European Commission

JRC TECHNICAL REPORT

Aspects of food and feed safety regarding the source of commodities used when rearing insects for consumption

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2021

Joint Research Centre

JRC124260

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EU Science Hub
https://ec.europa.eu/jrc

JRC124260

Geel: European Commission, 2021

How to cite this report: Joerg Stroka, Piotr Robouch, Carlos Goncalves, *Aspects of Food and Feed Safety regarding insects and the flow of commodities*, JRC, Geel, 2021, JRC124260

Introduction

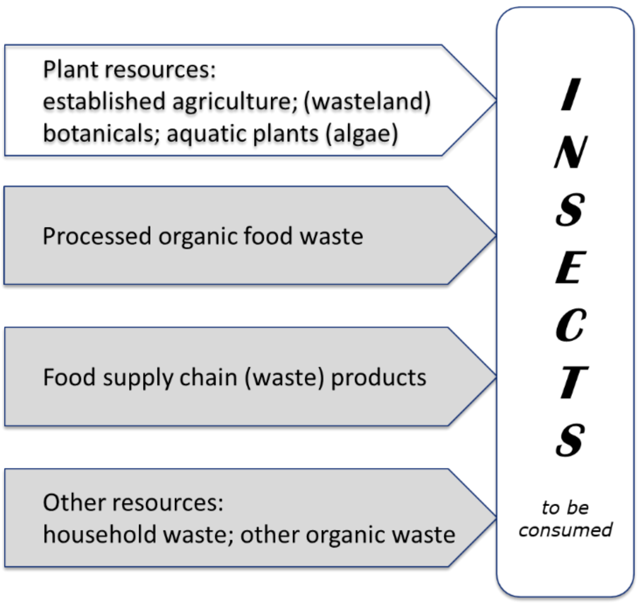
- *Edible insects are a booming sector with global economic impact in the next decade.*
- *Edible insects have a long tradition in our culture, but rearing of insects at industrial scale is a relatively new phenomenon that deserves special attention regarding consumer safety and animal welfare.*
- *The vastly expanding proposed possibilities in the utilization of novel substrates to rear edible insects is a key challenge in evaluation of edible insect safety.*

The use of insects as food and feed is a rapidly growing business sector. In Europe along the estimation of insect protein production ranges roughly from **2 to 5 million tons p.a.**, depending on EU legal framework that is forecasted for the insect sector. An assumed creation of **100.000 jobs** accompanies this economic growth by 2030 according to the International Platform of Insects for Food and Feed - IPIFF (2019).

A global forecast was published by GlobalNewswire (2020) that summarizes a more than 200 pages analysis report by Meticulous Research® with the title: "*Edible Insects Market by Product Type (Whole Insect, Insect Powder, Insect Meal, Insect Type (Crickets, Black Soldier Fly, Mealworms), Application (Animal Feed, Protein Bar and Shakes, Bakery, Confectionery, Beverages) - Global Forecast to 2030*". According to this summary, the global market value of the insect sector is projected to reach a value of **US$ 7.96 billion by 2030**, supported by a **Compound Annual Growth Rate (CAGR) of 24.4%.**

The profitable operation of this sector relates to a significant degree on the utilization of novel substrate sources. These substrates are likely to derive from currently unused sources as they appear in a circular economy and little studies are available on the food safety aspect when using such sources. Figure 1 depicts the different substrate sources for rearing insects, while Figure 2 summarises the different pathways via which insects can enter the food chain. The intention of this paper is to focus on the fate of undesired substances of natural origin (often classified as "natural toxins") when rearing insects as food and feed. This concerns in particular plant toxins, marine biotoxins and mycotoxins that have the potential to enter the food/feed chain as novel or cost effective substrates.

Figure 1: Different substrate sources for rearing insects

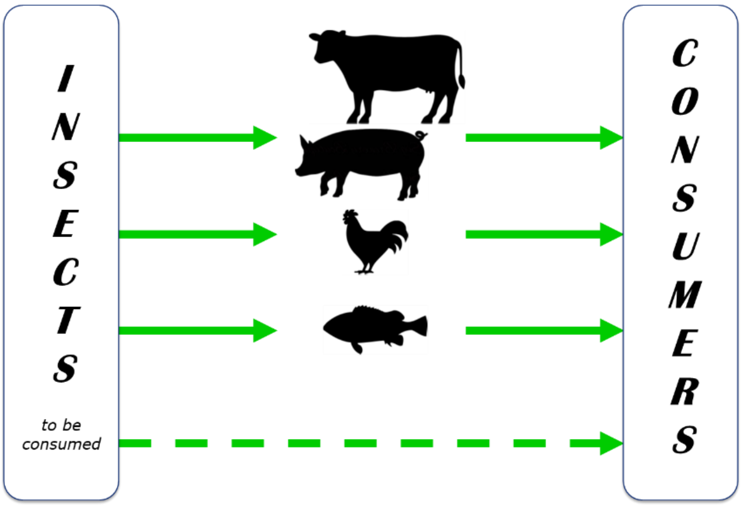


This diagram shows the different origins of resources that have a (technical) potential as substrate for rearing insects. Resources in grey will require specific processing to make them valuable as substrate for rearing.

Figure 2: Different pathways via which insects can enter the food chain**.**

Two main principle pathways are identified on how reared insects enter the food and feed chain: either insects are for animal consumption, or they are used for human consumption.

The requirements for insects as feed might differ depending on the requirements of the livestock.



Entomophagy (eating insects) is practised worldwide and even ancient Christian literature refers to insects as nutritious source of energy (Mark 1; 6: "John…ate locusts and wild honey"). In late 1800s cockchafer (*Melolontha melolontha*) soup and medicinal products such as cockchafer oil were described in France and Germany. Thus entomophagy and the use of insects as medicine are not completely new in European (historical) culture, though mostly forgotten in our times and can be considered as an underutilized bioresource (Rumpold *et al*. 2017).

The use of insects as food and feed is described in a number of studies and is summarized in an EFSA opinion on this topic. It must be mentioned that the majority of these studies refer to the use of insects grown in their natural habitats.

