




Review article:

DIOXINS DO NOT ONLY BIND TO AHR BUT ALSO TEAM UP WITH EGFR AT THE CELL-SURFACE: A NOVEL MODE OF ACTION OF TOXICOLOGICAL RELEVANCE?

Natalie C. Sondermann¹ , Christoph F. A. Vogel² , Thomas Haarmann-Stemmann^{1,*} 

¹ IUF – Leibniz Research Institute for Environmental Medicine, 40225 Düsseldorf, Germany

² Department of Environmental Toxicology and Center for Health and the Environment, University of California, Davis, CA 95616, USA

* **Corresponding author:** Thomas Haarmann-Stemmann, IUF – Leibniz Research Institute for Environmental Medicine, 40225 Düsseldorf, Germany. Tel.: +49 211 3389 204, E-mail: thomas.haarmann-stemmann@iuf-duesseldorf.de

<https://dx.doi.org/10.17179/excli2024-8038>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>).

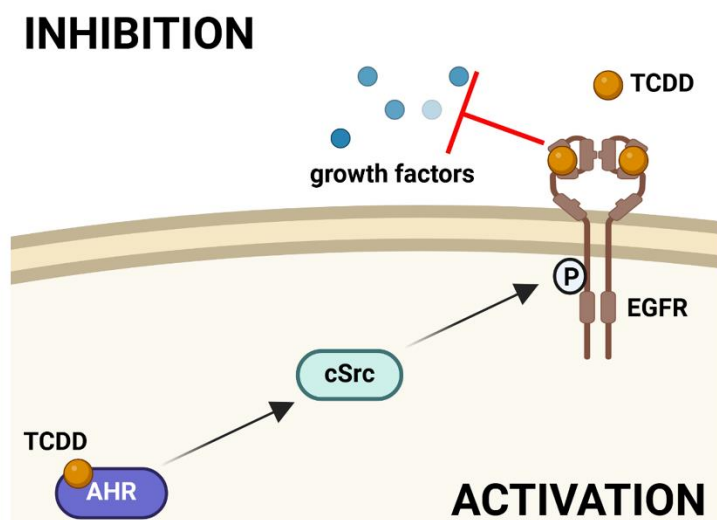


Figure 1: Graphical abstract

ABSTRACT

Dioxins and dioxin-like compounds (DLCs) are highly toxic organic pollutants whose production and use are prohibited by international law. Despite this, these biopersistent and lipophilic chemicals are prevalent in the environment and accumulate in the food chain, posing significant health risks to consumers even at low exposure levels. Acute dioxin intoxication can cause chloracne, while chronic exposure has been associated with a wide range of adverse health effects, including carcinogenicity, reproductive and developmental disorders,

immunotoxicity, and endocrine disruption. In the mid-1970s, scientists identified a transcription factor known as the aryl hydrocarbon receptor (AHR), which becomes activated upon binding of dioxins. AHR orchestrates numerous adaptive and maladaptive stress responses and is believed to mediate most, if not all, of the toxic effects triggered by dioxins and DLCs. Recent studies have provided mounting evidence that dioxins and dioxin-like polychlorinated biphenyls can inhibit growth factor-induced activation of the epidermal growth factor receptor (EGFR) by directly binding to its extracellular domain. This interaction prevents the activation of EGFR by polypeptide growth factors and downstream signal transduction. In this article, we explain this newly identified mechanism of action for dioxins and DLCs in detail and discuss its potential toxicological relevance by using two examples, i.e. breast cancer development and placental toxicity. Finally, we briefly refer to other environmental chemicals of global concern that, based on first published data, may act *via* the same mode of action.

Keywords: Aryl hydrocarbon receptor, epidermal growth factor receptor, allosteric inhibition, persistent organic pollutants, breast cancer, placental toxicity

INTRODUCTION

According to the World Health Organization, dietary exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds (DLCs) remains a significant public health concern (WHO, 2023). These persistent organic pollutants are pervasive in the environment, very lipophilic and tend to accumulate in the food chain. While chloracne is the characteristic symptom of acute intoxication (Furue et al., 2021; Panteleyev and Bickers, 2006), chronic exposure to low doses of dioxins and DLCs can disrupt endocrine functions and impair the immune, reproductive, and developing nervous systems (EFSA Panel on Contaminants in the Food Chain, 2018). Beyond efforts to reduce human exposure, a more comprehensive understanding of the modes of action of dioxins and structurally related chemicals may help to improve risk assessment.

In 1976, Alan Poland and colleagues identified the aryl hydrocarbon receptor (AHR) as a protein that binds radiolabeled TCDD (Poland et al., 1976). Subsequent studies on transgenic mice demonstrated that most of the adverse effects of dioxin exposure depend on AHR (Bunger et al., 2003; Fernandez-Salguero et al., 1996; Mimura et al., 1997; Vorderstrasse et al., 2001), leading to the prevailing view that the toxicity of dioxins and DLCs is exclusively mediated by AHR. However, as discussed below, this picture of a monogamous relationship between dioxins and

AHR does not necessarily reflect the true situation. In certain cell types, dioxins interact not only with AHR but also with another key player in cellular signal transduction, i.e. the epidermal growth factor receptor (EGFR).

In its resting state, AHR is part of a cytosolic multiprotein complex consisting of a heat-shock protein 90 dimer, AHR-interacting protein, co-chaperone p23 and the soluble tyrosine kinase c-Src (Figure 2) (Larigot et al., 2022; Vazquez-Rivera et al., 2022). Upon ligand binding, AHR undergoes conformational changes, leading to the dissociation of the multiprotein complex and its translocation into the nucleus, where it dimerizes with the AHR nuclear translocator (ARNT) to form an active transcription factor (Larigot et al., 2022; Vazquez-Rivera et al., 2022). In addition to this canonical AHR pathway, studies from the mid-1980s already showed that TCDD interferes with the activity of EGFR (Astroff et al., 1990; Hudson et al., 1985; Karenlampi et al., 1983; Madhukar et al., 1984, 1988), a receptor tyrosine kinase (RTK) integrated in the plasma membrane (Chen et al., 2016), in ways that cannot be explained by AHR activation alone. Specifically, anthropogenic AHR ligands were found to decrease the binding of ¹²⁵I-labeled EGF to the plasma membrane, an observation commonly referred to as EGFR downregulation (Astroff et al., 1990; Hudson et al., 1985; Karenlampi et al., 1983; Madhukar et al., 1984, 1988). It was suggested that this might be due to an AHR ligand-enforced internalization of EGFR, an

