document[72] effectively assigns independent studies a low impact, and in consequence, independent science is generally disregarded[73]. For example, of the hundreds of epidemiological studies of pesticide effects exposure on human health (discussed in chapter "Public health effects of low-level pesticide exposure" below), to our knowledge not a single one has been considered valid when setting toxicological reference values in EFSAs risk assessment in the approval process of pesticides.

Of course, epidemiological studies are not generally designed for the purpose of regulatory risk assessment. For example, epidemiological studies generally cover "real-life" situations with a co-exposure to various pesticides and other chemicals, and may assess exposure to single compounds, groups of pesticides, or overall pesticide exposure. In contrast, in regulatory risk assessment, all animal studies are performed using the individual compound, without consideration of mixed exposures. Nonetheless, the fact that no epidemiological study is regarded relevant for the regulatory risk assessment might indicate that systematic barriers exist against the inclusion of such studies, and puts focus on the question whether current regulatory risk assessment indeed uses all available knowledge. It should be mentioned that the approval process is intended not only to protect the environment and consumers from negative pesticide effects, but also farm workers. In many epidemiological studies, effects on farm workers are addressed. One example of what this can mean in practice is discussed in detail below, in section "In-depth example: Developmental neurotoxic effects of chlorpyrifos".

Another issue is that the studies submitted by the industry to EFSA are generally "protected" (not available for the public or for researchers).

Also, for some of the chronic diseases that have increased during recent decades in many countries, the mechanisms of disease onset are still unknown. This applies for example to allergies, Alzheimer's disease, type 2 diabetes, obesity, decreasing fertility, ADHD. Many of these diseases have been linked to expo-



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> *“… Alzheimer’s disease, type 2 diabetes, obesity, decreasing fertility, ADHD. Many of these diseases have been linked to exposure to endocrine disrupting compounds in animal and human studies.”*

sure to endocrine disrupting compounds in animal and human studies[74]. Lacking knowledge of the biochemical and physiological mechanisms, it is in some cases difficult or impossible to develop adequate tests that demonstrate the safety of active substances.

Furthermore, all toxicological risk assessment is based on extrapolations (with safety margins) from animal studies, and there is normally no direct knowledge of effects in humans. Direct toxicological tests in humans would be unethical. However, the structured collection of reported adverse effects after market release (e.g. from farmers) and the conducting of epidemiological studies (in farmers and consumers) are examples of viable approaches to measuring some potential “real-life” adverse effects in humans. Today, no such effort of validating the findings of the risk assessment after market release is done or required by the regulatory authorities.

There is substantially more focus on the active substance than on its metabolites in the safety assessment of pesticides. For example, the approval of the fungicide carbendazim has expired in the EU (in november 2014) without a chance of re-approval, because carbendazim is now classified in mutagenicity category 1B (“Substances to be regarded as if they induce heritable mutations in the germ cells of humans”), and therefore the cut-off criterion for mutagenicity (see section “Basics of regulation in the EU” above) applies.

The fungicide thiophanate-methyl forms carbendazim as a metabolite both in the field and after ingestion by mammals. The cut-off criterion for mutagenicity does, however, not directly apply for thiophanate-methyl, as it only applies for active substances, safeners, and synergists, but not for metabolites.

Another issue is that the EU member states have the possibility of temporarily authorizing the marketing of banned pesticides. This possibility was originally intended as an emergency response (to tackle dangers (e.g. outbreaks of plant diseases and insects) that could not be dealt with by other reasonable means), but has been used frequently. For example, in 2011, 230 such “derogations” were issued by the EU member states[75].

Pesticides in organic agriculture

Pesticides approved for organic agriculture in the EU are specified in Annex II of Regulation 889/2008[76], and the most recent update of this list can be found in Regulation 354/2014[77]. As a general principle, synthetic substances are not approved but natural substances (e.g. extracts from plants or microorganisms) can be approved. Pesticides approved in organic farming are evaluated according to the same EU regulations as described above for other pesticides.

In many cases, pesticides that are allowed in organic production are less effective than synthetic alternatives, potentially meaning that a higher number of "organic" pesticide applications are necessary in order to achieve the same effect as a "conventional" pesticide. However, fuelled by the non-availability of effective pesticides, organic agriculture has developed and is further developing preventive approaches to pest and weed control, such as crop rotations, mechanical weed control, the use of disease-resistant varieties, supporting natural enemies to pests, push-pull management, and others.

In Sweden, currently nine active substances are approved in organic agriculture (i.e. they are specified in Annex II of Regulation 889/2008[76] and at least one product containing that substances is approved for use in Sweden by the Swedish Chemicals Agency). Three of these may only be used in insect traps. The remaining six substances are pyrethrins, spinosad, rapeseed oil, iron (III), sulphur, and paraffin oil. Of these, only pyrethrins and spinosad are of toxicological relevance; EFSA has not assigned ADI or ARfD values to rapeseed oil, sulphur, and paraffin oil due to low toxicity. Iron is an essential metal to humans but has a long-term toxicity at higher amounts.

Furthermore, pheromones and pyrethroids (only deltamethrin or lambda-cyhalothrin) may be used in insect traps, with very little risk of spreading into the environment.

Probably the substance of highest concern among pesticides approved for organic agriculture in the EU is the pyrethrins, a mixture of insecticidal substances naturally occurring in the flower *Chrysanthemum cinerariifolium*. The pyrethrins share the same mechanism of neurotoxicity as their synthetic analogues, the pyrethroids. Generally, the synthetic pyrethroids are designed to be more stable than their naturally occurring analogues, meaning that fewer applications are necessary. On the other hand, a higher stability implies a higher risk for residues being present on the product in the shop, and the limited effectiveness of pyrethrins might limit their use. Pyrethrins are only rarely found as residues on food. For a risk assessment of actual spinosad and pyrethrins exposure, see section "Residues of pesticides approved for organic agriculture" below.

