Husbandry and Nutrition

Review

Aryl Hydrocarbon Receptor Agonists as Contaminants in the Feed of Production Animals

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ABSTRACT

Background: Human and animal health are closely related. A lot of foods and feeds may contain toxic substances, and though most chemicals have a safe use range, they can be harmful when consumed in high doses. **Aim.** To stress on the importance of environmental control to minimize the risk of poisoning by dioxin and dioxin-like substances in the production of feeds for farm animals, and foods for humans. **Development:** Dioxins and PCB dioxins (polychlorinated dibenzo-p-dioxins or PCDD comprise 75 dioxin-like substances), furans (polychlorinated dibenzo-furans comprising 135 furan-like compounds). Only a few substances from each group are toxic. The aryl hydrocarbon receptor (AHR), also known as dioxin receptor, is present in numerous animal species, activating gene expression in a ligand-dependent manner. The ligand prototype 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is an archetype dioxin known to be one of the most powerful dioxin-like substances. The presence of dioxins in animal tissue depends on feeding, at certain levels it may cause cancer, disorders of the immune and the nervous systems, liver lesions, and sterility. **Conclusions:** This study demonstrates the importance of environmental control to minimize the risk of poisoning by dioxins and dioxin-like substances in the production of feeds. The personnel in charge of animal production should know more about these compounds and collaborate in identifying the possible dangers and risk levels.

Keywords: farm animals, food contamination, dioxins, bHLH-PAS proteins, aryl hydrocarbon receptor (*Source*: *MESH*)

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INTRODUCTION

Managing widespread world sanitary risks, from disease control to global warming cannot be assumed individually, it requires total cooperation from the animal and human health sectors, and the environment. The acknowledgement of a shared responsibility between humans, animals, and the ecosystems has led to the concept of One Health, which aims to encourage multiple sectors to work together to achieve the best results. (Guardo, 2018).

Food science is in charge of the study of the physical, chemical, and biological properties of foods, safety, nutritional, sensorial, and sanitary quality, stability, manufacturing and preservation processes. Food chemistry, which is fundamental within food science, tackles food composition, properties, and chemical changes throughout handling, processing, and storage in environmental conditions compatible with life (Damodaran and Parkin, 2017).

Back in the sixteenth century, Paracelsus expressed the classic maxim of toxicology: "All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison." (Jiménez and Kuhn, 2009). This concept is often condensed as: "The dose makes the poison". Every drug and toxic substance are capable of causing an effect by joining to receptors, being named *agonists*, for which they must have affinity through the receptor and intrinsic activity (Jiménez and Kuhn, 2009). Harmful or toxic substances may also be part of foods accidentally, due to direct contamination, environmental contamination as a result of processing, or deliberate doctoring to achieve economic benefits. The key lies in identifying the safe level, or the level without adverse effects (NOAEL) (DeMan *et al*., 2018).

The Ah receptor (AHR) has been studied for almost five decades. However, there is not clear understanding of how this protein mediates the adverse effects of a variety of environmental contaminants, such as polycyclic aromatic hydrocarbons (PAH), chlorinated dibenzo-p-dioxins (dioxins), and many polyhalogenated biphenyls. The role of the Ah receptor (AHR) in human health and environmental toxicology continues to be an area of considerable interest (Mahringer *et al*., 2019; Avilla *et al*., 2020). In most cases, human exposure to dioxins derives from animal food, whose toxin burden comes mainly from feedstuffs.

Livestock raising is growing rapidly in the developing world, particularly through the intensification of livestock production systems characterized by high animal stocking density and land use, which require special attention in terms of biosafety, the occurrence of animal diseases, their control, and animal wellbeing and husbandry (FAO and IFIF, 2014). This paper aims to highlight the importance of environmental control to minimize the risk of poisoning by dioxin and dioxin-like substances in the production of feeds for farm animals, and foods for humans.

DEVELOPMENT

One health

The concept of One Health was introduced in the early 2000s to name a notion known for over a century: **human health** and **animal health** are **interdependent** and are **linked to ecosystems** where the they co-exist (*Soto, 2021*). FAO is promoting One Health in terms of food safety, sustainable agriculture, anti-microbial resistance (AMR), nutrition, animal and plant health, fishing, and living means (FAO, 2021).

