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Review

The toxicological profile of polychlorinated naphthalenes (PCNs)

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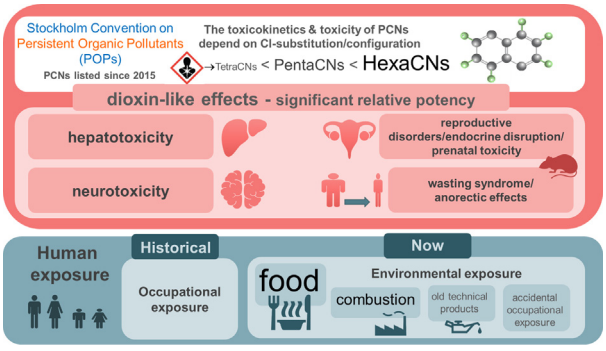
HIGHLIGHTS

- PCNs elicit a range of potent toxicological effects in humans and animals
- PCNs with Cl ≥5 (esp. H_6CNs) have higher REPs, so are toxicologically more significant
- Future studies should target chronic exposure of PCN congeners persistent in the diet

GRAPHICAL ABSTRACT



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ABSTRACT

The legacy of polychlorinated naphthalenes (PCNs) manufactured during the last century continues to persist in the environment, food and humans. Metrological advances have improved characterisation of these occurrences, enabling studies on the effects of exposure to focus on congener groups and individual PCNs. Liver and adipose tissue show the highest retention but significant levels of PCNs are also retained by the brain and nervous system. Molecular configuration appears to influence tissue disposition as well as retention, favouring the higher chlorinated (≥ four chlorines) PCNs while most lower chlorinated molecules readily undergo hydroxylation and excretion through the renal system. Exposure to PCNs reportedly provokes a wide spectrum of adverse effects that range from hepatotoxicity, neurotoxicity and immune response suppression along with endocrine disruption leading to reproductive disorders and embryotoxicity. A number of PCNs, particularly hexachloronaphthalene congeners, elicit AhR mediated responses that are similar to, and occur within similar potency ranges as most dioxin-like polychlorinated biphenyls (PCBs) and some chlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs), suggesting a relationship based on molecular size and configuration between these contaminants. Most toxicological responses generally appear to be associated with higher chlorinated PCNs. The most profound effects such as serious and sometimes fatal liver disease, chloracne, and wasting syndrome resulted either from earlier episodes of occupational exposure in humans or from acute experimental dosing of animals at levels that reflected these exposures. However, since the restriction of manufacture and controls on inadvertent production (during combustion processes), the principal route of human and animal exposure

Abbreviations: AhR, aryl hydrocarbon receptor; ALA-D, aminolevulinic acid dehydratase; ARNT, AhR nuclear translocator; CNS, central nervous system; CYP, Cytochromes P450 (family of enzymes); EDC, endocrine disrupting chemical; ERa/b, Estrogen receptors alpha (ERα) and beta (ERβ); FSH, follicle stimulating hormone; GABA, γ-aminobutyric acid; H_6CN, hexachlorinated naphthalene (also hexa-CN); *ip*, intraperitoneal; LH, luteinising hormone; LOAEL, lowest observed adverse effect level; PBDEs, polybrominated diphenylethers; PCBs, polychlorinated biphenyls; PCDD/Fs, polychlorinated dibenzo-*p*-dioxins and furans; PCNs, polychlorinated naphthalenes; *per os*, oral administration; POPs, persistent organic pollutants; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; REP, relative potency; T_4CN, tetrachlorinated naphthalene (also tetra-CN); TEQ, toxic equivalence; TRβ, thyroid hormone receptor β; TSH, thyroid stimulating hormone; URO-D, uroporphyrinogen decarboxylase; VMAT1, vesicular monoamine transporter 1 (protein); XRE, xenobiotic responsive element.

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is likely to be dietary intake. Therefore, further investigations should include the effects of chronic lower level intake of higher chlorinated PCN congeners that persist in the human diet and subsequently in human and animal tissues. PCNs in the diet should be evaluated cumulatively with other similarly occurring dioxin-like contaminants.