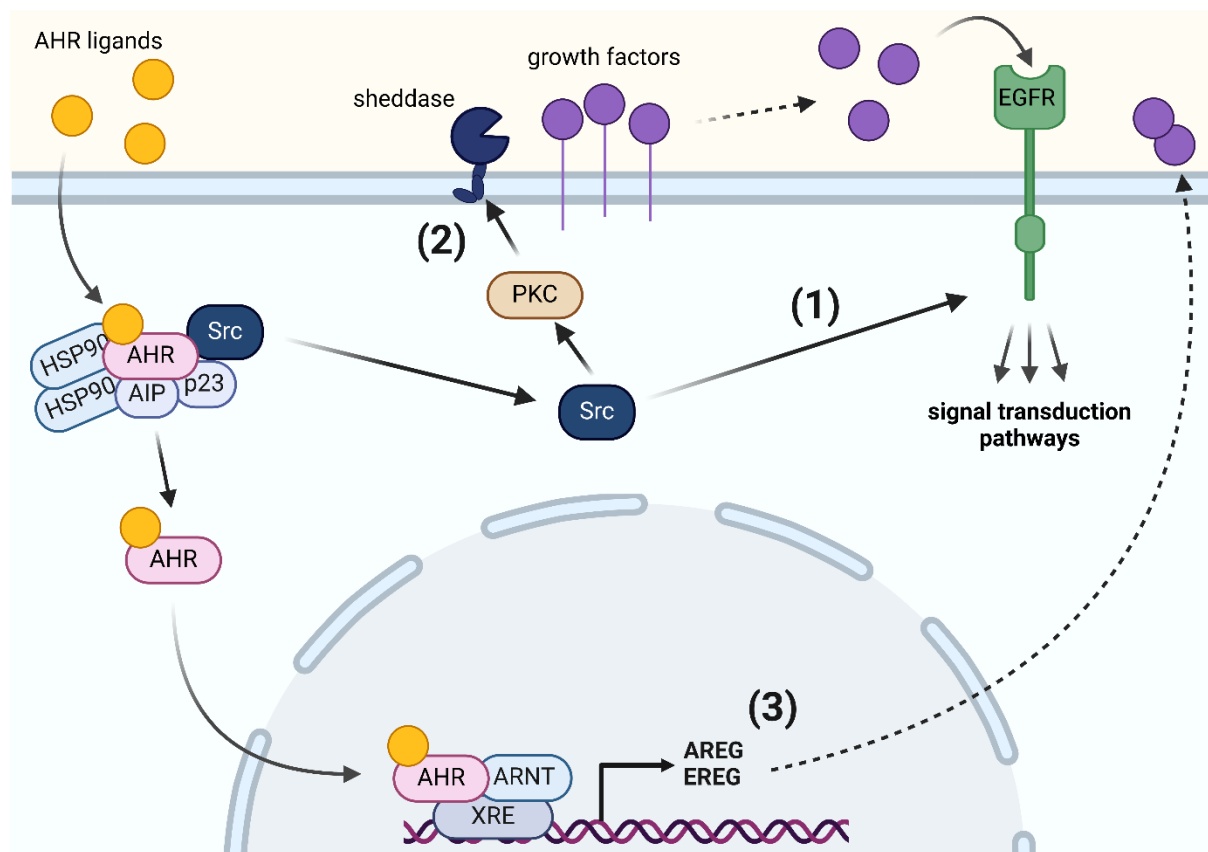


Figure 2: Ligand-induced activation of AHR and its impact on gene expression, EGFR activity and downstream signal transduction. Ligand-binding of AHR leads to the dissociation of the cytosolic multiprotein complex and the nuclear translocation of AHR. In the nucleus AHR dimerizes with ARNT, binds to the enhancer region of genes, for instance encoding the growth factors amphiregulin (AREG) and epiregulin (EREG), and induces their transcription (3). In addition, the ligand-induced dissociation of the cytosolic AHR complex leads to a release of the tyrosine kinase c-Src, which can directly activate EGFR by phosphorylating its intracellular domain (1). Moreover, c-Src sequentially stimulates protein kinase C (PKC) and sheddases, resulting in ectodomain-shedding of cell surface-bound EGFR ligands, such as AREG (2). The released growth factors accumulate and can activate EGFR and downstream signal transduction cascades (e.g. MAPK, PI3K-AKT) by binding to its extracellular domain.

event that follows dimerization, autophosphorylation and activation of downstream signaling molecules (Chen et al., 2016). Unlike polycyclic aromatic hydrocarbons (PAHs), another class of environmental AHR agonists that cause only a transient reduction in EGF binding, TCDD led to a prolonged reduction in EGF-binding capacity, i.e. up to 4 days *in vitro* and 40 days *in vivo* (Hudson et al., 1985; Madhukar et al., 1984). The molecular mechanism underlying this discrepancy remains poorly understood. It has been proposed that AHR ligand-induced internalization of EGFR

is due either to its phosphorylation by c-Src (Tice et al., 1999), which is released in the cytosol upon AHR activation (Dong et al., 2011; Kohle et al., 1999; Vogel et al., 2000) or to an enhanced AHR-driven production and release of growth factors that bind to EGFR (Campion et al., 2016; Choi et al., 1991; Du et al., 2005; John et al., 2014; Patel et al., 2006; Sun et al., 2022). However, neither mechanism fully explains the differences in signal transduction observed upon PAH and DLC treatment.

A NEW MODE OF ACTION: BINDING OF TCDD AND DIOXIN-LIKE PCBs TO CELL-SURFACE EGFR

A breakthrough came when Matthew Cave's laboratory for the first time demonstrated that the dioxin-like polychlorinated biphenyl (PCB) congener 126 (as well as non-dioxin-like PCB153) inhibit the growth factor-triggered activation of EGFR, presumably by binding to its extracellular domain (ECD) (Hardesty et al., 2018). Building on this intriguing work, we investigated the crosstalk of AHR and EGFR pathways in response to DLC and PAH exposure in more depth. Our study revealed that EGFR substantially shapes AHR ligand-induced responses in human epithelial cells (Figure 2) (Vogelely et al., 2022). Specifically, exposure to the PAH benzo[*a*]pyrene (BaP) as well as to PCB126 resulted in a rapid c-*Src*-mediated phosphorylation of EGFR within 5-15 minutes after treatment, which confirmed previous reports from TCDD-treated human macrophages and colon cancer cells (Cheon et al., 2007; Xie et al., 2012). In addition, both AHR agonists, BaP and PCB126, stimulated protein kinase C activity and enhanced the ectodomain shedding of cell surface-bound EGFR ligands, namely amphiregulin and transforming growth factor- α (Vogelely et al., 2022). However, only after BaP treatment, this resulted in a timely delayed (2 hours) second peak of EGFR activation and downstream ERK1/2 phosphorylation. Accordingly, hundreds of differentially expressed genes were identified when comparing the transcriptome of BaP-versus PCB126-treated keratinocytes. Subsequent *in silico* docking analyses and EGFR internalization assays confirmed that PCB118, PCB126 and TCDD, but not BaP and benzo[*k*]fluoranthene, bind to the ECD of EGFR and block its activation by polypeptide growth factors (Figure 3A, B). Two amino acid residues in close proximity to the binding site for EGF, i.e. Q8 and Q408, were identified to be critical for the binding of dioxins (Vogelely et al., 2022), with the latter residue being also involved in the binding of the EGFR monoclonal antibody cetuximab (Li et

al., 2005). The results from the docking simulations are compatible with a model where DLC binding distorts the ECD enough to block EGF binding and subsequent EGFR dimerization. Notably, treatment with PCB126 or TCDD reduced the amphiregulin-induced and EGFR-dependent DNA synthesis in both AHR-proficient and AHR-deficient keratinocytes (Vogelely et al., 2022). An inhibition of the amphiregulin-induced DNA synthesis in AHR-deficient HaCaT cells by the PCB mixture Aroclor 1254 as well as by the non-dioxin-like PCB47, is shown in Figure 2C. Moreover, the Cave laboratory has reported that treatment of C57Bl/6J mice with Aroclor 1260 resulted in a reduced phosphorylation not only of hepatic EGFR but also of its downstream effectors, such as AKT and mTOR (Hardesty et al., 2017).