Current European Commission action plans (e.g. the "**Green Deal**", the "**Bioeconomy Policy**" and others policies regarding a boost of circular economic aspects and a food systems transformation) indicate to reach out for novel sources in the food and feed supply chain. In particular unlocking the potential of the seas, oceans, the forest biomass and eventually wasteland biomass are discussed in recent scientific studies. Further, the use of former foodstuffs or the use of organic household waste, for generating insect protein have already been subject to exploratory research [Meneguez, *et al.* 2019]. These research initiatives are relatively young but a fast growing activity.

However **not all insects are edible for mammals**. Therefore as a precautionary measure, only a few insect species/products are currently authorised as novel food (or feed) in the EU.

Poisonous insects that inject their venom into potential attackers, like spiders, wasps and hornets shall however be excluded from discussion. However, few insects are intrinsically toxic to humans when eaten.

<u>Spanish fly</u>

A known example of such a toxic insect (in particular when consumed) is *Cantharis vesicatoria,* syn. *Lytta vesicatoria* (aka Spanish Fly). This insect produces cantharidin, a terpenoid that acts as skin irritant and can lead to death when ingested. Historically this insect gained a certain reputation as rather dangerous while doubtful virility booster. *Cantharis vesicatoria* is however not the only insect that produces cantharidin. The widely spread family of Oil beetles (*Meloidae*) that is also known as Blister beetles produce an oily cantharidin secretion upon stress, used to repel predators. However, a number of other insect sepcies are attracted by the secretion and feed on it using it for their own protection against predators. While *Meloidae* are present across Europe, the Near East, northern Africa and Asia, the European blister beetle *Meloe proscarabaeus* was awarded the title "Insect of the year 2020" by the Senckenberg Entomological Institute in Germany for its 4000 years back dating use in ancient Egyptian medicine.

<u>Silkworm larvae</u>

Other insects, which are traditionally consumed, such as the larvae of the silkworm *Anaphe venata* are neither *per se* safe. These larvae serves as protein source during the raining season in African countries. These larvae must be cooked for at least 15 minutes (@ 100 °C) to avoid a condition known as "African seasonal ataxia" (ASA) describing a severe vitamin B1 deficency. Reason for this condition is the enzyme thiaminase that degrades vitamin B1. Thiaminase and other vitamin B1 degrading substances can be found in some fish and numerous plants, too.

ASA is an example for toxicity related to an intentional consumption of wild harvested insects. While *Anaphe venata* is of little relevance in the EU, the late description between the link of ASA and *Anaphe venata* (Adamolekun, 1993) and the chemical principle behind (Nishimune *et al*., 2000) indicate the potential gaps of knowledge in this field. Nonetheless, a concise overview highlighting numerous complexity aspect and the potential of insect use as food and feed were published recently by van Huis *et al*. (2013).

In 2002 Donald Rumsfeld United States Secretary of Defence stated: "…*there are things we know we know. We also know there are known unknowns…. But there are also unknown unknowns…* (and) *throughout the history … it is the latter category that tend to be the difficult ones*".

With respect to the statement of the former US Secretary of Defence, it is also true here. This contribution therefore intends to focus where possible on the latter category of "things", in relation to natural toxins occurring in potential substrates for rearing insects as food and feed. As result of the numerous studies in the past on the fate of food and feed contaminants such as heavy metals or persistent organic pollutants (POPS), these do not fall into the topic of this work. Microbiological aspects are also excluded. Nonetheless, these fields are, also relevant as highlighted in the EFSA opinion (EFSA 2015).

The subject of **naturally-occurring secondary metabolites** that may enter the food or feed chain through changes in the established flows of materials for food and feed production, is however different from most of the above discussed scenarios.

The driver for this analysis below is the already on-going discussion on the valorisation of resources from new commodity (side) streams for rearing of insects. In particular former foodstuffs aka "food supply chain waste" (FSCW), forestry or wasteland biomass or new products from the marine ecosystem are such novel commodities that might enter the food and feed chain via insects.

A well known group of potential harmful substances in this view are the mycotoxins. They are produced by moulds (filamentous fungi) and can occur at any stage during food and feed production. A contamination may occur either "pre-harvest" during plant growth, or during storage or processing (post-harvest contamination) of agricultural commodities. In the EU pre-harvest contamination with mycotoxins is regulated for food and feed materials currently in practical use. Therefore this aspect will not be a main topic here. Any contamination with mycotoxins during storage or processing is a matter of good manufacturing practise (GMP) and applies to food an feed in practical use and relevance for public health.

The nature of fungi that can spoil novel substrates will likely differ from those that contaminate so far regulated food or feed commodities. This is because fungi target specific commodities and environmental conditions. Current Regulation on mycotoxins in food and feed in EU legislation is therefore product specific. Thus, new commodities like Food Supply Chain (waste) Products (FSCP) will require specific mycotoxin risk profiles for a safety assessment. It is therefore important that mycotoxins with a known and high toxic potential, that are currently not part of routine monitoring campaigns for food and feed are evaluated for their occurrence in FSCP or other novel insect rearing substrates. In particular, the mycotoxins sterigmatocystin and gliotoxin appear as potential contamination candidates as they possess a high toxic potential though occur not that frequently in the current food chain.

The scientific opinion of EFSA

- *Safety of insects as food and feed can be assessed for already regulated contaminants.*
- *Data on contamination is available for insects collected from their natural habitat.*
- *Little to no data is currently available for rearing insects on novel substrates*

The European Food Safety Authority shows in its Scientific Opinion the risk profiles of insects as food and feed. Various biological and chemical hazards relevant for farmed insects are discussed based on the already established food and feed commodity flows (EFSA 2015). The opinion clearly states that published data on hazardous chemicals in insects are scarce, in particular concerning reared insects. Few data is though available for insects collected in the wild.

EFSA pointed out that **insects** are particular compared to other animals for consumption, as they **can carry yeasts and fungi potentially hazardous to animals and humans**, with potential microbiological concern for human and animal health.

Regarding chemical hazards such as heavy metals, organochlorines, polybrominated diphenyl ethers and trace elements a few studies with insects have been conducted. Further, the use of veterinary drugs and biocides was considered as potential hazards (as a result of human intervention) by EFSA.

At present data regarding natural toxins was limited at publishing date, limited to the occurrence of aflatoxins in possibly improper processed/stored worms sold Botswana.