Contents

1. Introduction

Polychlorinated naphthalenes (PCNs) are industrial chemicals that were manufactured in vast quantities (up to 0.4 million tons) during the last century. As versatile products, they were used in a diverse range of applications such as temperature moderating fluids in electrical equipment, cable insulation, wood preservation, engine oil additives, electroplating masking compounds, feedstocks for dye production, flame retardants, plastic and rubber additives, fungicides, sealants, etc. (Federal Register, 1983; Crookes and Howe, 1993; Falandysz, 1998).

A range of adverse biological effects associated with PCN exposure has been reported, ranging from death through severe liver damage (mostly through occupational exposure during the early to mid-20th century in humans and accidental exposure through contaminated feed in farmed animals) to more subtle long term conditions such as pre-carcinogenesis. In recent years, the Stockholm Convention has listed PCNs as a persistent organic pollutant (POP) with the goal of ultimate elimination of its use and production as well as reducing unintentional production. This review begins with a brief contextual background on PCNs, highlighting diet as the principal human exposure pathway in the absence of occupational exposure, but it is oriented towards toxicological effects including more recent and more speciated data, i.e., on the effects of homologue groups or individual congeners, where possible. Detailed information on aspects of production, dispersion pathways, global contamination, food occurrence and human exposure have been adequately covered in other reviews (Falandysz, 1998, 2003; Bidleman et al., 2010; Fernandes et al., 2017). However, there is no recent collation of the biological effects of PCN exposure, particularly from studies that have emerged in the last two decades or so, that together with earlier findings would allow a more complete toxicological picture for risk assessment and management, regulation, future monitoring, and other control requirements. Although the effects of high levels (milligram quantities) of historical occupational exposure are briefly described, these are unlikely to occur again as PCNs are no longer produced, so although this review includes the effects reported from earlier studies, it has more emphasis on relatively recent studies that have investigated generally lower levels of exposure. The information will contribute to the understanding of the effects of our continuing exposure to these chemicals along with others that display similar (e.g., dioxin-like) toxicity.

1.1. Contextual background

The relatively simple manufacturing process used for PCNs involved the chlorination of molten technical grade naphthalene with Cl_2, an electrophilic substitution reaction that was catalysed, most commonly by $FeCl_3$ ($SbCl_5$ was also used) at temperatures ranging from 80 to 180 °C depending on the required degree of chlorination of the product (elevated temperatures yielded higher chlorinated naphthalenes). The resulting mixtures of variously chlorinated congeners could also be graded according to application with a physical appearance ranging from mobile oils (lower chlorination) to hard pale-yellow solids with the consistency of microcrystalline waxes (e.g., octachloronaphthalene) (WHO, 2001).

PCNs were used extensively for most of the 20th century and were manufactured in a number of European countries, e.g., Germany, UK, France, Poland, Italy, etc., and in the US and Japan (Crookes and Howe, 1993; Falandysz, 1998; WHO, 2001) from around 1910. The long period of manufacture and the lack of available records make it difficult to quantify the global production but figures of 150,000 to 400,000 metric tons have been estimated (Falandysz, 2003; Falandysz and Fernandes, 2020). It is important to note however that the estimates relate to intentional manufacture, and do not include the quantities that arise from inadvertent production. These include the unintended by-production of PCNs most notably during the manufacture of another legacy chemical that was manufactured in huge quantities – the polychlorinated biphenyls (PCBs) (Yamashita et al., 2000). Although PCB formation proceeds via the biphenyl substrate, the similarity of the technical manufacturing processes (catalysed chlorination of naphthalene or biphenyl) is thought to yield a similar distribution of congeners in the PCN by-product. They are also unintentionally produced during synthesis of chlorinated solvents and chlorinated paraffins (Takasuga et al., 2012; Zhang et al., 2015). Another important and ongoing source is combustion processes such as the incineration of municipal and hospital wastes, secondary non-ferrous metal smelting and iron-ore sintering (Falandysz, 1998; Liu et al., 2014). Other significant sources