Taken together, these findings may provide a mechanistic explanation for the diverging observations of the mid-1980's studies: Dioxins and DLCs interacted with the EGFR ECD and thereby disturbed the proper binding of (labeled) EGF. Since allosteric inhibition of EGFR may stimulate its subsequent degradation (Perez-Torres et al., 2006; Yao et al., 2020), an additional modulation of EGFR protein levels upon DLC treatment cannot be excluded. Given that ligand-induced AHR activation also results in a transcriptional upregulation and release of EGFR ligands, such as epiregulin, amphiregulin and transforming growth factor- α (Campion et al., 2016; Choi et al., 1991; Du et al., 2005; John et al., 2014; Patel et al., 2006), the extent and duration of this inhibition *via* ECD occupation is probably dose- and time-dependent. Importantly, the described mode of action is still compatible with a rapid endogenous activation of EGFR by dioxins *via* the AHR/c-*Src*-axis.

Worth mentioning is that there are reports in literature that are not in line with the proposed mode of action. A study assessing the impact of TCDD on hepatocarcinogenesis in rats, for instance, observed a reduced binding of radiolabeled EGF to hepatic EGFR in the orally-exposed animals (Sewall et al., 1993). Interestingly, the authors could not reproduce

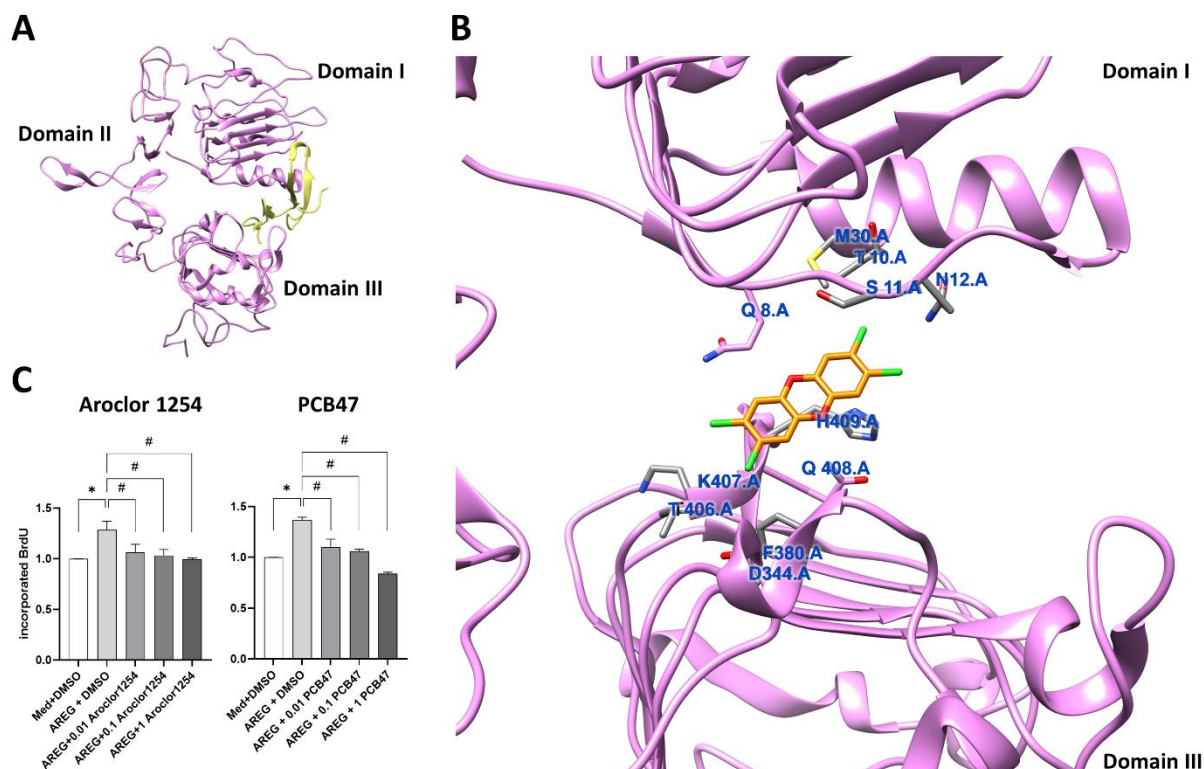


Figure 3: *In silico* docking analysis predicts the binding of TCDD to the EGFR extracellular domain and PCBs inhibit growth factor-induced DNA synthesis in AHR-mutant HaCaT keratinocytes. **A.** *In silico* docking analysis predicting the binding of EGF (yellow) to the EGFR extracellular domain (magenta). **B.** *In silico* docking analysis predicting the binding of TCDD to the EGFR extracellular domain in close proximity to the EGF binding site. **C.** Colorimetric BrdU incorporation assay to assess the influence of the PCB mixture Aroclor 1254 (0.01, 0.1, 1 μ M) and non-dioxin-like PCB47 (0.01, 0.1, 1 μ M) on DNA synthesis induced by 10 ng/ml amphiregulin (AREG). HaCaT-AHR-mut (DU26) keratinocytes were treated as indicated for 4 h. Absorption was measured at a wavelength of 370 nm (reference wavelength 492 nm). $n = 3$. *, $p \leq 0.05$ compared to DMSO. #, $p \leq 0.05$ compared to AREG/DMSO. For a detailed description of the *in silico* docking analyses, the generation and characterization of the HaCaT-AHR-mut (DU26) keratinocytes, and the BrdU incorporation assay please see Vogeley et al. (2022).

this effect in ovariectomized rats, indicating an involvement of estrogen-dependent signaling events (Sewall et al., 1993). However, in contrast to this observation, earlier studies reported a drop in the EGF-binding capacity of hepatic EGFR upon treatment of male rats, hamsters, and guinea pigs with TCDD (Madhukar et al., 1984, 1988).

In addition, multiple other AHR-independent effects of TCDD that do not necessarily involve an interaction with EGFR but possibly with other signaling molecules are described in literature. Examples are the inhibition of migration of AHR-non-responsive human glioblastoma cells (Liu et al., 2024), the induction of endoplasmic reticulum stress

in human neuroblastoma cells (Murillo-Gonzalez et al., 2024), and the induction of mitochondrial oxidative stress and insulin resistance in murine myoblasts (Im et al., 2022).

ALLOSTERIC INHIBITION OF EGFR BY DLCS: CLUES FOR TOXICOLOGICAL RELEVANCE?

The novel mode of action of dioxins and DLCs does not only explain ligand-specific differences in the AHR response, but may also account for cell- and tissue-specific effects. EGFR is predominantly expressed in epithelial cells, fibroblasts, and glia cells, and is of fundamental importance for physiology

and the development of diseases, including cancer (Chen et al., 2016). Moreover, EGFR-deficient mice die early after birth due to epithelial immaturity and multiorgan failure, demonstrating the critical role of the RTK for proper embryonic development (Miettinen et al., 1995; Sibiliala and Wagner, 1995). Hence, the allosteric inhibition of EGFR may be relevant for various diseases and disorders associated with TCDD or DLC exposure, especially those involving dysregulation of cell proliferation, migration, and differentiation.