Insect rearing and valorisation of novel commodities along the production chain

- *The EU invested in research on insects as food and feed.*
- *The valorisation of new substrate sources are a key element for future businesses.*
- *Little is known on the occurrence and fate of natural toxins in this scenario.*

Promoting entomophagy is one element in support of a sustainable food system for a growing population. It is achieved by optimising the use and a circular flow of agricultural or other natural resources. Thus, entomophagy is in line with current EU policy like the "European Green Deal", the bio-economy strategy as well as circular economy aspects. Scientific studies addressing these EU policies with regards to rearing insects have been conducted in the EU and on global level.

The opportunities and hurdles of edible insects in food and feed were reviewed recently (Dobermann *et al.*, 2017). The authors pointed out a great number of favourable aspects in rearing insects, like reduced land, water and energy requirements compared to cattle, swine or poultry production. Thus reducing the emission of greenhouse gases and the overall environmental impact, while on the other hand maintaining the amount of micronutrients in insect products. In addition the economic impact this sector can have for Europe, was demonstrated on the existing collection and distribution chains of farmed (and wild collected) insects in Southeast Asia. Authors concluded that for the combined insect market in the US, Belgium, France, UK, The Netherlands, China, Thailand, Vietnam, Brazil and Mexico has the potential to growth to 398 million GBP by 2023. However, this year's prediction by *Research and Markets* (2020) corrected this amount up to a global of $1.39 Bn for the insect feed market alone in 2024.

The hurdles that Dobermann et al. (2017) pointed out were mainly the lack of research and the need for innovation within the sector. Authors concluded that those natural toxins that were so far subject of research may not play a role as a hurdle. However, the aspect of the valorisation of not yet established insect feed resources was not sufficiently addressed to support this conclusion. However, the valorisation of new product streams play an ever growing role in the insect rearing sector.

The EU Community Research and Development Information Service lists numerous EU funded projects on the use of insects (cf. CORDIS 2019), such as the *International Platform of Insects for Food and Feed* (http://IPIFF.org), *SUSINCHAIN, INFOOFEE, PROteINSECT, BUGBOX, FARMYNG, inTECH, FreezeM, IFASA 2, Hexafly, ECBCBSFII, NextGenProteins, ENTOMICSBLUEGROWTH, MedFly* and *Zelcor*. The findings of these projects confirmed the importance of reared insects as food and feed and beyond.

Other EU projects listed in CORDIS focussed on the ecological and economical benefit of using (currently) economically low value substrate materials from commodity side streams for valorisation *(WaysTUP!, INTERWASTE, InDIRECT, SCALIBUR, SLYFEED, REFRESH, DyCLE*). However, the topic of possible natural contaminants present in such substrates was no subject in such projects.

All the above research projects nourish the trend towards growing insect rearing businesses as it was highlighted in the Belgian newspaper "*De Standaard*" in 2019 (De Standard 2019). Eventually a growing insect rearing sector will require sufficient input of caloric substrates and requires specific attention regarding its quality and safety.

Novel resources and production processes in the food and feed chain

- *The current EU food law is efficient to address known public health concerns and new potential threats once identified.*
- *The identification of potential and likely threats due to the use of novel substrates need urgent investigation.*
- *Expertise from additional scientific fields beyond established food/feed safety disciplines is key regarding the use of novel feeding substrates for insects.*

In Europe undesired substances (contaminants) of public health concern in food (and feed) have been largely assessed for their health risk by the European Food Safety Authority and are regulated whenever a potential health risk is identified.

Consequently, the current food and feed systems protect public health and animal welfare. A prerequisite for this is the (sufficiently) fundamental understanding of the "farm to fork" chain. These food systems and understanding of the food and feed chain set the basis for food and feed law-enforcement and facilitate a harmonised and transparent market for all stakeholders and consumers.

The valorisation of yet unused FSCW or other commodity side streams as novel sources to (re)enter the "farm to fork" cycle, can turn into a game changer (Morone et al. 2017). The processes and the associated risks must be sufficiently understood to avoid unexpected effects on human an animal health. The **entrance of commodity side streams for rearing insects is fundamentally different** from that used for vertebral animals due to their different metabolic features.

Therefore, the key question of entomophagy is not insects as such but the required food/feed safety provisions of valorising novel commodities that (re)enter the food or feed chain.

A further aspect is the difference between the production of whole insects and insect products. The processing of insects to e.g. protein powder, fats or chitin can **deplete or concentrate certain contaminants**, depending on their physico-chemical properties. The so called persistent organic pollutant (POPs) such as dioxins, PCBs, DDT and other organo-chlor pesticides generally tend to bio-accumulate in the food and feed chain as they are of robust chemical nature and lipophilic. Because of their persistence, the POPs are usually regulated horizontally across the food chain. The presence of natural (bio)toxins on the other hand cause safety concerns. As a result they are regulated only in specific products.

Nonetheless, a few cases are known, where biotoxins, transform into more critical substances than the parent toxin. A well known example is the endocrine active mycotoxin zearalenone. Others accumulate in the living animals without effects for the accumulating animal. In particular some marine biotoxins bio-accumulate this way.

Natural toxins and the valorisation of (novel) side streams for rearing insects

<u>Mycotoxins</u>

- *Valorisation of novel resources for rearing insects (e.g. marine algae, (food) waste as well as wasteland and forest biomass) need to verify as safe.*
- *A risk assessment is challenging where novel resources/processes are not established yet for livestock production.*
- *Additional expertise outside the current food and feed safety disciplines should be included for a safety assessment (e.g. marine and botanical scientists, environmental ecologists and mycologists).*

With respect to the public health risk related to the presence of **mycotoxins** in the current food and feed chain there is appropriate legislation in force. This legislation targets specifically toxins known to be potentially present at levels and occurrence rates relevant for public health.

Some mycotoxins might not necessarily be harmful for rearing insects as they are detoxified or excreted without any negative effects. The robustness of insects fed on mouldy cereals containing high levels of aflatoxin B_1 has been described (Zhao *et al*. 2018).

Aflatoxin B_1 conversion in black solder flies (BFS) has been described when fed extremely contaminated material. This lead to the metabolites aflatoxin P_1 and aflatoxicol; both similar toxic as aflatoxin B1 (Meijer *et al*. 2019). A number of additional metabolites from mycotoxins were studied and metabolite levels in insects were only quantifiable when insects were fed material exceeding significantly levels established for complete animal feed (Camenzuli *et al*. 2018). This gives indication that insects are rather tolerant to aflatoxins, but provisions must be taken that no further transfer of the aflatoxins or their metabolites happens along the food chain.