were production processes that used PCNs as lubricants and waste sludge from the chlor-alkali industry (Kannan et al., 1998). Although production effectively ended by the 1980s, PCNs remained in industrial use for almost a decade or more, later (Falandysz et al., 2008; Popp et al., 1997; Yamashita et al., 2004). Some PCN formulations were stockpiled until the end of the 20th century, e.g. from DuPont Dow Elastomers Ltd. based in Northern Ireland in the UK (Falandysz et al., 2008; Yamamoto et al., 2018). As a result of these diverse sources, almost all PCN congeners and homologue groups, from monochlorinated to octachlorinated (monoCNs – octaCN) may occur in environmental samples (Ba et al., 2010; Horii et al., 2004; Hanari et al., 2013, 2020; Falandysz et al., 1996; Ieda et al., 2011; Mari et al., 2008).

The commercially desirable properties of physical and chemical stability often bestow unfortunate side-effects such as persistence when these chemicals are released into the environment. These characteristics, combined with long-term open-ended use (oil additives, plasticizers, wood preservatives, fungicides etc.) has resulted in PCN contamination being reported in every environmental compartment – air, water, soil, sediments, (Helm et al., 2006; Bidleman et al., 2010; Li et al., 2016) including pristine environments such as remote forests and Polar Regions (Bidleman et al., 2010). In addition, the detection of PCNs in fish, shellfish and marine mammals from both hemispheres, including polar species, confirms global dispersion. Combined with the increasing knowledge of toxicological effects, these findings prompted a downturn in manufacture during the late 1970s and into the 1980s, but by this period, the legacy of almost a century of use resulted in routine PCN detection in most media – environmental as well as biological, including human tissues. These findings, including studies and data from remote locations, and unintentional production have been reviewed in recent years (Bidleman et al., 2010; Liu et al., 2014) and confirm the global nature of PCN contamination. A drastic decline in production by the largest PCN producer during the late 1970s was also prompted by the introduction of the Toxic Substances Control act in the US. PCNs were also included within the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations (REACH, 2006) in Europe, as chemicals that were subject to export controls or banned from export from the EU. It was therefore unsurprising that PCNs were proposed for listing as undesirable chemicals within the Stockholm Convention, in the earlier part of the current century (UNEP, 2019). Most countries ratified this decision by the end of 2016 and PCNs are now classified as POPs, listed in Annexes A and C, which require the elimination of PCN production and use, as well as the minimisation of unintentional release.

1.2. Occurrence in food and dietary intake — human exposure

Although the early reported cases of human poisoning and fatalities were principally a result of occupational exposure, this is now unlikely to be a significant exposure route for the majority of populations as PCNs are no longer produced as an industrial chemical. The main documented routes of historical exposure were dermal contact and inhalation. The vapours that were emitted during the high temperature (115-127 °C) handling of lower chlorinated PCN mixtures could be inhaled by the workers, but vapours condensing on exposed skin caused more immediate effects such as chloracne (Hamilton, 1943). In present times, dermal contact is unlikely but some respiratory exposure is still possible, e.g. workers inhaling fugitive emissions during incineration processes. However, the major pathway to current human exposure is likely to be via low levels of chronic dietary intake (Fernandes et al., 2017; Zacs et al., 2021). The presence of PCNs in all types of foods has been established and recently reviewed (Fernandes et al., 2017, 2020, 2022). The data show that despite the passage of almost a half-century since the decline of manufacture, PCNs still occur in foods, spanning a wide range of concentrations depending on the type of food. The patterns of accumulation appear to vary with the type of food, with the widest range of measured congeners occurring in plant-based foods and lower order animals. In higher order animals and humans, factors such as metabolic processes, selective uptake, congener prevalence in prey/food, etc., reduce this occurrence in tissues to a set of fewer, more persistent congeners (Fig. 1A, Kunisue et al., 2009).