The development of chloracne, for example, is linked to dioxin-induced disruptions in the differentiation processes of epidermal keratinocytes and sebocytes (Furue et al., 2021; Panteleyev and Bickers, 2006). *In vitro* experiments have shown that TCDD treatment reduces the proliferation of keratinocytes and accelerates their differentiation (Bhujji et al., 2021; Hudson et al., 1985; Lin et al., 2023; Sutter et al., 2019). The EGFR is an important regulator of keratinocyte function and fate and, accordingly, the switch from proliferation to differentiation can be induced by treating keratinocytes with EGFR inhibitors, too (Joly-Tonetti et al., 2021; Lichtenberger et al., 2013; Peus et al., 1997). In cancer patients, systemic EGFR inhibition is associated with several cutaneous side effects, including aberrant keratinocyte differentiation and skin barrier impairment (Gisondi et al., 2021; Lacouture, 2006). The clinical presentation of EGFR inhibitor-induced skin effects, however, differs from that of dioxin-induced chloracne. While the former are accompanied by inflammatory reactions (Lacouture, 2006), this is usually not the case with chloracne (Furue et al., 2021; Panteleyev and Bickers, 2006). Differences in the underlying pathomechanisms, e.g. EGFR inhibition *versus* EGFR inhibition/AHR activation, may be responsible for this.

However, since chloracne is more relevant in the context of accidental or intentional poisoning with high doses of dioxin, we have decided not to go into further depth but to focus instead on the development of breast cancer and placental toxicity.

Development and progression of breast cancer

Depending on cancer type and origin, overexpression or gain-of-function mutations of EGFR may contribute to tumor growth and progression (Uribe et al., 2021). In contrast to the predominating notion that TCDD and related DLCs act *per se* as tumor promoters, several reports also point to anticarcinogenic effects of these environmental contaminants. In fact, two independent studies assessing the chronic toxicity of TCDD in rats in unison reported an increased formation of neoplasms in the lung, liver and oral mucosa, but also a reduced incidence of thyroid, pituitary and mammary tumors (Kociba et al., 1978; Walker et al., 2006). Other studies on rodents revealed that TCDD and DLCs can interfere with tumor growth and progression: Intraperitoneal injection of the PCB mixture Aroclor 1254 reduced the growth of transplanted breast cancer cells in rats (Kerkvliet and Kimeldorf, 1977), TCDD treatment diminished the growth of 7,12-dimethylbenzanthracene-initiated rat mammary tumors (Holcomb and Safe, 1994), and in a mouse model for breast cancer TCDD inhibited metastasis (Wang et al., 2011). Population-based studies found an inverse association between exposure of women to TCDD and PCBs and the risk for hormone-independent breast cancer (Danjou et al., 2015; Gammon et al., 2002). Interestingly, this type of mammary tumor seems to express high levels of EGFR (Masuda et al., 2012).

In contrast to the anti-carcinogenic effects of TCDD, particularly in the context of breast cancer, multiple epidemiological studies have identified the exposure to other environmentally relevant AHR ligands, i.e. airborne PAHs and PAH-rich particular matter, as a risk factor for breast cancer (Amadou et al., 2021; Mordukhovich et al., 2016; Shen et al., 2017; Smotherman et al., 2023). And indeed, studies have shown that TCDD also exhibits procarcinogenic effects in breast cancer. However, as concluded by a recent systematic review and meta-analysis, the available epidemiological data provide no consistent evi-

dence for an increased risk of breast cancer from TCDD exposure (Cong et al., 2023). One study reporting a positive correlation between dioxin concentrations and breast cancer risk, for instance, is the Seveso Women's Health Study, in which a 10-fold increase in TCDD serum levels was associated with a 2.1-fold increase of the hazard ratio for breast cancer (Warner et al., 2002). Experimental studies on rodents revealed that a maternal exposure to TCDD predisposed the offspring to mammary tumorigenesis (Brown et al., 1998; Jenkins et al., 2007; La Merrill et al., 2010), which might be due to an epigenetic silencing and subsequent downregulation of breast cancer-1 gene expression in the mammary tissue of the maternally exposed offspring (Papoutsis et al., 2015). A study on prostate carcinoma-prone transgenic mice confirmed the procarcinogenic effects of maternal TCDD exposure, while treatment during adulthood significantly delayed the development of neuroendocrine prostate carcinomas in these animals (Moore et al., 2016). A recent study assessing the concentrations of organic pollutants in the adipose tissue of breast cancer patients revealed a positive association between increasing TCDD levels and tumor progression (Koual et al., 2019). With regards to breast cancer progression, activation of AHR, in particular the AHR/c-*Src* axis (Miret et al., 2022), might play a role (Benoit et al., 2022). In fact, several studies have shown that breast cancer patients with high AHR activity and low expression of the AHR repressor, a negative feedback regulator of AHR (Vogel and Haarmann-Stemann, 2017), experience shorter metastasis-free survival (Jeschke et al., 2019; Li et al., 2014; Vacher et al., 2018). Along the same line, inhibition of AHR through overexpression of AHR repressor decreased both tumor burden and lung metastasis in the polyoma Middle-T (PyMT) mouse model of breast cancer (Vogel et al., 2021).

Importantly, EGFR was found to switch its function from proliferative in primary breast tumors to growth-inhibitory in mammary tumor-derived pulmonary metastases (Wendt et al., 2015). Whereas the primary

tumor cells responded to Erlotinib treatment, the metastatic cells turned out to be resistant towards pharmacological EGFR inhibition (Wendt et al., 2015). Hence, TCDD may inhibit growth factor-driven EGFR signal transduction in early stages of breast cancer, whereas it is probably ineffective in doing so in advanced stages, when TCDD-activated AHR may dominate and drive tumor progression. However, if an allosteric inhibition of EGFR contributed to the experimentally and epidemiologically observed anticarcinogenic effects of dioxin and DLC exposure is currently not known and urgently requires further investigation.

Placental functions and fetal growth

The EGFR is highly expressed in the human placenta and its polypeptide ligand EGF plays a crucial role in regulating placental and fetal growth (Evain-Brion and Alsat, 1994; Fondacci et al., 1994; Rab et al., 2013). Accordingly, altered EGF expression pattern and dysregulated EGFR signal transduction is associated with intrauterine growth restriction (Evain-Brion and Alsat, 1994; Fondacci et al., 1994; Rab et al., 2013), which increases the risk for the development of cardiovascular diseases, type 2 diabetes and other health complications later in life (Knofler et al., 2019).

Given the high lipophilicity of dioxins and PCBs, these compounds accumulate in the human body and can easily cross the placental barrier and affect the developing life. Experimental studies on rats have shown that *in utero* treatment with TCDD affects the vascular remodeling in the placenta (Ishimura et al., 2006, 2009), a process which ensures proper blood supply to the fetus (Knofler et al., 2019). By making use of AHR-null and CYP1A1-null rats as well as different breeding and exposure protocols, Iqbal et al. demonstrated that the effects of *in utero* TCDD exposure on the development of the hemochorial placenta largely depend on maternal AHR signaling (Iqbal et al., 2021). However, a study comparing the effect of TCDD and 2-(1'H-indole-3'-carbonyl)-

thiazole-4-carboxylic acid methyl ester (ITE), a potent endogenous AHR ligand (Henry et al., 2006), in pregnant rats, revealed that only TCDD altered the development of the placental vasculature (Wu et al., 2014). Another study comparing the effects of *in utero* TCDD exposure in Holtzman and Sprague–Dawley rats, two rat strains with identical AHR gene sequence, revealed a clearly enhanced susceptibility of the Holtzman strain towards TCDD-induced placental dysfunction and fetal death (Kawakami et al., 2006), again arguing for an additional AHR-independent pathomechanism. Hence, at least in TCDD-exposed rats, AHR-dependent as well as AHR-independent processes may disturb vascular remodeling, an event that may result in undersupply of the fetus and poor fetal growth (Iqbal et al., 2021; Knofler et al., 2019).