Food chemistry

Food is every substance that contributes to the protection of every manifestation of animal life (production and reproduction) that consumes it. Food chemistry studies the structures, properties, and reactions of food components that bring about transformation that influences quality either negatively or positively. They take place during handling, making, processing, storage, conservation, and sales. It also deals with the study of contaminants that may be present in it. Food chemistry is thought of as the basic structure of foods in science and food technology, as it studies the biological substances and the changes they undergo when exposed to a broad range of environmental conditions, the chemical properties of hampered food tissue, unicellular sources (eggs and microorganisms), and one of the main biological liquids: milk (Badui, 2006; Damodaran and Parkin, 2017).

From a livestocking perspective, foods are every substance used by man to feed animals directly or indirectly, so they can maintain the vital functions normally, reach the corresponding body development, and yield the expected results. Feeding can never be considered a recipe, it is the farmer's responsibility; a dynamic process that demands knowledge, observation, and proper performance. Farmers should know best how the farm is going, the types of foods available, hay production, silage, or feeds, as well as the state of cattle, sheep or pigs (Rodríguez, 2001).

In principle, animal feeding seems like a simple task; cattle, swine, poultry, etc., have fed perfectly well for a long time without man's intervention. Whenever man has intervened in the domestication and selection of animals, improving breeds, and seeking production and yields that otherwise would not be accomplished in nature, animal nutrition has complicated. Accordingly, the study of diet composition is important. (Rodríguez, 2001).

In a broad sense, food safety means that when a food is consumed, it must be free from any harmful chemical or microbial contaminant. According to the *Codex Alimentarius*, it is the assurance that a food will not harm consumers when it is prepared or ingested, depending on the use given (PAHO/WHO, 2021).

Foods are the main source of exposure to pathogenic agents (viruses, parasites, bacteria), to which no one is immune. Certain levels of these contaminants lead to substantial risks to

consumer health, creating huge economic burdens to communities and nations (PAHO/WHO, 2021).

The chemical reactions caused by heat in the foods may be positive, as in the case of creating a desired flavor or other sensorial attributes; or they may be harmful, as in the generation of toxic chemical substances, such as polycyclic aromatic hydrocarbons (PAH) (Damodaran and Parkin, 2017). The concentration of PAH depends on the fat content in meat, roasting, and the heat source. Wong (2018) reported the presence of PAH in sausages, beef, pork, lamb, turkey, chicken, hamburgers, and bacon.

The aryl hydrocarbon receptor

Daily, animals and humans are exposed to a great variety of substances present in the air, water, foods, and feeds. Accordingly, they have developed a set of enzymes and carriers that facilitate the biotransformation and removal of these compounds (Larigot *et al*., 2018).

The aryl hydrocarbon receptor (AHR), also known as the dioxin receptor, is traditionally defined as a ligand-dependent transcription factor involved in biotransformation and carcinogenic/teratogenic effects of environmental toxins, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is an archetype dioxin known as one of the most powerful dioxin-like substances (Figure 1), toxic, halogenated aromatic hydrocarbons (HAH), and PAH (Corrada, Denison, and Bonati, 2017; Kawajiri and Fujii-Kuriyama, 2017; Weber *et al.*, 2018; Avilla *et al*., 2020; Falandysz, Smith, and Fernandes, 2020). The AHR belongs to the basic superfamily of helix-loop-helix (bHLH) / PER-ARNT-SIM (PAS) transcription factors, or simply, bHLH-PAS-type proteins. It is well conserved, and is found ubiquitously in mammal tissue, with variable expression levels between tissues, throughout life (Fribourgh and Partch, 2017; Wu and Rastinejad, 2017; Al-Ghezi *et al*., 2019; Mengoni *et al*., 2020; Kim *et al.*, 2020; Goya-Jorge *et al*., 2021; Torti *et al.*, 2021).