The substance rotenone, another substance of concern due to its neurotoxic effects, has earlier been approved in organic agriculture as an extract of certain plants. Rotenone has recently been removed from the list of pesticides approved for organic agriculture in the EU. ■

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Pesticide exposure

Pesticide residues

In Europe, an EU-coordinated pesticide residue monitoring programme and national control programmes coexist. EFSA coordinates a control programme with 33 food items, alternating over three years. The aim is to provide representative residue data for the 33 most common foods in Europe. For the latest available year (2012), aubergines, bananas, broccoli or cauliflower, peas (without pods), peppers (sweet), table grapes, wheat, olive oil and orange juice were tested for the presence of 188 pesticides; chicken eggs and butter were tested for 43 pesticides.

In this programme, each EU member state has to take a specified number of samples (depending on the size of the population) for each of these food items. A total of 10 235 samples were analysed. 0.9 percent of the samples exceeded the maximum residue limit (MRL) for at least one pesticide, 39.2 percent had measurable pesticide residues but below the MRL, and 59.9 percent of the samples had no residues or residues below the limit of quantification. Among unprocessed plant food items, Broccoli (2.8 percent) and cauliflower (2.2 percent) most often exceeded the MRL, while peas (without pods) (0.13 percent) and bananas and wheat (both 0.7 percent) exceeded the MRL in the least number of cases. Although samples from organic production are taken, their number is small, and these samples are not presented separately in the EU coordinated sampling program, so a systematic comparison of residues on organic and conventional products is not possible[78].

EFSA also collects and assembles data from national control programmes. These are designed by the individual countries and consist of surveillance and enforcement sampling. Surveillance samples are usually taken as random samples, although sometimes food items with a history of exceeding the MRL are oversampled. Enforcement samples are taken from specific suppliers as a follow-up of earlier exceeding of MRL, or other specific reasons. In 2012, 78 390 surveillance and enforcement samples were taken in national programmes in the EU, of which 4 576 were samples of organic food items. Over 800 pesticides and pesticide metabolites were analysed, although not all compounds were analysed in all samples; the average sample was analysed for 203 different pesticides.

Among all conventional surveillance and enforcement samples, 3.1 percent exceeded the MRL, and 53.1 percent were free of detectable pesticide residues. Among all organic samples, 0.8 percent exceeded the MRL, and 85.1 percent were free of detectable pesticide residues. The direct comparison is not without problems, though: the sampling is not systematic, i.e. countries use their own criteria in designing the sampling, and the different foods are not necessarily represented in the same proportions among conventional and organic samples. Also, some commonly found residues are likely related to naturally occurring plant compounds (e.g. bromide ion which is used as a measure of methyl bromide contamination, but which is also present naturally).

It is important to note here that a specific pesticide typically has different MRLs for different commodities. Primarily, the MRL reflects an upper limit of residues to be expected in crops when Good Agricultural Practice (GAP) is followed; that is, pesticides are applied in approved amounts and frequencies on crops that they are approved for, also taking pre-harvest intervals into account. The MRL for a specific pesticide on a specific crop is typically very low if there is no "authorised use", i.e. no approved use of that pesticide on that crop. Therefore, an exceeded MRL is primarily an indi-

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cation of not following GAP, rather than an indication of health risk from consuming a specific food. For "authorised uses", the toxicity is also reflected in the MRL because the GAP is defined with the toxicity of the pesticide in mind, e.g. when defining suitable pre-harvest intervals.

Pesticide residues in Swedish products

For Sweden, a comparison of organic and conventional products grown in Sweden (but not matched by commodity) (table 3) shows that foods from organic production only rarely contain pesticide residues, in contrast to samples from integrated and conventional production. Limitations of these comparisons include the low number of samples from organic production, the fact that it is unclear as to how far samples from organic and conventional production have been matched by commodity, and the fact that the choice of samples is not representative for the consumption in the Swedish monitoring program because commodities with a history of MRL exceedances are oversampled. It is therefore difficult to specify in detail how many more pesticide residues can be found in conventional compared to organic foods.

	Total number of samples 2008–2010	without residues	residues ≤ MRL	residues > MRL
Organic	25	96 %	4 %	0 %
Integrated production	310	49 %	50 %	1.3 %
Conventional	642	69 %	31 %	0.2 %

Table 3. Pesticide residues in fruit and vegetables from organic, integrated (IP), and conventional production. Data compiled from the Swedish Food Agency's data for 2008–2010 for samples grown in Sweden[80].

Fraudulent use of pesticides in organic agriculture, spray drift from conventional to organic farms, persistent pesticides from earlier conventional agriculture, fraud with labelling in the supply chain, contamination of organic products during transport and storage due to the use of, for example, the same containers or depots as conventional food may all lead to pesticide residues in products that are marketed as organic. It is, however, evident that there are far fewer pesticide residues in organic food compared to conventional food.

Residues of pesticides approved for organic agriculture

Two pesticides (both insecticides) approved for organic agriculture are part of the EU-coordinated monitoring program and dietary risk assessment: pyrethrins (likely mainly used in organic farming) and spinosad (extracted from a bacterium, and also frequently used in conventional farming). In the most recent EU-coordinated pesticide monitoring report[78], residues of pyrethrins were not found in any organic sample but in a small number of conventional samples. Spinosad was detected in 1.5 percent of all (organic + conventional) samples in the EU-coordinated program, and in 1.0 percent of all organic samples from the EU-coordinated and national programs. Copper is also approved in organic agriculture in some countries in the EU, and used in both conventional and organic agriculture. Copper was not included in the EU-coordinated monitoring program, but reported in some national programs. It is unclear in how many samples copper was analysed. In 2 organic samples (out of a theoretical maximum of 4 576 analysed samples) the MRL was exceeded; both were samples of pine nuts. In 26 conventional samples (out of a theoretical maximum of ca 73 000 analysed samples) the MRL was exceeded; most were animal samples, likely due to the use of copper as a food additive.