Similar provisions apply to the above mentioned mycotoxin zearalenone (ZON). Various studies on this mycotoxin showed that mealworms (and probably other insects as well) convert ZON to α-zearalenol (Hornung 1991) and other endocrine active metabolites (Stroka, *et al.* 2017, Camenzuli *et al*. 2018, Niermans *et al*. 2019). Despite the fact that mealworms excrete the zearalenone and its metabolites within 2 days, it must be considered that α-zearalenol has a 60 times higher endocrine (toxic) activity than ZON itself (EFSA 2017). The fate of the produced manure remains therefore a matter of concern even when worms fed with substrates complying with Commission Recommendation (2006/576/EC) that indicates a tolerable level of 3 mg/kg ZON.

Eventually manure might contain "zearalenone equivalent levels" equivalent to 60 mg/kg ZON based on the observed conversion rate of 30% from ZON to α-zearalenol (Stroka, *et al*. 2017).

Other mycotoxins deserve attention when resulting from substrate degradation, such as composting (Dellino *et al*. 2017). Given the case that composting food site streams become subject to valorisation by insects, the fungal strains involved in composting and their different toxin production profiles become need to be identified and controlled. A concise overview on mycotoxins with lesser relevance for public food safety was published already in 1994 (European Commission 1994). It is important to note that the synthesis of mycotoxins is a function of the substrate, the environmental factors and the fungi itself.

Two principle mycotoxin candidates that may gain relevance when processing former foodstuffs or food waste are sterigmatocystin (a mycotoxin with a similar toxicity and carcinogenicity as aflatoxin B1) and gliotoxin. Globally abundant fungi produce these toxins and the presence of these toxins is associated with "poor quality products" on the market. Their occurrence in "food waste" or processed FSCW has however not been studied yet.

Sterigmatocystin (STC) has been described in a number of processed products with a high fat content (e.g. cheese and fermented sausages). Despite its high carcinogenic potential, it is not regulated in the EU due to its assumed low occurrence rate. The European Food Safety Authority has published a scientific opinion on STC and came to the conclusion that more data is needed to allow a dietary exposure assessment (EFSA 2013). It was also pointed in the EFSA scientific opinion that the analytical methods need to have a sufficiently low limit of quantification (LOQ) to scrutinise the exposure avoiding the number of left censored data sets (→data below the LOQ).

Gliotoxin is produced by *Aspergillus fumigatus*. This is one of the few fungi that still can perfectly grow at 37° C. Thus not only its metabolites are critical to human health, but it has in addition the potential to infect endothermic "warm-blooded" animals including humans and causes a life threatening condition called aspergillosis. Its vivid spores have been isolated across the whole globe and seem to play an important role in the occupational exposure of poultry workers (de Oca et al. *2017*) and it targets the lung immunity (Arias *et al*. 2018). This might be - though hypothetical - of relevance during exposure with other lung pathogens like the SARS-CoV-2 virus. The natural habitat of *A. fumingatus* is soil and decaying organic matter such as compost. Eventually evidence based guidelines for insect rearing at industrial scale seem of need ensuring that fungal pathogens and their metabolites do not interfere with public health. The number of fungi that can infect insects and possibly produce lesser-known mycotoxins is higher than that of endothermic livestock. Conditions for safe operation in this new sector is therefore an important aspect.

The general principle of valorising organic household waste and its conversion to insect biomass was recently studied (Meneguez *et al*. 2019). In parallel the transformation of other novel substrates such as forestry biomass for rearing insects was studied (Varelas & Langton 2017). A similar target is followed by the *SLYFEED* project. The aim is to transform paper mill waste to feed for fish. Such transformation of paper mill waste can be achieved by chemical and/or biological (enzymatic) processing, involving insects.

These insects than may serve for animal production in a comparable manner as described by Biancarosa *et al*. 2019. A key aspect in such studies is the reduction of process energy. The utilization of processed resources not only needs to consider the occurrence and possible accumulation or depletion of undesired substances but also the fate of nutritive consituents like trace elements and minerals.

The methodologies to study the presence of numerous mycotoxins are at hand, but need to be tailored to fit the substrates under investigation. Screening methods such as the ones developed for numerous mycotoxins and other microbiological metabolites (Habschied *et al*. 2019; Malachová *et al*. 2014) consequently will give a deeper understanding in the profiles of natural contaminants in FSCW. However, such methods require sufficiently low limits of detection (LOD) as pointed out before (EFSA 2013).

Plant toxins

- *Numerous abundant plants produce natural toxins or anti-nutritive factors.*
- *Insects can make use of such toxins for their own survival, or tolerate relative high levels*
- *The valorisation of plant biomass in insect rearing requires a specific risk assessment*

Regarding toxic substances of plant origin, the European Food Safety Authority listed around 900 botanicals in its *Compendium of botanicals reported to contain naturally occurring substances of possible concern of human health when used in food and food supplements* (EFSA 2012). Such botanicals could unintentionally also find a way into the food or pharmaceutical product chain when co-harvested as it was reported in recent years (Adamse *et al*. 2014, Letsyo *et al*. 2017). On the other hand, their toxins may also enter the food chain via insects (Kempf *et al*. 2011). Globally the number of toxic plants on wasteland is by multitudes larger than those 900 botanicals listed in (EFSA 2012).

Great efforts are made by the Network on Natural Toxins in Aquatic systems (NaToxAq) identifying those plants that are potentially relevant for ground and surface water contamination (e.g. when leaching out with rain during decay). It is important to note that only plants with a wide, even though geographical locally, occurrence play a relevant role. A list of such candidates is published on the project page of the *NaToxAq* consortium. The likelihood that such plants will unintendedly valorised deserves consideration. The possible transfer of their toxins along the food chain via reared insects barely known. The sustainability aspects and the safety assessment using insects-based bio-refinery conversion of organic-matter side-streams into multiple marketable products were addressed by the EU projects *InDIRECT* (http://www.bbi-indirect.eu/) and *ZELCOR* (http://zelcor.eu/). This indicating the safety interest of novel products. However the focus of these projects did not consider the here discussed concerns of natural toxins.