The majority of the available epidemiological studies assessing the impact of maternal DLC exposure on fetal growth indicate an inverse association between DLC serum levels and/or serum AHR activity and birth weight (Govarts et al., 2012; Karmaus and Zhu, 2004; Konishi et al., 2009; Long et al., 2022; Tsukimori et al., 2012; Van Tung et al., 2016; Yen et al., 1994). For example, reduced birth weights correlated with increasing maternal DLC levels in women affected from two mass poisonings in Southeast Asia (Yusho, Japan, 1968 and Yu-Cheng, Taiwan, 1979), during which larger parts of the local population were exposed to PCBs *via* contaminated rice oil (Tsukimori et al., 2012; Yen et al., 1994). Mechanistic studies on placental tissue from mothers four years after being exposed in the Yu-Cheng incident confirmed an intoxication of the tissue with DLCs, which was associated with an elevated expression and activity of CYP1 isoforms (Lucier et al., 1987; Sunahara et al., 1987). However, whereas the capacity of EGFR to autophosphorylate was markedly reduced in the placental tissue of the exposed women, an analysis of the ¹²⁵I-EGF-binding behavior of EGFR did not show any DLC exposure-related differences (Lucier et al., 1987; Sunahara et al., 1987). These findings

indicate that the impact of DLC exposure on birth weight is indeed associated with an inhibition of EGFR activity, but this is not necessarily due to a competition between growth factors and DLCs for ECD-binding. However, a study comparing the effect of BaP treatment on the ¹²⁵I-EGF-binding capacity of EGFR in cells isolated from early gestation placentae *versus* cells isolated from term placenta, revealed marked differences (Guyda et al., 1990). Indeed, BaP decreased the capacity of EGFR to bind EGF in the early but not in the term placental cells, suggesting that the inhibitory effect of DLCs on the EGFR ECD might also be of functional relevance only during early placental development. Another process that might contribute to the placental alterations in response to TCDD exposure is the AHR-dependent secretion of IL-24 by chorionic stromal cells, which subsequently inhibited the migration and invasion of placental trophoblasts (Liu et al., 2022), possibly by interfering with growth factor-induced EGFR activation (Poindexter et al., 2010).

However, especially in the light of the novel mode of action discussed in this article, a thorough reassessment of the molecular mechanism responsible for these alterations in placental biology is indicated in order to identify the key event for the developmental toxicity of DLCs.

CONCLUSION

We conclude that in addition to cytosolic AHR, EGFR may serve as a sensor molecule for dioxins and DLCs at the cell-surface. Importantly, this might not only hold true for DLCs but also for other environmental pollutants of global concern, including phenolic benzotriazoles (Sondermann et al., 2024a), polybrominated diphenyl ethers (Sondermann et al., 2024b), bisphenols (Ticiani et al., 2021, 2023) and non-dioxin-like PCBs (Figure 3C) (Hardesty et al., 2018; Hardesty et al., 2017), as well as for the sedative drug phenobarbital (Mutoh et al., 2013). Therefore, exposure to environmental matrices consisting of several of these environmental chemicals can be expected to cause additive effects. However,

experimental studies to assess the toxicological relevance of this novel mode of action of organic pollutants have not yet been conducted. Allosteric inhibition of EGFR is an active area of research in oncology (Rybak et al., 2023; To et al., 2022; Yao et al., 2020) and we hope that the arguments summarized in this perspective stimulate further research on this new mode of action in environmental toxicology and will raise the awareness of risk assessors for it.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

Research in the laboratory of THS is funded by the German Research Foundation (DFG), projects HA 7346/5-1 and HA 7346/6-1. NCS was supported by the Jürgen Manchot Foundation. The National Institute of Environmental Health Sciences (NIEHS)-funded UC Davis EHSC under P30 ES023513, NIEHS R01ES032827 and R01ES036338 supported research in the laboratory of CFAV. The graphical abstract (Figure 1) and Figure 2 were created with BioRender software (www.biorender.com; agreement number TI27NQ6484 and FT27KQ3M1R).

REFERENCES

- Amadou A, Praud D, Coudon T, Deygas F, Grassot L, Faure E, et al. Risk of breast cancer associated with long-term exposure to benzo[a]pyrene (BaP) air pollution: Evidence from the French E3N cohort study. *Environ Int.* 2021;149:106399.
- Astroff B, Rowlands C, Dickerson R, Safe S. 2,3,7,8-Tetrachlorodibenzo-p-dioxin inhibition of 17 beta-estradiol-induced increases in rat uterine epidermal growth factor receptor binding activity and gene expression. *Mol Cell Endocrinol.* 1990;72:247-52.
- Benoit L, Jornod F, Zgheib E, Tomkiewicz C, Koual M, Coustillet T, et al. Adverse outcome pathway from activation of the AhR to breast cancer-related death. *Environ Int.* 2022;165:107323.
- Bhujji J, Olesen KM, Muenyi CS, Patel TS, Read RW, Thompson L, et al. Cutaneous effects of in utero and lactational exposure of C57BL/6J mice to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxics.* 2021;9(8):192.
- Brown NM, Manzillo PA, Zhang JX, Wang J, Lamartiniere CA. Prenatal TCDD and predisposition to mammary cancer in the rat. *Carcinogenesis.* 1998;19:1623-9.
- Bunger MK, Moran SM, Glover E, Thomae TL, Lahvis GP, Lin BC, et al. Resistance to 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity and abnormal liver development in mice carrying a mutation in the nuclear localization sequence of the aryl hydrocarbon receptor. *J Biol Chem.* 2003;278:17767-74.
- Campion CM, Leon Carrion S, Mamidanna G, Sutter CH, Sutter TR, Cole JA. Role of EGF receptor ligands in TCDD-induced EGFR down-regulation and cellular proliferation. *Chem Biol Interact.* 2016;253:38-47.
- Chen J, Zeng F, Forrester SJ, Eguchi S, Zhang MZ, Harris RC. Expression and function of the epidermal growth factor receptor in physiology and disease. *Physiol Rev.* 2016;96:1025-69.
- Cheon H, Woo YS, Lee JY, Kim HS, Kim HJ, Cho S, et al. Signaling pathway for 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced TNF-alpha production in differentiated THP-1 human macrophages. *Exp Mol Med.* 2007;39:524-34.
- Choi EJ, Toscano DG, Ryan JA, Riedel N, Toscano WA, Jr. Dioxin induces transforming growth factor-alpha in human keratinocytes. *J Biol Chem.* 1991;266:9591-7.
- Cong X, Liu Q, Li W, Wang L, Feng Y, Liu C, et al. Systematic review and meta-analysis of breast cancer risks in relation to 2,3,7,8-tetrachlorodibenzo-p-dioxin and per- and polyfluoroalkyl substances. *Environ Sci Pollut Res Int.* 2023;30:86540-55.
- Danjou AM, Fervers B, Boutron-Ruault MC, Philip T, Clavel-Chapelon F, Dossus L. Estimated dietary dioxin exposure and breast cancer risk among women from the French E3N prospective cohort. *Breast Cancer Res.* 2015;17:39.
- Dong B, Cheng W, Li W, Zheng J, Wu D, Matsumura F, et al. FRET analysis of protein tyrosine kinase c-Src activation mediated via aryl hydrocarbon receptor. *Biochim Biophys Acta.* 2011;1810:427-31.