In an assessment of acute consumer risk, the highest risk from a pyrethrins containing sample (conventional sweet pepper) was at 12.3 percent of the ARfD (highest risk from various dietary scenarios). Spinosad does not have an ARfD due to low acute toxicity. For comparison, the highest risk from a sample containing synthetic pesticides was at 24 500 percent of the ARfD (triazophos in conventionally grown sweet pepper). For an assessment of this risk of chronic intake, pyrethrins intake was at 0.00 percent of the ADI, and spinosad intake at 1.06 percent of ADI. For comparison, the highest long-term risk from the intake of pesticides approved for conventional agriculture were chlorpyrifos (51.4 percent of ADI), dimethoate (18.6–62.1 percent, depending on scenario), and dithiocarbamates (10–93.5 percent, depending on scenario). This indicates that the consumer risk from residues of pesticides approved for and used in organic agriculture is low, compared to pesticides approved for and used in conventional agriculture.

Exposure of the general population

On several occasions below, we use the organophosphate insecticide chlorpyrifos as an illustrative example. Chlorpyrifos is one of the compounds that have attracted a lot of attention from researchers.

It is evident that most of us are constantly exposed to pesticides. A study of eleven pesticides and pesticide metabolites in the urine of 128 women in the Swedish region of Scania revealed that six of the investigated pesticides and pesticide metabolites could be detected in over 50 percent of the participating women; two pesticides (metabolites) were detected in all participants. Choosing organic food is one way of decreasing this exposure: in a study of 23 children in Seattle (USA), researchers collected urine from the participating children during 15 days. During five days in the middle of the study period, most of the children's food was replaced by organic products. During this phase, the pesticide content in the urine of the children decreased sharply[81]. In a similar Australian study, 13 adult participants consumed during one week predominantly (>80 percent) conventional food, and during another week predominantly organic food. After one week of eating organic food, levels of organophosphate insecticide metabolites in urine were on average 89 percent lower compared to after one week of eating conventional food[82].

Of highest, direct relevance for studying the effects of dietary pesticide exposure in the general population is to compare health outcomes in a group of people that are unexposed with a group of people that have a "normal" exposure; both groups should not differ in their lifestyles otherwise. It is, however, not easy to find groups that are unexposed to common pesticides. Second best is a comparison where people with a "normal" exposure (e.g. via diet) are compared to people with a higher exposure, and relevant health outcomes are followed over time.

One major difficulty that many studies face is the fact that it is difficult to find a good measure for long-term pesticide exposure. For example, most people are daily exposed to dozens of different pesticides via our food. Some common pesticides we may be exposed to every day, others only occasionally, and the type and amount depend not only on our food habits, but also on the origin of the food, the season, farmers' agricultural practices and so on. For an accurate measure of an individual's exposure, one would have to test all food that the person eats and record the amounts of food eaten, or frequently take urine or blood samples. For a long term study, this is difficult to accomplish and very expensive. Some of the most well designed studies take urine or blood samples a few times during several years from the participants, and use this as an estimate for overall exposure.

An alternative way of estimating pesticide exposure relies on questionnaires, interviews, and/or logbook data. Information on residential exposure (via e.g. insect spray at home) can be relatively easy obtained by asking the study participants. Some people use such products, some do not, and people are likely to have a good memory of their (non-) use of such products at home. Also, the occupational exposure of farmers can be estimated using memory recall or logbooks. In rural populations, the proximity of homes to fields with pesticide applications can be used to estimate exposure via spray drift.

Results from such studies do not directly translate into estimates of health effects from dietary exposure, because exposure routes and patterns differ between residential, occupational and dietary exposure. Nonetheless, adverse pesticide effects observed in pesticide applicators or home users are still of potential relevance for the general population: Effects found in such studies with comparatively high and well-defined exposure may aid in finding similar effects in the general population.

For understanding the relevance of epidemiological studies of pesticide effects in agricultural workers for the consumer, it is critical to understand the relative exposure of workers and consumers. Intuitively, one might expect occupational users of pesticides to have a higher pesticide exposure than home users, and the exposure of the general population via pesticide residues in food to be even lower. It is, however, not straight-forward to confirm this, and it is rare that scientific studies directly compare the relative exposure of different groups. Two publications have assembled data from various studies on the exposure of different population groups to the organophosphate pesticide chlorpyrifos, measured as the concentration of one specific metabolite (TCPy) in urine[83, 84]. The populations and the methods of analysis are diverse, so small differences between individual studies should be interpreted with caution.

In one of the best controlled studies, farmers delivered urine samples before and after they applied chlorpyrifos on the farm. The urinary concentrations of the chlorpyrifos metabolite TCPy was