A number of plants producing toxic substances of public health concern like the invasive and wide spread plants *Senecio jacobea* (aka ragwort) or *Equisetum palustre* (aka horsetail) have gained recently attention regarding the safety for bee keeping (honey) and forage production.

Senecio species produce the carcinogenic pyrrolizidine alkaloids (PAs) that cause seneciosis in animals (aka Schweinsberger disease) and liver failure in humans. In many cases animals avoid grazing for PA plants. However, they feed on it when presented as silage (see Picture 2). PAs are taken up by bees when collecting nectar and may end up in honey. However different than the before discussed insect species that target PA sources, the transfer by bees seem to consequential when collecting nectar on flowers of PA producing plants, rather than intentional. PAs can also can be detected in other animal products (e.g. goat cheese or eggs) if taken up by poultry or goats.

What makes this scenario somewhat complex is that **numerous (specialised) insects employ special metabolic pathways to transform and accumulate PAs** from the plants they consume in their natural habitat. The substances are believed to serve the insect as protection-agents from potential predators. A well-known European example is the larva of the cinnabar moth (*Thyria Jacobaeae*) that accumulates the carcinogenic pyrrolizidine alkaloids (PA) to levels 10 times higher than it occurs in the plant they graze on (*Senecio Jacobea*). The cinnabar moth is shown in *Picture 1* later in this report. The same accumulation occurs in African grasshoppers of the genus *Zonocerus*, a known agricultural pest in Africa (Bernays, *et al*. 1977). In fact, these insect species target plants with the highest toxin level as these benefits their survival. Also a number of butterflies target PA containing plants to stock PA for their eggs (protection) but also for pheromone production. These examples relate to the favoured toxin uptake by the insect and eventually bio-accumulation.

Own research at the JRC-Geel has shown that not only *Zonocerus* but also the (non specialised) grasshopper *Locusta mirgrtoria* may hold PA when fed on *Senecio jacobea*. However, levels found are significantly lower than those found for *Zonocerus*. Yet, following the recommendations by the Federal Institute for Risk Assessment (BfR) in Germany (daily intake limit of PA 0.007 µg/kg of body weight) the levels result that a consumption of these grasshoppers would limit to less than one gram per day if they are fed on *Senecio jacobea* and consumed immediately.

Picture 1: Various aspects of *Senecio jacobea*

Partially harvested wasteland meadows infested with *S. jacobea* in Germany (with permission of *Arbeitskreis Jakobkreuzkraut e.V.*) and *Thyria Jacobaeae* grasing on *S. Jacobea* at the JRC in Geel.

Horse selectively avoding *Senecio* while grasing. (with permission of *Landwirtschaftskammer Nordrhein-Westfalen*).

E. palustre (horsetail) produces toxic alkaloids as well as a thiaminase, resulting in debility of affected animals. Outbreaks often occur when plain landscapes are used for the production of forage. This is promoted as it is the only cost effective husbandry method to maintain these valuable landscapes for breeding birds. The increasing occurrence of both plants in Europe are due to other changes in land use (e.g. use as flood zone to protect urban areas) as well as invasive plant migration. The toxic potential of products containing these plants is not always properly identified. Proper guidance and rules are needed for stakeholders of the insect rearing sector in order to provide suitable (non-toxic) products when making use of products from natural landscape resources.

Picture 2: Plain landscape of wasteland that is typically fested with *E. palustre* and often utilised by farmers for forage production (Ochsenmoor, Germany) with exemplary detailed view of *E palustre* alone (bottom right).

Picture (large) with permission of *Oliver Lange (NLWKN - Naturschutzstation Dümmer)*
Picure (bottom right) with permission of Luc Viatour - https://Lucnix.be

Some European plants with a lower awareness level regarding their toxicity can become a risk factor, too, when are co-harvested during attempts to valorise other resource. The phenomena of the Balkan Endemic (Familial) Nephropaty (BEN or BEFN) is such an example. According to Debelle *et al*. (2008) at least 25.000 individuals suffered from BEN and suspect figures exceeded 100.000 individuals in 2008. BEN was initially associated with dietary mycotoxin (ochratoxin A) intake. However recent research points to aristolochic acid (AA) as causative agent, a toxin produced by plants of the genus *Aristolochia*. Similar to the behaviour of ptaquiloside from bracken fern, AA can be taken up by the roots of other agricultural plants from the soil when *Aristolochia* plants decay in direct neighbourhood (Chan *et al*. 2019). In any case, the epidemiological effects observed with BEN indicate that a long-term sub chronic exposure is the likely cause. This leads to fatal renal dysfunction and cancer as it occurs in the concerned regions along the Danube river (*Picture 3*).

The fact that insects specifically interact with *Aristolochia* has recently been described (Slancarova *et al*. 2015) and it was demonstrated that certain South American butterfly larva which preferably feed on *Aristolochia chilensis*, take up AA during larva development (Urzúa *et al*. 2013). *Aristolochia elegans* plants grown on the premises of the JRC-Geel have shown insects bites leading to the assumption that local insects prefer to feed on their leaves in nature, too.

Given that insects are potential prey for free-running poultry, a insect→chicken→egg route could be another, yet rather hypothetical contributor for BEN. This route leads indeed to further fragmentation of the already discussed possible routes. Nonetheless, the route *Plant →Insect→Livestock* could involve a risk factor if aristolochic acid enters the insect rearing cycle.

Picture 3: Balkan endemic nephropathy map

Topographical distribution of Balkan endemic nephropathy. The geographical foci (brown areas) show the areas with endemic nephropathy associated with urothelial cancer. https://commons.wikimedia.org/w/index.php?curid=24724241

Harmful plants with potential

- *Not all plants viewed as harmful need to be a problem for the insect rearing sector*
- *Toxin decomposition by insects can be a gateway to utilize otherwise critical resources*
- *Research should close knowledge-gaps on the use of "unconventional plants" for valorisation*

Other plant species that are considered toxic or harmful have a history as forage or even as valuable food resource. Bracken ferns are very abundant and spread across Europe. This makes them a potential candidate for substrates in the insect rearing sector. In the past bracken ferns have been used to feed cattle or even as specialty food (in Japan). However, a link between the consumption of milk from cows feeding on bracken ferns and human cancer based on epidemiological data (Alonso-Amelot & Avendano, 2002) since their carcinogenic potential was identified for ruminant and non-ruminant animals (Shahin *et al*., 1998). The toxic substances found in bracken fern is the possibly carcinogenic *sesquiterpene* ptaquiloside. As this can cause problems for drinking water suppliers the topic is research subject within the *NaToxAq* network. At this moment there is no information available about the risks when bracken fern is used as insect feeding substrate. Information on the metabolism in insects and possible process degradation of ptaquiloside would be value for the insect rearing sector as it could open a way to a safe valorisation of these plants.