- Du B, Altorki NK, Kopelovich L, Subbaramaiah K, Dannenberg AJ. Tobacco smoke stimulates the transcription of amphiregulin in human oral epithelial cells: evidence of a cyclic AMP-responsive element binding protein-dependent mechanism. *Cancer Res.* 2005;65:5982-8.
- EFSA Panel on Contaminants in the Food Chain (CONTAM). Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA J.* 2018;16(11):e05333.
- Evain-Brion D, Alsat E. Epidermal growth factor receptor and human fetoplacental development. *J Pediatr Endocrinol.* 1994;7:295-302.
- Fernandez-Salguero PM, Hilbert DM, Rudikoff S, Ward JM, Gonzalez FJ. Aryl-hydrocarbon receptor-deficient mice are resistant to 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced toxicity. *Toxicol Appl Pharmacol.* 1996;140:173-9.
- Fondacci C, Alsat E, Gabriel R, Blot P, Nessmann C, Evain-Brion D. Alterations of human placental epidermal growth factor receptor in intrauterine growth retardation. *J Clin Invest.* 1994;93:1149-55.
- Furue M, Ishii Y, Tsukimori K, Tsuji G. Aryl hydrocarbon receptor and dioxin-related health hazards-lessons from Yusho. *Int J Mol Sci.* 2021;22(2):708.
- Gammon MD, Wolff MS, Neugut AI, Eng SM, Teitelbaum SL, Britton JA, et al. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol Biomarkers Prev.* 2002;11:686-97.
- Gisondi P, Geat D, Mattiucci A, Lombardo F, Santo A, Girolomoni G. Incidence of adverse cutaneous reactions to epidermal growth factor receptor inhibitors in patients with non-small-cell lung cancer. *Dermatology.* 2021;237:929-33.
- Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, et al. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European birth cohorts. *Environ Health Perspect.* 2012;120:162-70.
- Guyda HJ, Mathieu L, Lai W, Manchester D, Wang SL, Ogilvie S, et al. Benzo(a)pyrene inhibits epidermal growth factor binding and receptor autophosphorylation in human placental cell cultures. *Mol Pharmacol.* 1990;37:137-43.
- Hardesty JE, Wahlang B, Falkner KC, Clair HB, Clark BJ, Ceresa BP, et al. Polychlorinated biphenyls disrupt hepatic epidermal growth factor receptor signaling. *Xenobiotica.* 2017;47:807-20.
- Hardesty JE, Al-Eryani L, Wahlang B, Falkner KC, Shi H, Jin J, et al. Epidermal growth factor receptor signaling disruption by endocrine and metabolic disrupting chemicals. *Toxicol Sci.* 2018;162:622-34.
- Henry EC, Bemis JC, Henry O, Kende AS, Gasiewicz TA. A potential endogenous ligand for the aryl hydrocarbon receptor has potent agonist activity in vitro and in vivo. *Arch Biochem Biophys.* 2006;450(1):67-77.
- Holcomb M, Safe S. Inhibition of 7,12-dimethylbenzanthracene-induced rat mammary tumor growth by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Cancer Lett.* 1994;82(1):43-7.
- Hudson LG, Toscano WA, Jr, Greenlee WF. Regulation of epidermal growth factor binding in a human keratinocyte cell line by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol Appl Pharmacol.* 1985;77:251-9.
- Im S, Kang S, Kim JH, Oh SJ, Pak YK. Low-Dose dioxin reduced glucose uptake in C2C12 myocytes: the role of mitochondrial oxidative stress and insulin-dependent calcium mobilization. *Antioxidants (Basel).* 2022;11(11):2109.
- Iqbal K, Pierce SH, Kozai K, Dhakal P, Scott RL, Roby KF, et al. Evaluation of Placentation and the role of the aryl hydrocarbon receptor pathway in a rat model of dioxin exposure. *Environ Health Perspect.* 2021;129(11):117001.
- Ishimura R, Kawakami T, Ohsako S, Nohara K, Tohyama C. Suppressive effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on vascular remodeling that takes place in the normal labyrinth zone of rat placenta during late gestation. *Toxicol Sci.* 2006;91:265-74.
- Ishimura R, Kawakami T, Ohsako S, Tohyama C. Dioxin-induced toxicity on vascular remodeling of the placenta. *Biochem Pharmacol.* 2009;77:660-9.
- Jenkins S, Rowell C, Wang J, Lamartiniere CA. Prenatal TCDD exposure predisposes for mammary cancer in rats. *Reprod Toxicol.* 2007;23:391-6.
- Jeschke U, Zhang X, Kuhn C, Jalaguier S, Colinge J, Pfender K, et al. The prognostic impact of the aryl hydrocarbon receptor (AhR) in primary breast cancer depends on the lymph node status. *Int J Mol Sci.* 2019;20(5):1016.
- John K, Lahoti TS, Wagner K, Hughes JM, Perdew GH. The Ah receptor regulates growth factor expression in head and neck squamous cell carcinoma cell lines. *Mol Carcinog.* 2014;53:765-76.