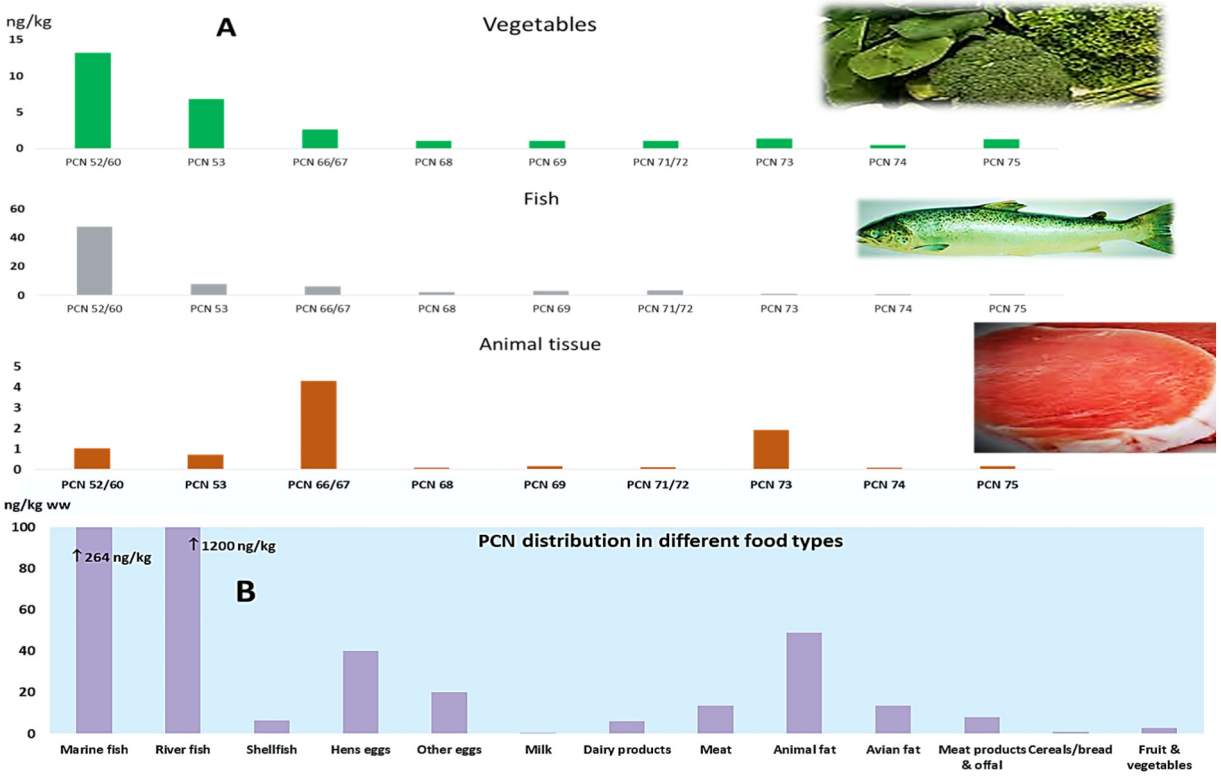

Fig. 1. A: PCN congener distributions in different foods showing metabolic effects in a range of fish species and animal tissues (ovine/bovine) and B: relative concentrations in foods.

The effect is more enhanced in older individuals with higher metabolic capacity than juveniles (Falandysz et al., 1996). Fig. 1B shows the relative distribution of PCN occurrence in different food types. At the upper end of the scale, edible marine and fresh water fish show concentrations in the low parts per billion range (a recent report by Gewurtz et al. (2018) reports a maximum of 6.7 μg kg^{-1} wet weight) but low and sub-ppt (ng kg^{-1}) levels occur in other foods such as vegetables and cereals (Fig. 1B). It is notable that the sources of such data are limited. There does not appear to be any regular monitoring for PCNs in food in any country or region, and reported data is often the result of explorative research studies. Another feature is the limited number of observations - most commonly, data for tens of samples are reported. The choice and number of congeners reported also varies between studies, with more congeners being reported in the most recent studies (Zacs et al., 2021; Pagano and Garner, 2021), corresponding to the better availability of reference standards. The resulting collations of data (e.g., Fernandes et al., 2017) provide periodic snapshots rather than a temporal picture of where the background levels actually lie. These limitations combined with the absence of data from many countries make it difficult to gauge global PCN distributions or allow comparison of human exposure between regions.