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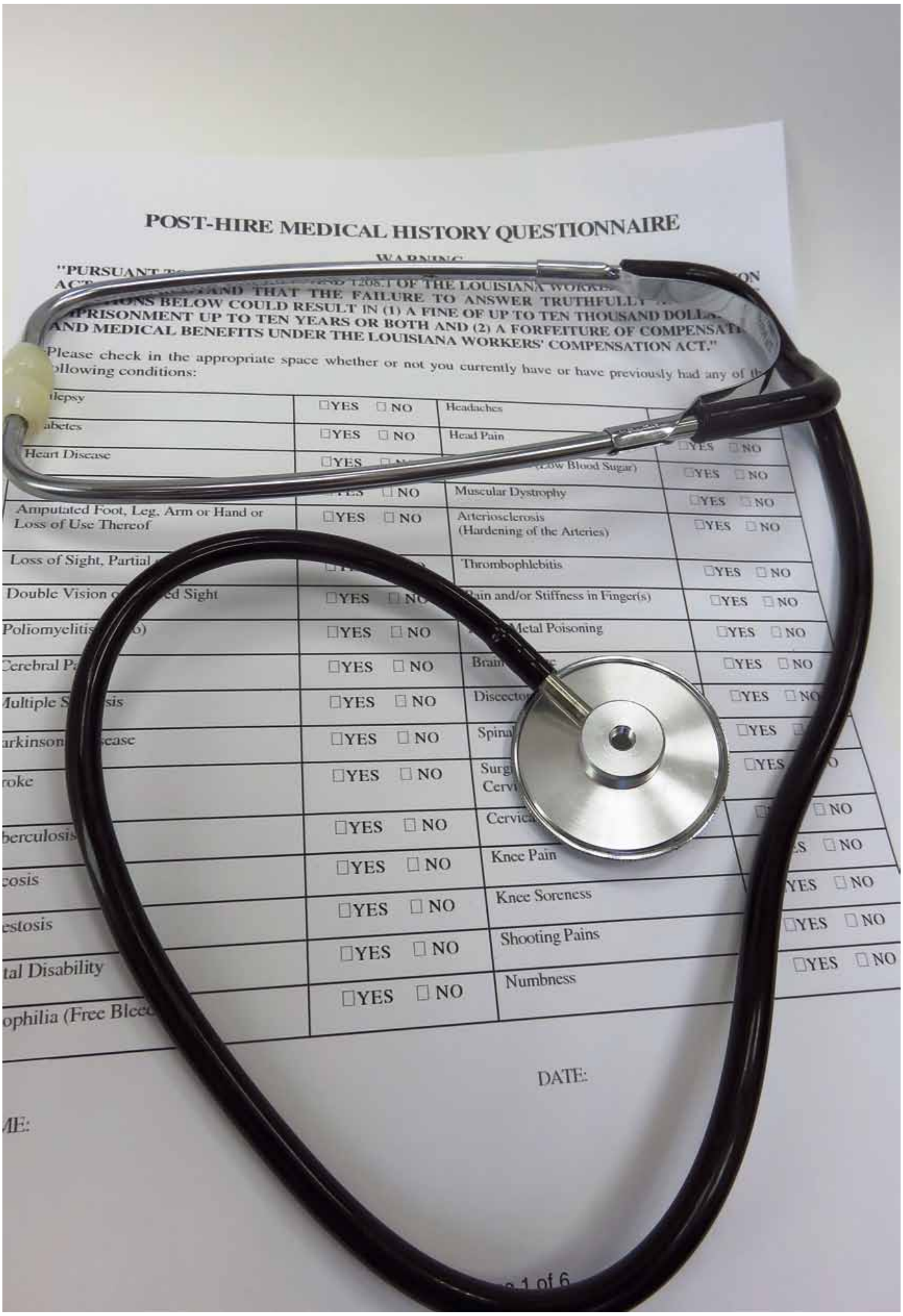
ca 2-3 times higher on the day after chlorpyrifos spraying than before[85]. In some other studies, the exposure of farmers was typically between 10 and 100 times higher than the exposure of the general population for this specific pesticide around the time of pesticide spraying[83]. For a farmer who applies this pesticide only a few times per year, the accumulated annual exposure will be only modestly increased compared to other people, but with peak exposures just after the spraying event(s). It should be noted that these numbers are for one well-researched pesticide (chlorpyrifos), and could be different for other pesticides.

EFSAs risk assessments of active pesticide substances allow to some degree for an estimation of the relative exposure of workers and consumers. In many cases, the Acceptable Daily Intake (ADI) (for consumers) and the Acceptable Operator Exposure Level (for agricultural workers and bystanders) are similar. In the risk assessment, both a Theoretical Maximum Daily Intake (in percent of the ADI, for consumers, according to various dietary scenarios) and exposure scenarios for workers (in percent of the AOEL, for various application methods and protective equipment) are estimated. These values can also be compared to the actual chronic exposure for consumers, which is assessed by EFSA in annual reports[78].

The start of one study investigating long term health effects of chlorpyrifos exposure at birth coincided with the phasing out of home use of chlorpyrifos in the USA. In that study, participants who were enrolled before the ban had on average a five times higher chlorpyrifos concentration in the umbilical cord blood, compared to pregnant women who were enrolled after the ban[86]. This can give an indication that the exposure from indoor use of this insecticide is (on average) approximately 5 times higher than the exposure from other sources (probably food).

The route of exposure is different for indoor and outdoor use (via inhalation and/or skin) compared to dietary exposure, and the route of exposure is in general relevant for the uptake and potentially also for effects. However, all the examples above are measurements of exposure in the blood and in urine, and should therefore be directly comparable.

In summary, people using pesticides in their homes, and people who are exposed at work (e.g. farmers) have a higher exposure to the specific pesticides they are handling. However, the exposure is generally not drastically higher, so health effects that are observed in these population groups are potentially of relevance for the general population as well. ■



POST-HIRE MEDICAL HISTORY QUESTIONNAIRE

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Heart Disease	☐YES	(Low Blood Sugar)	☐YES ☐NO
	☐NO	Muscular Dystrophy	☐YES ☐NO
Amputated Foot, Leg, Arm or Hand or Loss of Use Thereof	☐YES ☐NO	Arteriosclerosis (Hardening of the Arteries)	☐YES ☐NO
Loss of Sight, Partial		Thrombophlebitis	☐YES ☐NO
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Public health effects of low-level pesticide exposure

What are the potential adverse effects for consumers? In general, consumers in the EU need not worry about acute toxic effects of pesticide exposure via food. Only rarely have such intoxications been reported. EFSA also concludes, using risk assessments based on dietary scenarios, measured pesticide residues on food, and Acceptable Daily Intakes (ADI), that long-term health effects on the health of consumers are unlikely[78]. That is, the intake for all pesticides included is below the ADI for all dietary scenarios. On the other hand, some epidemiological studies have found associations between a low-level, long-term exposure to various pesticides and chronic diseases. Such an association is not to be confused with a proof of a causal relationship.