Picture 3: Bracken fern in various locations in Europe

Bracken fern near Malaga, Spain

Bracken fern near York, UK

The geographic spread of this plant species and its ability to incur large areas with different climatic conditions show its invasive character
(Pictures with permission of *Daniel B. Garcia Jorgensen – University of Copenhagen*)

Picture 4: Bracken fern biomass and landscape coverage potential

Bracken fern near Humleore, Denmark

Bracken fern near Gribskov, Denmark

This picture demonstrates the magnitude of hight that bracken fern can reach in summer (<200 cm) with a density of about 1 kg dry matter per square-meter as well as the invasive coverages of plain areas (Pictures with permission of *Daniel B. Garcia Jorgensen – University of Copenhagen*).

Invasive plants by nature have an evolutionary advantage. This is in particular true for hogweed, which is considered a pest in Europe (Stojanović *et al*. 2017; Vladimirov *et al*. 2019) and beyond. In particular, *giant hogweed* and *Sosnowsky's hogweed* (*Heracleum mantegazzianum; H. sosnowskyi*) have migrated along international traffic routes from the Baltic and occurs in 19 European countries (Pyšek *et al*. 2010). Hogweed produces phototoxic furanocoumarins, leading to massive skin burns when damaged parts of the fresh (!) plant are touched. As a result, it is actively controlled and fought (Kabuce & Priede, 2010).

However, hogweed found a niche for cultivation in the past. It was grown for silage production, but also as honey plant and fowl forage (hogweed seeds) in the former USSR mid of last century. The cultivating was at large scale due to the frugalness of hogweed regarding intervention and soil quality, while being of nutritional value for livestock. As result of the availability of other cost effective alternative feed sources in the USSR, hogweed lost its attractiveness.

Currently hogweed occupies roughly 50 Mio ha in the region from Caucasus to Europe as the result of uncontrolled spreading following its cultivation. Combatting the spread of hogweed is more an economical than a technological factor. Having in mind that hogweed has a proven history as livestock fodder, an unorthodox approach fighting the uncontrolled spread could be its valorisation for rearing insects.

If research shows its safety this could lead to new business sectors, given hogweeds modesty in need of intervention and soil quality. Nonetheless, such a projection is hypothetical and its realisation would require a suitable political and safety framework. It nonetheless shows that noxious plants may also surprise with constructive aspects for novel feed sectors, leading to incentives for combatting their uncontrolled spread.

A plant that plays an important nutritional role in Africa is cassava. A known issue is that in particular those cassava varieties with a higher level of (toxic) cyanogenic compounds show a higher resistance against pests under environmental stress conditions (drought). If preparation allows a sufficient degradation of the toxic substances, cassava is suitable for human consumption. If degradation is not complete, poisoning outbreaks can occur and have been described (Centers for Disease Control and Prevention 2019). As the degradation of the cyanogenic toxins is usually done enzymatically the pest resistant cassava varieties might be a suitable substrate for insects possessing a detoxifying capability. In return, the toxic crop offers advantages under stress compared to low toxin varieties. However, the identification of suitable crop- tolerant insect matches will be prerequisite for a successful implementation of such an approch. Though this example is somewhat hypothetical, it indicates the possibilities making use of nutritionally unattractive crops while inheriting other important advantages when appropriate insects can act as game changer. Candidate insects for such approaches have been discussed recently by Zagrobelny *et al*. (2018).

The examples above demonstrate how invasive species that may populate large landscapes as dominant or solely species can gain attraction as target for valorisation in circular ecology.

The silent neurotoxins – Latherysm and Amyotrophic Lateral Sclerosis/Parkinsonism–Dementia Complex (ALS/PDC)

- *Neurotoxins can occur on our plate e.g. when biomagnified along the food and feed chain*
- *Neurodegenerative diseases are a challenge of an aging society and an active research field*

Pea grass (*Lathyrus sativus*) is remarkably robust to climatic stress that resists to droughts and tolerates a variety of soil composition while yields are moderate compared to other plants cultivated for food and feed production. The flour of its seeds was used for long as staple food in tough times. However, the prolonged consumption lead to permanent paralysis of the limbs.

Francisco de Goya drew "*Gracias a la Almorta*" (1812) depicting the public health issue of latherysm in Spain in his times. Note: Almorta is the Spanish name for *Lathyrus sativus.*

Oxalyldiaminopropionic acid (ODAP) is the chemical agent causing latherysm (Rao *et al*. 1964), an analogue to the neurotransmitters derived from glutamic acid (Figure 3).

Figure 3: Glutamic acid and its toxic analogs

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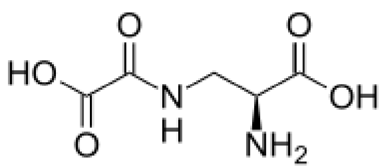
<td>
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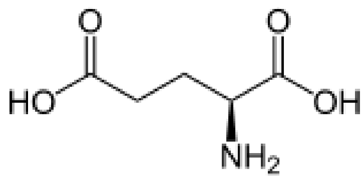
<td>
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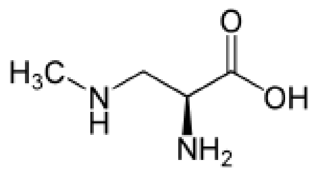
<td>
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<tr>
<td>Oxalyldiaminopropionic acid (ODAP)</td>
<td>glutamic acid</td>
<td>beta-methylamino-L-alanine (BMAA)</td>
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Pea grass has a potential as a forage and energy source, for insects. Hence, the possible transfer of ODAP into the human diet should be carefully assessed if used for the production of insect as food.

Another toxic analogue of glutamate is produced by various cyanobacteria (CB) (Cox *et al*. 2005). These CB produce a compound called β-N-methylamino-L-alanine (BMAA) Figure 3.