- Joly-Tonetti N, Ondet T, Monshouwer M, Stamatias GN. EGFR inhibitors switch keratinocytes from a proliferative to a differentiative phenotype affecting epidermal development and barrier function. *BMC Cancer*. 2021;21(1):5.
- Karenlampi SO, Eisen HJ, Hankinson O, Nebert DW. Effects of cytochrome P1-450 inducers on the cell-surface receptors for epidermal growth factor, phorbol 12,13-dibutyrate, or insulin of cultured mouse hepatoma cells. *J Biol Chem*. 1983;258:10378-83.
- Karmaus W, Zhu X. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study. *Environ Health*. 2004;3(1):1.
- Kawakami T, Ishimura R, Nohara K, Takeda K, Tohyama C, Ohsako S. Differential susceptibilities of Holtzman and Sprague-Dawley rats to fetal death and placental dysfunction induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) despite the identical primary structure of the aryl hydrocarbon receptor. *Toxicol Appl Pharmacol*. 2006;212:224-36.
- Kerkvliet NI, Kimeldorf DJ. Antitumor activity of a polychlorinated biphenyl mixture, Aroclor 1254, in rats inoculated with Walker 256 carcinosarcoma cells. *J Natl Cancer Inst*. 1977;59:951-5.
- Knofler M, Haider S, Saleh L, Pollheimer J, Gamage T, James J. Human placenta and trophoblast development: key molecular mechanisms and model systems. *Cell Mol Life Sci*. 2019;76:3479-96.
- Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, et al. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. *Toxicol Appl Pharmacol*. 1978;46:279-303.
- Kohle C, Gschaidmeier H, Lauth D, Topell S, Zitzer H, Bock KW. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-mediated membrane translocation of c-Src protein kinase in liver WB-F344 cells. *Arch Toxicol*. 1999;73:152-8.
- Konishi K, Sasaki S, Kato S, Ban S, Washino N, Kajiwara J, et al. Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight. *Environ Res*. 2009;109:906-13.
- Koual M, Cano-Sancho G, Bats AS, Tomkiewicz C, Kaddouch-Amar Y, Douay-Hauser N, et al. Associations between persistent organic pollutants and risk of breast cancer metastasis. *Environ Int*. 2019;132:105028.
- La Merrill M, Harper R, Birnbaum LS, Cardiff RD, Threadgill DW. Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence in mice. *Environ Health Perspect*. 2010;118:596-601.
- Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer*. 2006;6:803-12.
- Larigot L, Benoit L, Koual M, Tomkiewicz C, Barouki R, Coumoul X. Aryl Hydrocarbon receptor and its diverse ligands and functions: an exposome receptor. *Annu Rev Pharmacol Toxicol*. 2022;62:383-404.
- Li S, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P, Ferguson KM. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell*. 2005;7:301-11.
- Li ZD, Wang K, Yang XW, Zhuang ZG, Wang JJ, Tong XW. Expression of aryl hydrocarbon receptor in relation to p53 status and clinicopathological parameters in breast cancer. *Int J Clin Exp Pathol*. 2014;7:7931-7.
- Lichtenberger BM, Gerber PA, Holcman M, Buhren BA, Amberg N, Smolle V, et al. Epidermal EGFR controls cutaneous host defense and prevents inflammation. *Sci Transl Med*. 2013;5(199):199ra111.
- Lin LW, Durbin-Johnson BP, Rocke DM, Salemi M, Phinney BS, Rice RH. Environmental pro-oxidants induce altered envelope protein profiles in human keratinocytes. *Toxicol Sci*. 2023;197:16-26.
- Liu G, Jia J, Zhong J, Yang Y, Bao Y, Zhu Q. TCDD-induced IL-24 secretion in human chorionic stromal cells inhibits placental trophoblast cell migration and invasion. *Reprod Toxicol*. 2022;108:10-17.
- Liu Y, Zhu R, Xu T, Chen Y, Ding Y, Zuo S, et al. Potential AhR-independent mechanisms of 2,3,7,8-Tetrachlorodibenzo-p-dioxin inhibition of human glioblastoma A172 cells migration. *Ecotoxicol Environ Saf*. 2024;273:116172.
- Long M, Wielsoe M, Bonefeld-Jorgensen EC. Dioxin-like activity in pregnant women and indices of fetal growth: The ACCEPT birth cohort. *Toxics*. 2022;10(1):26.
- Lucier GW, Nelson KG, Everson RB, Wong TK, Philpot RM, Tiernan T, et al. Placental markers of human exposure to polychlorinated biphenyls and polychlorinated dibenzofurans. *Environ Health Perspect*. 1987;76:79-87.

- Madhukar BV, Brewster DW, Matsumura F. Effects of in vivo-administered 2,3,7,8-tetrachlorodibenzo-p-dioxin on receptor binding of epidermal growth factor in the hepatic plasma membrane of rat, guinea pig, mouse, and hamster. *Proc Natl Acad Sci U S A*. 1984; 81:7407-11.
- Madhukar BV, Ebner K, Matsumura F, Bombick DW, Brewster DW, Kawamoto T. 2,3,7,8-Tetrachlorodibenzo-p-dioxin causes an increase in protein kinases associated with epidermal growth factor receptor in the hepatic plasma membrane. *J Biochem Toxicol*. 1988;3: 261-77.
- Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. *Breast Cancer Res Treat*. 2012;136:331-45.
- Miettinen PJ, Berger JE, Meneses J, Phung Y, Pedersen RA, Werb Z, et al. Epithelial immaturity and multiorgan failure in mice lacking epidermal growth factor receptor. *Nature*. 1995;376(6538):337-41.
- Mimura J, Yamashita K, Nakamura K, Morita M, Takagi TN, Nakao K, et al. Loss of teratogenic response to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in mice lacking the Ah (dioxin) receptor. *Genes Cells*. 1997; 2:645-54.
- Miret NV, Zarate LV, Erra Diaz F, Leguizamon MA, Pontillo CA, Chiappini FA, et al. Extracellular acidosis stimulates breast cancer cell motility through aryl hydrocarbon receptor and c-src kinase activation. *J Cell Biochem*. 2022;123:1197-206.
- Moore RW, Fritz WA, Schneider AJ, Lin TM, Branam AM, Safe S, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin has both pro-carcinogenic and anti-carcinogenic effects on neuroendocrine prostate carcinoma formation in TRAMP mice. *Toxicol Appl Pharmacol*. 2016;305: 242-9.
- Mordukhovich I, Beyea J, Herring AH, Hatch M, Stellman SD, Teitelbaum SL, et al. Vehicular traffic-related polycyclic aromatic hydrocarbon exposure and breast cancer incidence: The Long Island Breast Cancer Study Project (LIBCSP). *Environ Health Perspect*. 2016;124(1):30-8.
- Murillo-Gonzalez FE, Garcia-Aguilar R, Limon-Pacheco J, Cabanas-Cortes MA, Elizondo G. 2,3,7,8-Tetrachlorodibenzo-p-dioxin and kynurenine induce Parkin expression in neuroblastoma cells through different signaling pathways mediated by the aryl hydrocarbon receptor. *Toxicol Lett*. 2024;394:114-27.
- Mutoh S, Sobhany M, Moore R, Perera L, Pedersen L, Sueyoshi T, et al. Phenobarbital indirectly activates the constitutive active androstane receptor (CAR) by inhibition of epidermal growth factor receptor signaling. *Sci Signal*. 2013;6(274):ra31.
- Panteleyev AA, Bickers DR. Dioxin-induced chloracne--reconstructing the cellular and molecular mechanisms of a classic environmental disease. *Exp Dermatol*. 2006;15:705-30.
- Papoutsis AJ, Selmin OI, Borg JL, Romagnolo DF. Gestational exposure to the AhR agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin induces BRCA-1 promoter hypermethylation and reduces BRCA-1 expression in mammary tissue of rat offspring: preventive effects of resveratrol. *Mol Carcinog*. 2015;54:261-9.
- Patel RD, Kim DJ, Peters JM, Perdew GH. The aryl hydrocarbon receptor directly regulates expression of the potent mitogen epiregulin. *Toxicol Sci*. 2006;89: 75-82.
- Perez-Torres M, Guix M, Gonzalez A, Arteaga CL. Epidermal growth factor receptor (EGFR) antibody down-regulates mutant receptors and inhibits tumors expressing EGFR mutations. *J Biol Chem*. 2006;281: 40183-92.
- Peus D, Hamacher L, Pittelkow MR. EGF-receptor tyrosine kinase inhibition induces keratinocyte growth arrest and terminal differentiation. *J Invest Dermatol*. 1997;109:751-6.
- Poindexter NJ, Williams RR, Powis G, Jen E, Caudle AS, Chada S, et al. IL-24 is expressed during wound repair and inhibits TGF α -induced migration and proliferation of keratinocytes. *Exp Dermatol*. 2010;19: 714-22.
- Poland A, Glover E, Kende AS. Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. Evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase. *J Biol Chem*. 1976;251:4936-46.
- Rab A, Szentpeteri I, Kornya L, Borzsonyi B, Demendi C, Joo JG. Placental gene expression patterns of epidermal growth factor in intrauterine growth restriction. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):96-9.
- Rybak JA, Sahoo AR, Kim S, Pyron RJ, Pitts SB, Guleryuz S, et al. Allosteric inhibition of the epidermal growth factor receptor through disruption of transmembrane interactions. *J Biol Chem*. 2023;299: 104914.