Hundreds of studies have investigated the potential adverse health effects of pesticides. These studies show a huge diversity in study design, type of exposure, study population (e.g. agricultural workers, general public), health outcomes measured, and estimations of pesticide exposure. Below, one recent meta-analysis is discussed. Also, as an in-depth example, neurodevelopmental effects of the organophosphorus insecticide chlorpyrifos are discussed. Furthermore, an issue which is currently of great interest, namely endocrine disruption, is discussed in some detail.

A recent meta-analysis of health effects

Recently, a meta-analysis of epidemiological studies of health effects of pesticides commissioned by the EFSA[87] was published. In this meta-analysis of 603 studies published between 2006 and 2012, effects of pesticides on 23 categories of health outcomes were measured. For most categories, the researchers found that the study designs and health outcomes differed too much between studies to allow for a formal meta-analysis. For some health outcomes, a formal meta-analysis was possible. Most notably, for childhood leukemia and Parkinson's disease, both earlier meta-analyses and a sufficient number of new studies were identified, and the authors argue that these are the most reliable findings of their meta-analysis:

The researchers found a significant association between pesticide exposure and childhood leukemia. When considering all available studies, the association was especially strong for insecticide exposure during pregnancy (mainly indoor home use) and childhood leukemia (almost 70 percent increased risk for exposed compared to unexposed, nine studies) and for exposure during childhood and childhood leukemia (50 percent increased risk, eight studies), but not for exposure before pregnancy and childhood leukemia.

For Parkinson's disease, researchers found a approximately 50 percent higher risk of developing the disease for people who had been occupationally exposed, compared to those not exposed (based on 26 studies).

According to the meta-analysis, the risk for other diseases was also increased after pesticide exposure, namely breast cancer (25 percent increase, 11 studies), stomach cancer (79 percent, 6 studies), liver cancer (150 percent, 5 studies), abortion (52 percent, 6 studies), Amyotrophic Lateral Sclerosis (58 percent, 6 studies), diabetes type 1 (89/76 percent, DDE/DDT exposure, 8/6 studies) and diabetes type 2 (29 percent, 4 studies, DDE exposure). On the other hand, there was no increased risk for adult leukemia (6 studies) and Hodgkin's lymphoma (7 studies), testicular cancer (5 studies, DDE exposure), cryptorchidism (8 studies), hypospadias (6-9 studies) after pesticide exposure. For some endocrine diseases, namely asthma, allergy, diabetes and obesity, the authors see an increased risk after exposure and point out that this should be followed up. For other disease categories, the study designs and/or the chosen disease outcomes were too diverse to allow a formal meta-analysis.

It should be noted that in general, the diversity between study designs was high. Also, a substantial number of studies were based on pesticides that are today banned (although some persistent pesticides are still wide-spread in the environment). The authors also highlight that the measurement of pesticide exposure is an area of concern; it is still difficult to make reliable measurements of long-term exposure.

Most studies in this meta-analysis adress occupational exposure, or other population groups with and without exposure from indoor or outdoor use. As described in the section "Exposure of the general population" above, this is not necessarily, but possibly, of relevance for health effects for a general population that is mainly exposed via the diet.

In summary, this meta-analysis, the most comprehensive one to date, gives an indication of which diseases might be more common today due to widespread pesticide use now and in the past.

In-depth example: Developmental neurotoxic effects of chlorpyrifos

Organophosphate insecticides, especially chlorpyrifos, are quite unique among pesticides because three epidemiological studies are ongoing that are designed to investigate developmental neurotoxicity of these compounds. Results from these studies suggest adverse effects at levels of current dietary exposure, but these results are in contrast to animal studies which are the basis of the regulatory approval process. Chlorpyrifos is therefore an interesting example to illustrate how different types of studies are weighted by the regulatory authorities.

Beginning in the mid-1990s, researchers observed that in animal studies, compounds of a group of insecticides called organophosphates have a negative effect on the development of the brain and nervous system of the offspring. This effect is called neurodevelopmental toxicity; the rationale is that small damages to the developing brain may have life-long consequences.

Evidence of effects for cognitive skills

In 1998, Guilette and co-workers provided some of the first evidence of the negative effects of pesticides on the development of cognitive skills in children. Four to five-year-old Yaqui children in Mexico were exposed or non-exposed to pesticides, depending on whether they lived in the Yaqui valley (with pesticide-intensive agriculture) or the nearby foothills (with low or no pesticide use). Exposed children had "decreases in stamina, gross and fine eye-hand coordination, 30-minute memory, and the ability to draw a person"[88].

Starting around the year 2000, three large cohort studies (observational studies that repeatedly follow up participants) were initiated, measuring the exposure of pregnant women and infants to organophosphate pesticides, and later measuring various cognitive outcomes in the children at several ages. One study, the "Columbia Center for Children's Environmental Health Study"[89], is designed to investigate the effect of prenatal exposure to air pollutants, amongst them chlorpyrifos (as a household insecticide), on neurodevelopment in children, in a low-income urban community in New York.

The second study, the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) cohort study, assesses how children are exposed to pesticides and other pollutants during their mothers pregnancy, infancy and childhood. The study is designed to investigate the effect of these exposures on children's growth, neurodevelopment, and other health parameters[90].

The third study, the "Children's Environmental Health Cohort" of the Mount Sinai Hospital in New York, is designed to investigate the impact of the prenatal exposure to some indoor pesticides on the growth and development of children[91].

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All three studies report to have taken into account a range of potential confounding factors (chemical, socio-economic, and others). Although the studies vary in design, methods and populations, some important common trends are apparent. Mental development at age 7–9 was negatively affected in children that had been exposed to chlorpyrifos/organophosphates during pregnancy.

Three studies discovered similar effects

In the Columbia study, the full-scale IQ at age seven was lower in children with a higher exposure during pregnancy. Also, the working memory was negatively affected by chlorpyrifos exposure during pregnancy, but not perceptual reasoning, verbal comprehension, and processing speed[92]. Also, in the Columbia study, a high exposure to chlorpyrifos during pregnancy was associated with changes in brain morphology at age 6–11[93].