Even though CB are not normally included in the food and feed chain, they are present throughout the ecosystem, ranging from terrestrial habitats to fresh water and oceans (Cox *et al*. 2005) and they can metabolically interact with higher plants (Ray *et al*. 2000). Unfortunately, certain ethnic groups did consume BMAA that accumulated along the food chain, hence triggering an increase of devastating neurodegenerative diseases (ALS/PDC) as observed on the pacific island of Guam. Recent and on-going research evidenced a biomagnification of BMAA throughout the food chain. Elevated levels are found in shark fins (Mondo et al. 2012) and certain bats (Banak and Cox 2003). Similarly, regional sporadic occurrence of neurodegenerative diseases in Europe and North America seem to be related to BMAA exposure (Masseret *et al*. 2013, Andersson *et al*. 2013, Field *et al*. 2013) as BMAA was found in the dissected brain tissue of former patients (Bradley and Mash 2009). However, there are also different views that question the impact of BMAA to cause neurodegenerative diseases (Chernoff *et al*. 2017).

In view of the increasing number of neurodegenerative diseases in an aging society, the valorisation of natural resources like forest biomass waste (Varelas and Langton 2017) or novel marine products (Alburquerque *et al*. 2019) as insect or other livestock fodder requires proper risk assessments.

The toxins from the marine world

- *A number of algae currently studied in the feed chain (for edible insects) classify as safe*
- *A recent migration of toxic algae (into European waters) and changing algal metabolism makes it difficult to predict the risk of uncontrolled algae use in the insect sector, as marine biotoxins count for some of the most potent toxins known to man.*

Macro alga will play an important role in the future for fish feed in aqua culture. The increasing prices for fishmeal as feed led to the search for alternative protein sources in livestock production (Yu *et al*. 2020) and aqua culture. Since fish do not tolerate carbohydrate rich feed (e.g. cereals) insects are a very valuable substitute to fishmeal. An elegant and novel way introducing the marine nutrients into the fish feeding cycle is rearing insects preferably on a mix of cereals (to deliver the caloric energy) in combination with marine substrates such as macro alga. This procedure allows the substitution of fish meal to a large degree.

Recent publications address feed safety aspects regarding the use of macro alga and its potential to replace fish meal (Liland *et al*. 2017; Biancarosa *et al*. 2019). While this seems to be a prosperous practise, future developments in the change of the marine eco-system need consideration for sustainable practices.

The global and frequent re-occurring seaweed tides in recent years (Smetacek & Zingone 2013) could turn to low-cost resources for fish aqua culture. Similar valorisation practices are currently studied for other agronomic purposes (Alburquerque *et al*. 2019). It was however recently reviewed that a number of seaweed species that are consumed in the pacific region also can lead to severe intoxications or lead to death, as seaweeds have the capacity to produce numerous potent toxins (Kumar & Sharma 2020). One group of highly toxic group of substances was identified in animal experiments as prostaglandins, which are also mentioned by Barbier *et al*. (2019). As a result, Kumar & Sharma (2020) highlight the "need of guidelines over the limit and quality of consumption of the seaweeds by the regulatory bodies including specific drug seaweed interactions". If such seaweed enters the feed chain via edible insects, the statement by Kumar & Sharma deserves expansion.

In addition, the observed global migration of toxin-producing dinoflagellates (single cell algae) and marine bacteria need consideration for the safe valorisation of seaweed. This development cannot be neglected as some toxic single cell algae reside – visually unapparent - as epiphyte on seaweed.

In particular, the current migration trends of the dinoflagellate *Gambierdiscus toxicus* to new regions in the oceans is such an example. *G. toxicus* produces the so-called chigua toxins (CTX) shown in Figure 4, a group of very potent toxins that cause severe and long lasting health issues as well as death in humans. Alarming is that *G. toxicus* appears to possess the ability to reside on virtually any marine seaweed and has recently spread to European coastlines. As a result, the EuroCigua project, co-founded by EFSA, targets possible counteraction strategies to protect EU citizens from this threat since autochthonic intoxication cases are on the rise in Europe (EuroCigua 2015).

Different from most other dinoflagellates that are responsible for various types of shellfish poisoning, CTX bio-accumulates along the feed chain that starts commonly with smaller fish, which graze on the macro algas' surface for *G. toxicus* (and other micro alga). It however does not affect any fish along the feed/food chain. Until now, human CTX intoxication (including death and long lasting neurological effects) is exclusively associated with the consumption of larger predator fishes like red snapper, barracuda, grouper, amberjack, sea brass or Spanish mackerel. Due to the enormous toxicity, the tolerated levels in fish for consumption have been set by the US FDA, to <0.1 µg/kg for cigua toxins of the CTX-1 group (e.g. in the Atlantic) and <0.01 µg/kg for the Pacific CTX group.

It seems possible that CTX, like any other lipophilic polyether toxin of this group (e.g. maitotoxin shown in Figure 5), will also accumulate along the chain: "Seaweed → edible insects → fish". As the edible insect rearing sector is relatively new and *G. toxicus* occurance relatively rapid expanding virtually no data is published on this matter. The potential bio-accumulation and metabolism of marine biotoxins in insects are urgent questions requiring scientific answers.

Figure 4: Ciguatoxin (CTX)