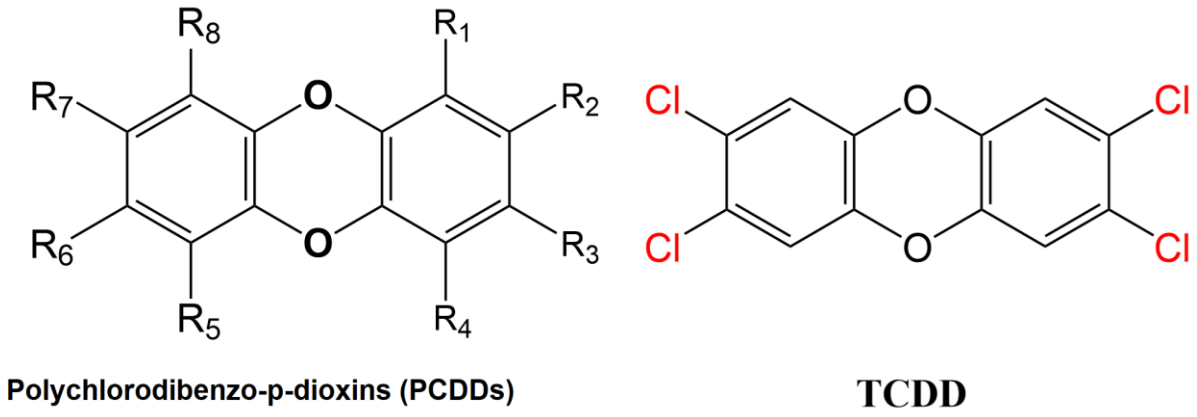

Figure 1. Dioxin-type structure with a polychlorodibenzo-p-dioxins (PCDDs) nucleus at position substitution of chlorine atoms. Structure of Tetrachlorodibenzodioxin (TCDD)

The AHR has conserved through evolution both in its domain structures and its functions; it is expressed in several tissues and plays a variety of functions in homeostasis. Upon ligand binding, AHR is translocated from the cytoplasm to the nucleus where it associates with the AHR nuclear transporter (ARNT) whose complex is further bound to the xenobiotic response element (XRE). The AHR heterodimeric complex: ARNT functions as a transcription factor responsible for the expression of genes that belong to the cytochrome family P450 (CYP), especially CYP1A1, CYP1A2, and CYP1B1. The first studies of AHR focused mainly on the toxicological aspect, due to its activation by dioxins, which are environmental toxic substances (Kawajiri and Fujii-Kuriyama, 2017; Wu and Rastinejad, 2017; Schulte *et al.*, 2017; Hattori *et al*., 2018; Larigot *et al*., 2018; Al-Ghezi *et al*., 2019; Aranguren-Abadía *et al*., 2020; Roztocil *et al.*, 2020; Kim *et al.*, 2020; Furue *et al*., 2021; Haidar *et al*., 2021; Kou and Dai, 2021). The activation of AHR is associated with an increase of the oxidative metabolism, and consequently, with the formation of, for instance, reactive oxygen species. Hence, this interaction with DNA in XRE is highly associated with the onset of further toxicity events that include carcinogenicity due to a prolonged AHR activity, development and reproductive toxicity, and immunological deterioration, known as dioxin toxicity effects (Szöllősi *et al.*, 2016; Corrada, Denison, and Bonati, 2017; Schulte *et al.*, 2017; Tuomisto *et al.*, 2017; Hattori *et al*., 2018; Danjou *et al*., 2019; Mengoni *et al.*, 2020; Sadik *et al.*, 2020; Goya-Jorge *et al*., 2021; Haidar *et al*., 2021; Zhai *et al.*, 2021). However, extensive studies during the last two decades have identified many endogenous AHR ligands, and have revealed numerous physiological functions of AHR, which are important for normal *in vivo* development, and for the regulation of the cardiovascular, gastrointestinal, nervous, and immunological systems, as well as on the skin and the circadian rhythm (Khazaal *et al*., 2018; Abdullah *et al.*, 2019; Esser, 2021; Kou and Dai, 2021).

AHR ligands

The TCDD, a sub-product of the orange agent, was identified as an AHR agonist, mainly because of chloracne, a skin disease caused by that product. Further analyses revealed that other xenobiotic compounds with TCDD-like structures, especially HAH and PAH, are also efficient AHR agonists, though their binding affinity to the AHR cavity and their transactivating activity may differ substantially. These compounds are quite abundant and persistent in the environment due to their long mean life and bioaccumulation in the trophic chain. Their toxicity in humans and other species has been widely documented, estimating that more than 90% of human exposure occurs through contaminated foods (Hattori *et al*., 2018; Torti *et al.*, 2021). Among the endogenous AHR ligands, there are a series of metabolites and tryptophan metabolic products, which have an important impact on homeostasis, by regulating AHR activity (Kawajiri and Fujii-Kuriyama, 2017; Hattori *et al*., 2018; Larigot *et al*., 2018; Furue *et al*., 2021; Goya-Jorge *et al*., 2021; Kou and Dai, 2021).