In the CHAMACOS study, children of the 20 percent of women with highest exposure to chlorpyrifos during pregnancy had on average a score seven points lower on the IQ scale at age seven compared to children of women with the 20 percent lowest exposure. Also working memory, processing speed, verbal comprehension and perceptual reasoning at age 7 were negatively affected by high chlorpyrifos exposure during pregnancy[94]. The Mount Sinai study, with a smaller number of children in this analysis, found comparable but not statistically significant effects[95]. Importantly, the observed associations of exposure during pregnancy and the effect on neurodevelopment were consistent over three different study populations, and their magnitude was quite large. It is also important to note that associations found in epidemiological studies are not a proof of causality. However, the Bradford Hill criteria of causation[96], a group of originally nine criteria that have recently been further developed, can provide guidance on whether there is adequate evidence for a causal relationship in epidemiological studies.

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Based on results from these and other epidemiological studies, scientists have recently added chlorpyrifos to a list of compounds known to exert developmental neurotoxicity[97]. A recent systematic review summarises all available epidemiological studies on the developmental neurotoxicity of organophosphate pesticides and finds that "most of the studies evaluating prenatal exposure observed a negative effect on mental development and an increase in attention problems in preschool and school children"[98].

In contrast to these epidemiological studies, in animal studies carried out as part of the regulatory approval process according to specific guidelines, such neurodevelopmental effects of chlorpyrifos have not been found; adverse effects have only been observed at much higher concentrations than in the human studies. It is important to note, however, that knowledge of neurodevelopmental effects has increased greatly in recent years, while the test of neurodevelopmental effects used in the regulatory process dates from 1998[99]. That test is probably not able to detect decreases in the IQ scale of the magnitude observed in the epidemiological studies.

The most frequently discussed cause of developmental neurotoxicity of chlorpyrifos is the ability of the chlorpyrifos oxon, a metabolite of chlorpyrifos, to block (inhibit) the enzyme acetylcholinesterase (AChE) which is important in the development and function of the brain and nervous system. AChE inhibition is the mode of action of chlorpyrifos, as well as of other organophosphorus and carbamate insecticides. Apart from AChE inhibition, a number of other potential modes of action have been proposed[84, 100]. However the animal studies that authorities base their toxicological assessment on, focus solely on the AChE inhibition under various exposure scenarios; no other potential modes of action are investigated. The lowest daily dose of chlorpyrifos found in animal studies that causes AChE inhibition in long-term studies in animals is roughly 1 000 times higher than the exposures that are associated with observed adverse effects on children's neurodevelopment in the epidemiological studies[100].

It is a characteristic of the current regulatory assessment practices that in such cases, epidemiological studies have lower weight, although the application of the Precautionary Principle is anchored in

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PHOTO & TEXT: ISTOCKPHOTO © NANDY NEHRING: *Watsonville, California, USA – January 24, 2011: Farm workers spot spraying artichokes with herbicide. Workers are dressed in protective clothing to reduce their expose to chemicals. Use of pesticides in fields near housing developments such as this is an issue in California.*

relevant EU regulation[61]. For example, for the most prominent and most widely used organophosphate pesticide, chlorpyrifos, EFSA summarizes the evidence from epidemiological studies:

> "In summary, the weight of evidence suggest that the results of the three cohort studies in concert with the animal studies indicate that maternal CPF [*chlorpyrifos*] exposure would be likely associated with adverse neurodevelopmental outcomes in humans. However, the exposure to multiple cholinesterase-inhibiting pesticides or other neurotoxicants might result in additive or interactive effects. The Columbia study was considered the most robust because it measured CPF in maternal and cord blood (rather than non-specific metabolites). The epidemiology human studies should not be considered quantitatively to establish reference dose."[100]

That is, although the association between chlorpyrifos exposure and negative effect is likely and EFSA acknowledges that the epidemiological studies are of high quality, EFSA does not regard the causality to be established. Therefore, these epidemiological studies are disregarded when the toxicity of chlorpyrifos is assessed, and an ADI is established based on AChE inhibition in the red blood cells of rats[101].

Accordingly, EFSA requires a causality to be established before epidemiological studies can be taken into account, although the precautionary principle should apply, according to Regulation 1107/2009[61]. It is also remarkable that the potential causality apparently has not been evaluated using e.g. the Bradford-Hill criteria[96].

Endocrine disruption

It is today generally challenging to study endocrine effects in epidemiology. For the development of children, it is often suspected that certain time windows of exposure are critical, but these are not always known or well described. It may therefore be difficult to measure the exposure in a relevant way. A group of Danish researchers found an interesting approach to studying some endocrine ef-