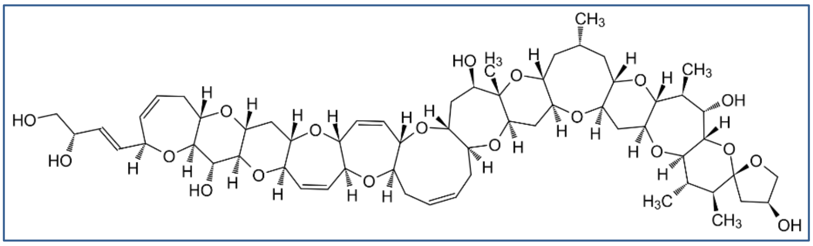
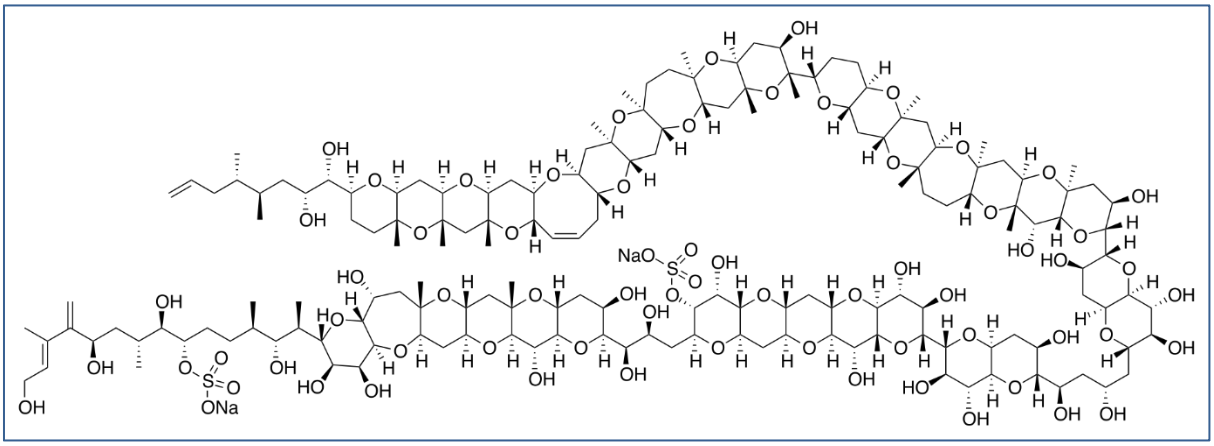


Figure 5: Maitotoxin



The situation where seaweed of various kinds, other than the proposed seaweed *Ascophyllum nodosum* (Liland *et al*. 2017; Biancarosa *et al*. 2019) will end up as substrate for edible insect rearing is an consequential step, as soon as economic pointers signal profitability. This will add to the generic risk of unintentional use of native toxic seaweed as it has been described (Yotsu-Yamashita *et al*. 2004; Kumar & Sharma 2020).

A recent overview on the use of aqua cultured seaweed for the European market is given in the report regarding *European Guidelines for a Sustainable Aquaculture of Seaweeds, COST Action FA1406* (Barbier *et al*. 2019). This report addresses also marine biotoxins, but it limits the examples to prostaglandins and kainic acid.

The role of regulatory bodies

- *EU legislation regulating the market in order to promote consumer safety is often viewed critical by investors in the food market.*
- *Historical examples however show that consumer protection regulation can be beneficial to all stakeholders, leading to safer products, higher market prices and broader global marketability.*
- *Predictions on the regulatory effect on markets therefore need a holistic view for a sound conclusion.*

Safeguarding animal and human health along the food chain, while setting a legal framework protecting stakeholders from unfair and unsafe competition always is a challenge. In particular, the edible insect sector requires regulatory action to serve all involved parties.

The setting of different legal frames at various national and the international level to regulate safe market operations regarding edible insects has already critically been described (Lähteenmäki-Uutela *et al. 2018*). Legal frames nonetheless promote fair and transparent trade. They eventually support the stability of the market and trade when properly supported by adequate action plans.

A good example for such a development was the introduction of a European regulatory frame on the presence of mycotoxins in food at the beginning of this millennium. The initial concerns of the World Bank were that this European Union initiative would results in drastic negative effects for importing country leading to inequity (Otsuki et. al., 2001).

In the aftermath, this projection had to be revised 4 years later by the Worldbank (2005). The inevitable changes that exporters had to adopt to in order to continue trading with the EU, led largely to benefits for the exporting countries. The (obligatory) implementation of HACCAP systems and Good Manufacturing Practice (GMP) schemes in combination with specific training programs organised by the European Union, resulted in better quality and safer produce. The implementation of the whole initiative eventually had a positive effect on the trade relations with 3^{rd} countries, as it allowed producers to sell for higher international market prices. This is a good example for a win-win situation for all stakeholders, which was driven by EU strategies to improve consumer protection.

Conclusion

- *The edible insect sector supports EU policy to eliminate hunger in a greener environment*
- *The vastly expanding possibilities in edible insect production require a safe and adequate legal frame.*
- *The JRC has the capacity by proven expertise to provide scientific support to the legislators*
- *Establishing a common platform for legislators, researchers and stakeholder with relation to rearing insects and the valorisation of novel resources is highly advisable.*

Entomophagy is a valuable element in the strategy to eliminate hunger, foster a circular economy and a number of other political ambitions such like the European Green Deal. Rearing insects for food and feed will have to be accompanied by use of novel nutritional resources used for rearing. These resources are likely to be different from those used for conventional (vertebrate) livestock production. A number of novel substrates for insect rearing are proposed in the literature for valorisation, like organic matter from forestry, seaweed from the oceans as well as materials from other side streams of the food chain. Such activities will create new business models for insect producers. A critical view on the safety of these substrates is therefore needed to protect human health.

The fate of already known but yet not completely identified (natural) contaminants requires attention in the process of rearing edible insects, as the toxicological properties of some novel feeding substrates are not sufficiently understood. Resultantly any future risk assessment on the use of reared edible insects must in addition on the substrate properties, rather than insects *per se*.

Any valorisation of novel substrates without such a proper risk assessment would conflict with the food safety policy of the European Union and extensively discussed as a general issue by Morone *et al*. (2017). A main challenge for conducting such risk assessments is the involvement of experts beyond classical food and feed safety as the valorisation of novel substrate resources includes resources outside the current food and feed chain as this adds to the complexity of this new sector.

An initial step getting hold on this challenge could be gathering recognised experts from the various relevant fields and organise targeted symposia with scientists, private stakeholders and legislators (risk assessors and managers) to identify and discuss gaps of knowledge. In particular the here highlighted aspects like environmental ecology, agronomy, mycology, botany, toxicology, industrial processing, entomology and nutrition seem to deserve attention. A list with action plans for research needs should be a target outcome of such symposia.

The JRC has the capacity to organise such symposia and has shown in the past that such approach can bring all stakeholders from industry, research and regulatory bodies ahead to deliver the basis for consumer safety in combination of prosperous markets and income in such a sector.

Acknowlegements

Authors wish to acknowledge Prof. Dr. Hendrik Emons for his valuable comments and reviewing of the manuscript, and Mrs Katrien Bouten for many inspiring discussions and providing the latest literature.

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