- Sewall CH, Lucier GW, Tritscher AM, Clark GC. TCDD-mediated changes in hepatic epidermal growth factor receptor may be a critical event in the hepatocarcinogenic action of TCDD. *Carcinogenesis*. 1993;14:1885-93.
- Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB. Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. *Br J Cancer*. 2017;116:1229-33.
- Sibilia M, Wagner EF. Strain-dependent epithelial defects in mice lacking the EGF receptor. *Science*. 1995;269(5221):234-8.
- Smotherman C, Sprague B, Datta S, Braithwaite D, Qin H, Yaghjyan L. Association of air pollution with postmenopausal breast cancer risk in UK Biobank. *Breast Cancer Res*. 2023;25(1):83.
- Sondermann NC, Momin AA, Arold ST, Haarmann-Stemmann T. Benzotriazole UV stabilizers disrupt epidermal growth factor receptor signaling in human cells. *Environ Int*. 2024a;190:108886.
- Sondermann NC, Momin AA, Arold ST, Haarmann-Stemmann T. Polybrominated diphenyl ether flame retardants inhibit growth factor-induced activation of EGFR by binding to its extracellular domain. *Arch Toxicol*. 2024b;epub ahead of print. doi:10.1007/s00204-024-03926-9.
- Sun Y, Miao X, Zhu L, Liu J, Lin Y, Xiang G, et al. Autocrine TGF- α is associated with Benzo(a)pyrene-induced mucus production and MUC5AC expression during allergic asthma. *Ecotoxicol Environ Saf*. 2022;241:113833.
- Sunahara GI, Nelson KG, Wong TK, Lucier GW. Decreased human birth weights after in utero exposure to PCBs and PCDFs are associated with decreased placental EGF-stimulated receptor autophosphorylation capacity. *Mol Pharmacol*. 1987;32:572-8.
- Sutter CH, Olesen KM, Bhujji J, Guo Z, Sutter TR. AHR Regulates metabolic reprogramming to promote SIRT1-dependent keratinocyte differentiation. *J Invest Dermatol*. 2019;139:818-26.
- Tice DA, Biscardi JS, Nickles AL, Parsons SJ. Mechanism of biological synergy between cellular Src and epidermal growth factor receptor. *Proc Natl Acad Sci U S A*. 1999;96:1415-20.
- Ticiani E, Gingrich J, Pu Y, Vettathu M, Davis J, Martin D, et al. Bisphenol S and epidermal growth factor receptor signaling in human placental cytotrophoblasts. *Environ Health Perspect*. 2021;129(2):27005.
- Ticiani E, Villegas JA, Murga-Zamalloa C, Veiga-Lopez A. Binding sites in the epidermal growth factor receptor are responsible for bisphenol S effects on trophoblast cell invasion. *Chemosphere*. 2023;318:137960.
- To C, Beyett TS, Jang J, Feng WW, Bahcall M, Haikala HM, et al. An allosteric inhibitor against the therapy-resistant mutant forms of EGFR in non-small cell lung cancer. *Nat Cancer*. 2022;3:402-17.
- Tsukimori K, Uchi H, Mitoma C, Yasukawa F, Chiba T, Todaka T, et al. Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease. *Environ Int*. 2012;38:79-86.
- Uribe ML, Marrocco I, Yarden Y. EGFR in cancer: signaling mechanisms, drugs, and acquired resistance. *Cancers (Basel)*. 2021;13(11):2748.
- Vacher S, Castagnet P, Chemlali W, Lallemand F, Meuseure D, Pocard M, et al. High AHR expression in breast tumors correlates with expression of genes from several signaling pathways namely inflammation and endogenous tryptophan metabolism. *PLoS One*. 2018;13(1):e0190619.
- Van Tung D, Kido T, Honma S, Manh HD, Nhu DD, Okamoto R, et al. Low birth weight of Vietnamese infants is related to their mother's dioxin and glucocorticoid levels. *Environ Sci Pollut Res Int*. 2016;23:10922-9.
- Vazquez-Rivera E, Rojas B, Parrott JC, Shen AL, Xing Y, Carney PR, et al. The aryl hydrocarbon receptor as a model PAS sensor. *Toxicol Rep*. 2022;9:1-11.
- Vogel CFA, Haarmann-Stemmann T. The aryl hydrocarbon receptor repressor - More than a simple feedback inhibitor of AhR signaling: Clues for its role in inflammation and cancer. *Curr Opin Toxicol*. 2017;2:109-19.
- Vogel C, Boerboom AM, Baechle C, El-Bahay C, Kahl R, Degen GH, et al. Regulation of prostaglandin endoperoxide H synthase-2 induction by dioxin in rat hepatocytes: possible c-Src-mediated pathway. *Carcinogenesis*. 2000;21:2267-74.
- Vogel CFA, Lazennec G, Kado SY, Dahlem C, He Y, Castaneda A, et al. Targeting the Aryl hydrocarbon receptor signaling pathway in breast cancer development. *Front Immunol*. 2021;12:625346.
- Vogele C, Sondermann NC, Woeste S, Momin AA, Gilardino V, Hartung F, et al. Unraveling the differential impact of PAHs and dioxin-like compounds on AKR1C3 reveals the EGFR extracellular domain as a critical determinant of the AHR response. *Environ Int*. 2022;158:106989.

- Vorderstrasse BA, Steppan LB, Silverstone AE, Kerkvliet NI. Aryl hydrocarbon receptor-deficient mice generate normal immune responses to model antigens and are resistant to TCDD-induced immune suppression. *Toxicol Appl Pharmacol.* 2001;171:157-64.
- Walker NJ, Wyde ME, Fischer LJ, Nyska A, Bucher JR. Comparison of chronic toxicity and carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in 2-year bioassays in female Sprague-Dawley rats. *Mol Nutr Food Res.* 2006;50:934-44.
- Wang T, Wyrick KL, Meadows GG, Wills TB, Vorderstrasse BA. Activation of the aryl hydrocarbon receptor by TCDD inhibits mammary tumor metastasis in a syngeneic mouse model of breast cancer. *Toxicol Sci.* 2011;124:291-8.
- Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect.* 2002;110:625-8.
- Wendt MK, Williams WK, Pascuzzi PE, Balanis NG, Schiemann BJ, Carlin CR, et al. The antitumorigenic function of EGFR in metastatic breast cancer is regulated by expression of Mig6. *Neoplasia.* 2015;17(1):124-33.
- WHO, World Health Organization. Dioxins. <https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health>. Geneva: WHO, 2023. Accessed 08 December 2024.
- Wu Y, Chen X, Zhou Q, He Q, Kang J, Zheng J, et al. ITE and TCDD differentially regulate the vascular remodeling of rat placenta via the activation of AhR. *PLoS One.* 2014;9(1):e86549.
- Xie G, Peng Z, Raufman JP. Src-mediated aryl hydrocarbon and epidermal growth factor receptor cross talk stimulates colon cancer cell proliferation. *Am J Physiol Gastrointest Liver Physiol.* 2012;302:G1006-15.
- Yao N, Wang CR, Liu MQ, Li YJ, Chen WM, Li ZQ, et al. Discovery of a novel EGFR ligand DPBA that degrades EGFR and suppresses EGFR-positive NSCLC growth. *Signal Transduct Target Ther.* 2020;5(1):214.
- Yen YY, Lan SJ, Yang CY, Wang HH, Chen CN, Hsieh CC. Follow-up study of intrauterine growth of transplacental Yu-Cheng babies in Taiwan. *Bull Environ Contam Toxicol.* 1994;53:633-41.
-