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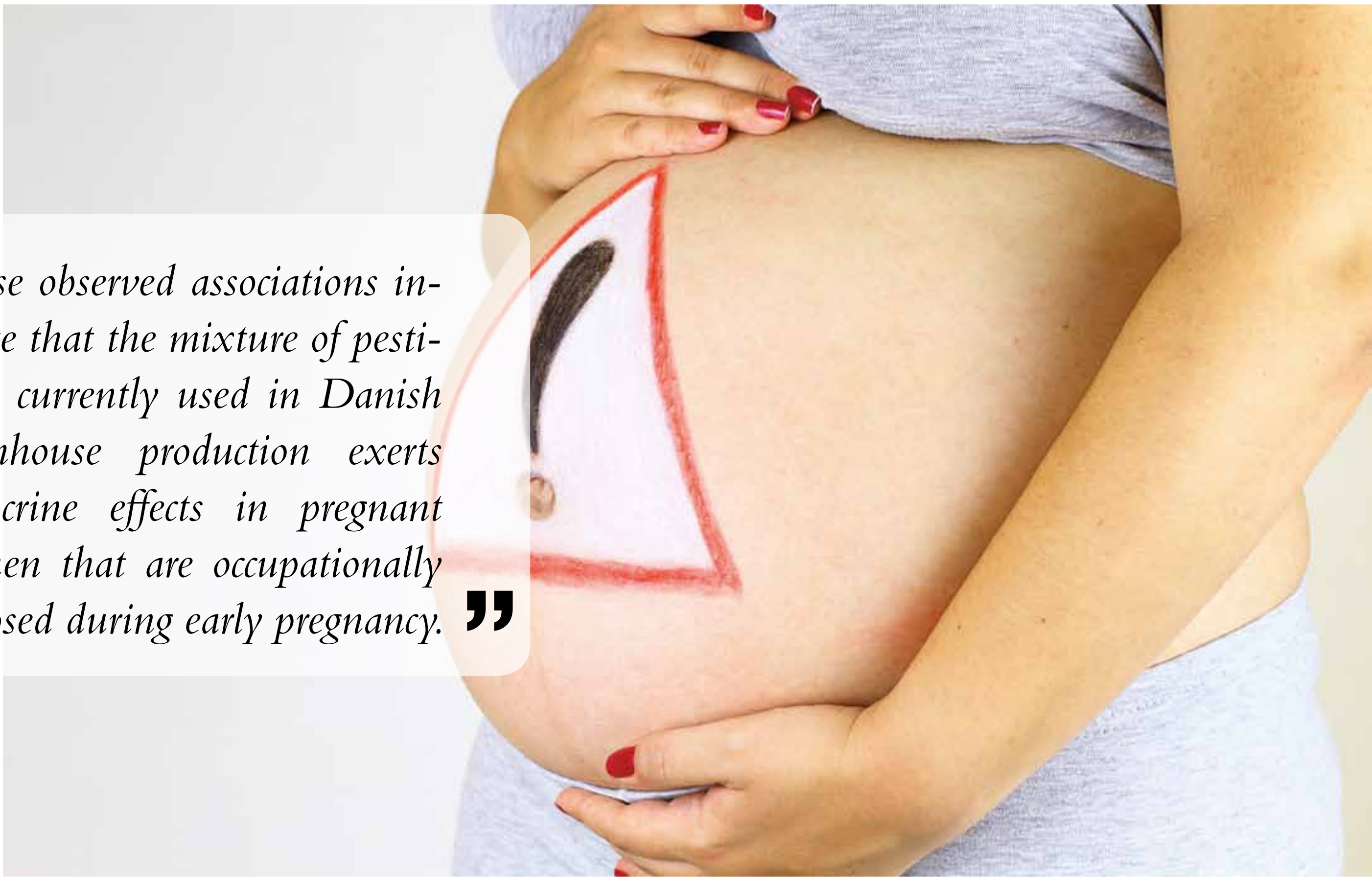

> *"These observed associations indicate that the mixture of pesticides currently used in Danish greenhouse production exerts endocrine effects in pregnant women that are occupationally exposed during early pregnancy."*

fects of currently used pesticides on child health. Their study followed the development and health of children of mothers who had been working in greenhouses during early pregnancy. These mothers were either exposed or not exposed to pesticides during their work. Researchers found that for boys, the development of genitals was delayed in the group of sons of exposed mothers, compared to the unexposed group[102]. Also, daughters of exposed mothers had an earlier onset of breast development than daughters of unexposed mothers[103]. These observed associations indicate that the mixture of pesticides currently used in Danish greenhouse production exerts endocrine effects in pregnant women that are occupationally exposed during early pregnancy.

The relevance of these findings for the general population is unknown: probably, the exposure of occupationally exposed women is higher than the exposure of the general population (see section "Exposure of the general population" above). It is, however, for endocrine effects not generally true that a higher exposure causes a larger effect. Instead, dose-response curves may be non-monotonous, or it may be the timing of exposure, rather than the dose, that is crucial. It is therefore possible that the associations observed in these studies are of direct relevance for the general population. This is especially topical because there is a trend over the recent decades towards earlier puberty, and towards lower male fertility, which is congruent with the observations in this study. It should also be noted that it is not likely that effects of the magnitude observed in this epidemiological study would be observed in the animal studies included in the current regulatory process of pesticide approval, because endocrine effects are still not included in the regulatory assessment (see section "Gaps in risk assessment" above).

Natural pesticides

Based on work and reasoning by Ames and coworkers from 1990[104], it is sometimes claimed that the plants' content of own defence compounds ("natural pesticides") far outweigh residues from synthetic pesticides; accordingly, residues of synthetic pesticides in food would pose a negligible risk. In that work, it is discussed that of 52 tested "natural pesticides", 27 were carcinogenic in rodent studies when fed isolated at very high concentrations over prolonged periods. Furthermore, all defence compounds are termed "toxins" in that work.

Today, the presence of a large body of epidemiological research alone (summarised in previous chapters) weakens the above argument that risks from synthetic pesticides need not to be considered.

Ames also states that grains such as white flour contain only small amounts of toxins, but wholemeal products contribute substantially to the exposure of dietary toxins. Likewise, vegetarians are more highly exposed to natural toxins than non-vegetarians. These statements are today in contradiction to the recognized beneficial effects of a high fibre content in the diet, and a high intake of fruits and vegetables.

Furthermore, we now understand that the beneficial effects of fruit and vegetable consumption are in part due to their high content of plant defence compounds. Examples include phenolic compounds, flavonoids, or glucosinolates. For a high number of plant compounds, beneficial effects at low doses and adverse effects at high doses have been demonstrated, in cell and animal studies[105-107]. Therefore, the collective description of all plant defence compounds as "toxins" is probably misleading.

One often-cited example from the work of Ames is coffee: 13g roasted coffee (average daily consumption) contains 765 mg of the toxins chlorogenic acid, neochlorogenic acid, caffeic acid, and caffeine, of which the former three have been shown to be carcinogenic in isolated high amounts in rodent studies. Today, these same and other compounds, however not in isolation but in their coffee matrix, are believed to mediate some of the beneficial effects of coffee. It is now known that coffee consumption is consistently associated with a lower risk for e.g. hepatocellular cancer[108, 109] and Parkinson's disease[110].