Dioxins and Feeding

The compounds of two well-differentiated structures are grouped under the name of dioxins: Polychlorodibenzo-p-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs), which belong to the group of lipophilic and persistent organic compounds. Depending on the level of chlorination (1-8 atoms of chlorine), and the substitution position, there may be 75 different PCDDs and 135 PCDFs known as dioxin-like. This paper refers to dioxins as the chemical structures present in figure 1. Other contaminating derivatives of foods and the environment include compounds with substitutions of bromide atoms (polybrominated dibenzo-p-dioxins, PBDDs) (Zhou and Liu, 2018; Falandysz, Smith, and Fernandes, 2020).

Dioxins accumulate in the fat at high levels, so extremely low levels of dioxins in feedstuffs can be significant throughout the lifespan of animals, and can generate unacceptable residues in the food for humans, such as meat, milk, and eggs (FAO and IFIF, 2014). In animal production, the incorporation of dioxins can occur from the soil, water that is drunk, or supplied feeds. According to WHO (World Health Organization), 90% of human exposure is produced by ingesting meat, dairy, fish, and shellfish. Chronic exposure to these substances may cause toxic effects in humans, which can include immunological, endocrine, reproductive problems, and so forth. In relation to reproduction animals, poultry and fish are more susceptible to intoxication by dioxins due to their high contents of body fat (digital veterinary, 2021).

Of all dioxins and dioxin-like substances, only a few substances from each group are toxic. The bromide derivatives have been found to contaminate aquatic foods and the food chains of animals and man (Weber *et al.*, 2018; Dai *et al*., 2020; Falandysz, Smith, and Fernandes, 2020).

Based on the fact that in 1968, more than 2000 inhabitants of the west of Japan were poisoned by high concentrations of polychlorinated dibenzofurans (PCDF), polychlorinated quaterphenyls, polychlorinated dibenzodioxins (PCDD), and polychlorinated biphenyls (PCB), which contaminated the edible oil from rice bran, it is important to monitor the factor of toxic equivalence (FTE), and toxic equivalent (TEQ) of each dioxin-like substance in foods (for instance, TCDD, FTE = 1) (Furue *et al*., 2021).

The contaminants of feed are substances that were not added intentionally, they may appear as the result of contamination from the environment (Weber *et al.*, 2018), and are a risk to animal health. Hence, in 2018, the European Food Safety Authority (EFSA) confirmed that food exposure to dioxins and dioxin-like PCBs (environmental contaminants occurring at low levels in foods and feeds) are a health problem (efsa.europa.eu, 2021).

In 1999, in Belgium, an incident motivated by the detection of high levels of dioxins and PCB in animal products occurred due to the utilization of highly dioxin-contaminated industrial oils to

manufacture feeds. Therefore, and to evaluate the risks caused by the exposure to these substances, in the 1980s, the concepts of toxic equivalent (TEQ), and factor of toxic equivalent (FTE) were defined. It helped establish a criterion that offers a relatively simple system to estimate the overall toxicity of toxins. In 2018, EFSA set a weekly tolerable ingestion (WTI) of 2 pg WHO-TEQ/kg body weight and week ((EFSA *et al*., 2018).

Dioxins and dioxin-like substances can cause cancer; disorders of the immune and the nervous systems; liver lesions; and sterility. Perhaps it is due to the high AHR conservation level. Figure 2 shows the binding site of the ligand in the human AHR PAS-B domain, the alignment of the amino acid sequences and identity percentages for the animal species AHR obtained from the UNIPROT database (UniProt, 2021), and analyzed using CLUSTAL Omega (Madeira *et al.*, 2019). The amino acid residues are highly conserved in different species of animals used in the production of foods, which in many cases feed on feedstuffs and forages. The five amino acid residues which are important in the AHR cavity interaction (Panda, Cleave, and Suresh, 2012; Szöllősi *et al.*, 2016) with TCDD, are highlighted in red, of which, two are conserved and the others are variable. Hence, the AHR agonists described as contaminants of feeds are highly likely to cause damage and accumulate, thus affecting animal production and cause damage throughout the food chain.