Despite these limitations, the data does provide some characterisation of PCN occurrences in widely consumed food types (fish, shellfish, eggs and meat were generally more contaminated) and allows preliminary estimations of human exposure resulting from dietary intake. Additionally, the data and the intake estimates also allow a comparative evaluation with other similar contaminants such as the PCBs and PCDD/Fs, etc., that promote similar concerns in terms of long-term toxic responses. Earlier reports on PCN dietary intake were based on summed congener totals or homologue group totals (e.g., Marti-Cid et al. (2008), reported a PCN intake of 7.25 ng day^{-1} or 0.1 ng kg^{-1} (bw) day^{-1} for a 70 kg adult), but more recent studies have been able to further characterise the occurrences and have estimated intakes using the toxic equivalents of individual congeners (Fernandes et al., 2010, 2011, 2017; Kim et al., 2018; Li et al., 2020; Zacs et al., 2021). Higher level (97.5 percentile) exposures for adults and children were estimated at 0.39 pg TEQ kg^{-1} (bw) day^{-1} and 0.98 pg TEQ kg^{-1} (bw) day^{-1}, respectively (Fernandes et al., 2010). In perspective, when these are added to the estimated average dietary intakes of polychlorinated dibenzo-*p*-dioxins/polychlorinated dibenzofurans (PCDD/Fs) and PCBs the combined intake values of 0.7 and 1.5 pg WHO-TEQ kg bw^{-1} day^{-1} (adults and young children, respectively), suggest a significant contribution from PCN toxicity. More recent estimates (Kim et al., 2018) are based on individual foods such as fish, rather than the full range of dietary constituents, but exposures are similar, and the most recent data on foods within the same country (Fernandes et al., 2019) suggests little change in the concentrations relative to a decade ago (Fernandes et al., 2010).

2. Toxicokinetics

2.1. Absorption, disposition and target organs

Toxicokinetically, PCNs appear to behave in a similar manner to other closely related chlorinated aromatic contaminants. The historical data based on human occupational exposure documented absorption via dermal and respiratory routes and more recent studies on animals have established that oral absorption may be dependent on the degree of chlorination (Oishi and Oishi, 1983, Asplund et al., 1986, Kilanowicz et al., 2004, 2012).

Comparative studies on tissue distribution have been performed for technical mixtures of PCNs (Asplund et al., 1994; Jakobsson et al., 1994; Klasson-Wehler et al., 1996) and also for several individual PCN congeners (Kilanowicz et al., 2004, 2012) in test animals. These studies documented a slow turnover rate of the tested compounds, which, especially in the case of repeated exposure, may persist in tissues resulting in long-term storage. 1,2,3,5,6,7-H_6CN showed the greatest propensity for accumulation, and the distribution of this compound (based on the mean of five replicate measurements at time points ranging from 24 to 504 h following single doses: 0.3 mg per rat) decreased in the following order: liver > adipose tissue > spleen = adrenals > sciatic nerve > kidney = lungs = brain > blood > muscle (Kilanowicz et al., 2012). This indicates that of all the target organs studied, the liver showed the greatest retention, especially of the higher chlorinated congeners, i.e., hexaCNs, as demonstrated in studies on rats (Asplund et al., 1994; Kilanowicz et al., 2012). An additional confirmation of the high lipophilic affinity of 1,2,3,5,6,7-H_6CN for the liver is the determined liver/adipose tissue ratio, which showed several times higher concentrations in the liver compared to adipose tissue. Comparatively, 1,2,3,4-T_4CN and 1,2,3,4,5-P_5CN showed a lower level of retention in the liver (Kilanowicz et al., 2004). Interestingly, all analyzed tissues showed varying levels of decrease of 1,2,3,5,6,7-H_6CN during the measurement interval, except for the brain and sciatic nerve, in which there was an increase or a sustained value, respectively, over a period of 24–120 h. This data indicates that 1,2,3,5,6,7-H_6CN passes through the blood/brain barrier and suggests that the nervous system may be an important target for the higher chlorinated PCNs congeners (Kilanowicz et al., 2012; Lisek et al., 2020, 2022), especially in terms of long-term toxicity resulting from hexaCN exposure.