There are, of course, also natural plant devence compounds that are of concern in our food; some well-known examples are the compound gyromitrin, which can be found in the mushroom false morel (*Gyromitra esculenta*), and the alkaloid solanin in potatoes. Nonetheless, since 1990, compelling epidemiological evidence of beneficial effects of fruit and vegetables has emerged, we now know that many "natural pesticides" exhibit beneficial effects at low concentrations, and numerous epidemiological studies indicate negative health effects of synthetic pesticide exposure. The original argument of Ames, that we can disregard synthetic pesticides effects because of a high content of natural pesticides in plant foods, is therefore probably no longer relevant.

It should be noted that natural toxic compounds other than plant defence compounds may be present in food in amounts of concern, for example cadmium and mold toxins. These are treated in next chapter.

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How to deal with uncertainty

Risk assessments from European regulatory bodies conclude that long-term health effects from pesticide residues in food are unlikely to occur. This view is for example expressed in a recent Norwegian evaluation of potential health effects of organic food[111], and this is also the long-standing position of EFSA[78]. As described in earlier chapters, epidemiological evidence is not considered in such risk assessments. Numerous epidemiological studies indicate negative health effects from pesticide exposure through various exposure routes. However, observational epidemiological research does provide statistical associations, but not definitive proofs of such effects.

Fruits and vegetables are the most important dietary sources of pesticides. As discussed earlier, there is strong evidence that a high consumption of fruits and vegetables has favourable health effects, e.g. a lower mortality[2]. Such studies of health effects of fruit and vegetable consumption are generally performed without consideration to the agricultural production system. Most fruits and vegetables in such studies are probably of conventional origin, and thus are contaminated with pesticide residues to a "normal" extent. It is therefore important to note that a high consumption of fruits and vegetables is beneficial for human health, irrespective of the produce's conventional or organic origin. Accordingly, it would be unwise to abstain from, or lower, fruit and vegetable consumption in order to avoid pesticide exposure.

In summary, choosing organic instead of conventional food lowers dietary exposure to pesticides, which is the most important source of pesticide exposure for the general population. There is evidence of a range of adverse health effects of various pesticides; most of this evidence originates from studies of occupational or household exposure. There are known uncertainties in the risk assessment of pesticides, because some types of effects (e.g. endocrine disruption) are disregarded or cannot be detected. Moreover, associations of exposure and effect found in epidemiological studies have a low impact on the risk assessment of pesticides. People who choose organic fruits and vegetables in order to minimize their pesticide exposure find good scientific reasons to do so, if their intention is to avoid potential health effects that are not covered by today's regulatory risk assessment. People who avoid eating fruits and vegetables in order to minimize their pesticide exposure have no good scientific reasons to do so, because fruit and vegetable consumption carries clear and recognized health advantages. ■

Other food qualities

Antibiotic resistant bacteria

One of the great medical achievements is the development of antibiotics, which has drastically reduced mortality from bacterial infections and contributed to increased life expectancy during the last 100 years.

The preventive use of antibiotics is generally more restricted or completely rejected in organic husbandry compared to conventional husbandry. Although overall pathogen contamination is similar in organic and conventional meat products, it has been shown that the risk of contamination with bacteria that are resistant to three or more classes of antibiotics is substantially higher in conventional chicken and pork meat (16 percent in organic vs. 48 percent in conventional products) in a meta-analysis based on several studies from e.g. Spain and the US[18].

The development of drug resistant bacteria, a natural process in response to the use of antibiotics, has been accelerated by excessive and inappropriate use of antibiotics in humans and in animal husbandry, among other factors[112]. Researchers are concerned that we may be facing a situation where antibiotics will be useless, and infectious diseases that are easily treated today may become fatal once again[113]. In an agricultural context, it is worrying that antibiotics are routinely used as a preventative against infections, and as a growth promoter in livestock production in many countries (although the use as a growth promoter is banned in the EU). For a detailed summary and discussion of antibiotic use and resistance in the context of organic and conventional animal husbandry, I would like to refer to an upcoming report[114].

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Cadmium and other heavy metals

Cadmium is of great concern to public health. The Swedish Chemicals Agency has recently estimated the annual societal cost of bone fractures from cadmium intake via food to be approximately 430 million Euro (other routes of exposure and other health effects excluded)[115]. The reduction of cadmium exposure of the general population is therefore an important public health priority. Cadmium is present naturally in many soils. Cadmium is also contained in many mineral fertilizers, as a contaminant of phosphate minerals. The influx of cadmium via fertilizers used in conventional agriculture is therefore of concern. Organic agriculture is free from this direct influx, but organic farmers in many countries import farmyard manure from conventional farms to their farms, which also increases cadmium levels in soils.

Smith-Spangler[18] has assembled cadmium data from 15 original studies and found no significant differences in cadmium content between organic and conventional crops. In contrast, Barański[19] reported a higher cadmium content in conventional crops in a meta-analysis based on 22 studies, with a moderate overall reliability. It is of high importance to follow up on the potential long-term effects of cadmium influx from phosphate minerals into the entire agricultural system.

Lead[18, 19] and other heavy metals[19] were found in similar levels in organic and conventional crops.

Mycotoxins

For some crops, specifically cereal crops, fungal toxins are an important cause of crop loss in Europe and North America. For example, cereals with too high levels of deoxynivalenol (DON) cannot be used for human consumption or as animal feed. Smith-Spangler found that DON contamination was significantly lower in organic grain crops (10 original studies available)[18]. The reason for this is still unclear, but it may be that the application of (non-specific) fungicides in conventional agriculture damages the fungal community in the soil and on plants, and that *Fusarium* species, which produce DON, are able to populate the empty niche faster than other species.

Another mycotoxin, ochratoxin A, did not differ in concentration between the conventional and organic crops studied[18]. ■

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