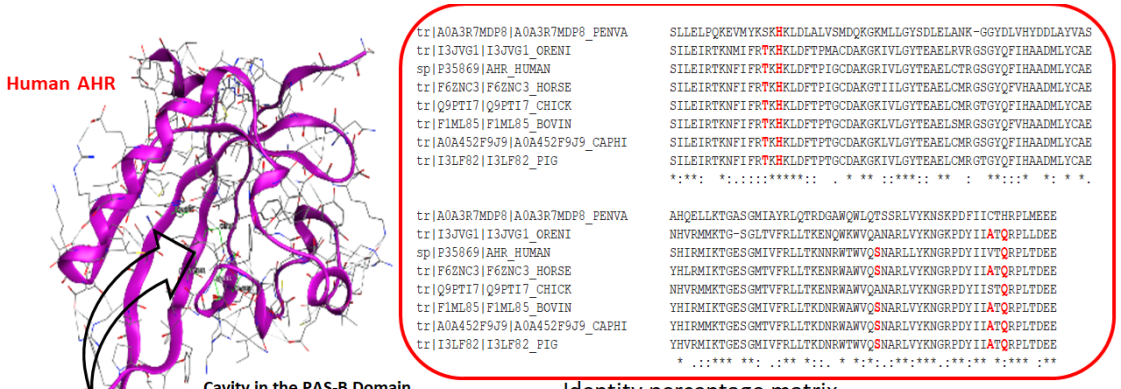

Figure 2. Ligand binding site in the PAS-B domain of human AHR. Alignment of amino acid sequences in the PAS-B domain, and their identity percentages for different species. UniProtKB: 1) P35869 (AHR_HUMAN) human, 2) I3LF82 (I3LF82_PIG) pig, 3) F6ZNC3 (F6ZNC3_HORSE) horse, 4) F1ML85 (F1ML85_BOVIN) cattle, 5) A0A452F9J9 (A0A452F9J9_CAPHI) goat, 6) Q9PTI7 (Q9PTI7_CHICK) chicken, 7) I3JVG1 (I3JVG1_ORENI) Nile tilapia, 8) A0A3R7MDP8 (A0A3R7MDP8_PENVA) white leg shrimp. The residues in red are associated with the ligand interaction in the cavity.

In most farm species, the existing studies have demonstrated that dioxins and BPC accumulate in the body fat and liver, but are also excreted in eggs and milk.

Exposure of food-producing animals and accumulation of PCDD/F, and PCB

Some types of livestock tend toaccumulate PCDD/F and PCB. The food-producing animals have been classified according to the risk of exposure to PCDD/F in the soil. The bioaccumulation of PCDD/F and PCB depends on the dioxin-like congener, the species, and tissue. As a result, the bioaccumulation from feedstuffs/soil to the food from animals changes the dioxin-like congener patterns considerably. The specific dioxin-like congener transference (transference rates) from the soil/feeds to farm products (meat, eggs, milk) can be determined (Weber *et al.*, 2018).

Poultry are especially prone to environmental contamination. They are on the soil longer than other farm animals per body weight. Contents of PCDD/F in the diet of 0.4 ng EQT/kg dry mass (dm) found in approximately 50% of the maximum EU level for feedstuffs (0.75 ng PCDD / EQT-F / kg 88% dm) is sufficient to surpass the maximum EU level for PCDD/F in eggs (Weber *et al.*, 2018).

Livestock incorporates PCB and PCDD/F from feeds, even feeds contaminated with soil particles (for instance, grass, grass silage, or hay) (Weber *et al.*, 2018). In principle, sheep and goats are subject to the same procedure as cattle. Sheep are among the most sensitive animals, since they graze near the soil surface, and the proportion of ingested soil may be high, up to 20% of forages (Weber *et al.*, 2018). Boars and outdoor pigs are within the category of animals with the highest exposure to PCDD/F, along with chicken, since most of their food is found on the soil. (Weber *et al.*, 2018)

PCDD/F and BPC are more accumulated in bluefish filet (trout or salmon), than in whitefish. The main sources of dioxins associated with feeds in aquaculture fish are often fish oil and fish meal. Besides, the composition of feeds and transference of dioxins to the filets depends on the species, animal growth, and the levels of dioxins in water and sediments (FAO and WHO, 2018).

CONCLUSIONS

This study has demonstrated the importance of environmental control throughout the food chain to minimize the risk of poisoning by dioxins and dioxin-like congeners in the food, and therefore the ensuing poisoning of people and animals that consume these foods and feeds, respectively. The farmers engaged in food production from animals, and manufacture animal products must study these compounds and collaborate in the identification of the possible dangers to consumer health.

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AUTHOR CONTRIBUTION

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CONFLICT OF INTERESTS

The authors declare the existence of no conflicts of interests.