Successive elimination of moderately to higher chlorinated congeners from the liver and adipose tissue was observed in Sprague-Dawley rats, following the order: tetra-, penta- and also heptaCNs and octaCN, but this was after much longer retention of up to 32 days (Asplund et al., 1986). When dosed at 0.053 mg kg^{-1} bw, some congeners, particularly hexaCNs (1,2,3,4,6,7-H_6CN, 1,2,3,5,6,7-H_6CN and another unidentified H_6CN) were selectively retained (Asplund et al., 1994). 1,2,3,5,6,7-H_6CN (0.3 mg per rat) accumulated to an almost ten-fold higher extent in adipose tissue and liver regardless of the route of administration (*i.p.* or *per os*) (Kilanowicz et al., 2012), differing significantly from the lower retention of 1,2,3,4-T_4CN and 1,2,3,4,5-P_5CN (both dosed at 10 mg kg^{-1} bw) (Kilanowicz et al., 2004). These patterns of disposition were also observed in humans where a range of tetra- to hexaCNs were reported in a greater proportion in the liver relative to adipose tissue (Weistrand and Norén, 1998).

2.2. Metabolism and elimination

PCNs are likely to be metabolized like other similar chlorinated hydrocarbons (e.g., PCBs) and show increasing resistance to enzymatic oxidation as the number of substituted halogens increases (Falandysz et al., 1996, 2014). As the liver is one of the main organs involved in detoxification, it becomes a primary target for xenobiotics such as PCNs. The liver also produces bile to aid the digestion of consumed lipids which are the vehicles for these lipophilic chemicals. As part of its detoxification function, the activity of hepatic enzymes can be regulated to respond to low level of toxicants such as PCNs and other chlorinated hydrocarbons. This process facilitates the conversion of PCNs to hydroxylated or other water-soluble derivatives that can be excreted (Asplund et al., 1994; Kilanowicz et al., 2012).

Lower chlorinated PCNs (mono- to tri-) which have a larger proportion of vicinal hydrogen-substituted carbons are metabolized mainly via hydroxylation to arene oxide intermediates and by hydroxylation-dechlorination (Falandysz et al., 2014). The major products are phenolic and conjugated hydroxylated metabolites which are excreted through the kidneys. This metabolic pathway declines in significance with increasing degree of chlorination and the kidneys are not a particularly important route of elimination for penta- to octa-chlorinated congeners (IPCS, 2001).

On the other hand, fecal elimination of PCNs dominates in the case of higher chlorinated PCNs. Over 60% of a single dose, administered *ip*, of 1,2,3,4-T_4CN and 1,2,3,4,5-P_5CN, was eliminated through the faeces over 5 days (65% and 70% respectively) but elimination of 1,2,3,5,6,7-H_6CN was much slower, with only 35% of the administered dose being eliminated over the same period. This corresponds well with the high retention of 1,2,3,5,6,7-H_6CN in organs, mainly in adipose tissue and liver (Kilanowicz et al., 2004, 2012).

The decline of 1,2,3,5,6,7-H_6CN in Wistar rat plasma was typical of the two-compartment open model (half-lives for phases I and II were 6 and 350

h, respectively) (Kilanowicz et al., 2012). Half-lives were longer in rat liver and adipose tissue: 36 and 41 days, respectively (Asplund et al., 1986; IPCS, 2001).

Chlorination degree and molecular configuration have been seen as an influence on the biomagnification of PCNs. Biomagnification factors reported (Guruge et al., 2004) for chickens and pigs show a tendency to higher values for some of the highly chlorinated congeners, including some P_5CNs and H_6CNs but also 1,2,3,4,5,6,7-H_7CN. Similarly, the compositional pattern of PCNs seen in the tissues of harbour porpoises and herring (Falandysz and Rappe, 1996; Ishaq et al., 2000) show a marked dominance of these congeners indicating selective and structure-dependent metabolism.

In the case of human blood samples collected during the Yusho (1968) and Yu-cheng (1979) incidents which involved exposure to PCB mixtures that also contained a range of PCNs, half-lives were estimated at between 1.5 and 2.4 years (Ryan and Masuda, 1994). Similarly, the PCN content in Swedish human milk samples collected between 1972 and 1992 showed a decrease to 16% over this period, indicating a half-life of 8 years (Norén and Meironyte, 2000). These observations confirm that absorption, metabolism and elimination (both urinary and fecal) of PCNs are influenced by both, the degree of chlorination and molecular configuration. Based on the limited observations, these molecular characteristics may also affect the elimination half-lives, but studies on a wider range of congeners would be required to confirm this.

2.3. Toxicokinetics following prenatal exposure

There are very few studies that have documented the cross-placental transfer of PCNs (Omura et al., 2000; Kilanowicz et al., 2019a; Stragierowicz et al., 2018). Two studies describe the maternal-fetal distribution in pregnant Wistar rats after a single administration of 0.3 mg per dam of 1,3,5,8-T_4CN [PCN-43, ring-U-^{3}H] (Kilanowicz et al., 2019a) and 1,2,3,5,6,7-H_6CN [^{14}C] (Stragierowicz et al., 2018). Both sets of compounds crossed the placental barrier as was evidenced by nearly 2% of these compounds being deposited in the maternal-fetal compartment (placenta, amniotic fluid and litter). The results of these studies also confirmed that the highest accumulations of PCNs were in the liver and adipose tissue. However, the affinity of administered 1,3,5,8-T_4CN to the liver tissue of pregnant mothers was almost five times lower in comparison to 1,2,3,5,6,7-H_6CN [^{14}C] with observed mean concentrations of 1.1 mg g^{-1} and 5.4 mg g^{-1} tissue respectively. In addition, unlike the hexaCN, 1,3,5,8-T_4CN [ring-U-^{3}H] accumulated to a lower extent in adipose tissue than in the liver. Interestingly, both congeners showed an affinity for reproductive tissues (uterus and ovaries). Concentrations recorded in these tissues were 2–4 times higher than in maternal blood. Relatively high concentrations of both 1,3,5,8-T_4CN [ring-U-^{3}H] and 1,2,3,5,6,7-H_6CN [^{14}C] were also founded in the sciatic nerve, brain and adrenal glands (higher than blood levels), which may indirectly indicate the possible toxic effects of the tested compounds on the central and peripheral nervous systems (CNS and PNS), as well as on the endocrine system (Kilanowicz et al., 2015).

Within the fetuses, the highest concentrations of both congeners were recorded in the brain and kidneys. The similarity in the organ distribution in dams and the extent to which transplacental transport of 1,3,5,8-T_4CN [ring-U-^{3}H] and 1,2,3,5,6,7-H_6CN [^{14}C] occurs does not appear to be related to the toxic effects that these compounds cause during prenatal exposure. While both tested compounds showed fetotoxic effects (delay in ossification), embryotoxic effects were only characteristic of 1,2,3,5,6,7-H_6CN (Kilanowicz et al., 2015).

3. Toxic effects

The toxicity associated with occupational exposure to PCNs has been recognised for almost a century. However, our understanding of the range of toxic effects, for example neurological effects, disrupted steroidogenesis, effects on haemostasis and including those mediated by the aryl hydrocarbon receptor (AhR), are only gradually evolving along with the more recent knowledge of human exposure which now occurs mainly through dietary intake (IPCS, 2001; Fernandes et al., 2017; Zacs et al., 2021), in the absence of occupational exposure.

Some of the earliest documented indications of undesirable biological effects on humans were associated with the accelerated use of PCNs in the production of military equipment in the period before and during the Second World War. These studies (Flinn and Jarvik, 1936; Collier, 1943; Good and Pensky, 1943), associated PCNs with hepatic toxicity, which was fatal in some cases (McLetchie and Robertson, 1942; Strauss, 1944; Ward et al., 1996), but also with visible dermal conditions like severe chloracne (Shelley and Kligman, 1957) which was referred to as “Halowax rash” or “Cable rash” in personnel who worked on the electric cabling material. Most of the exposures in these workers were likely to arise from inhalatory or dermal absorption of PCNs during the heating of technical mixtures or the handling of products such as electric cables. During this period, other fatalities related to PCN manufacturing were also documented in the US (Flinn and Jarvik, 1936; Collier, 1943; Strauss, 1944), and in Germany for different reasons – the post-war consequences of food deprivation and hunger resulted in a number of fatalities following the consumption of a PCN product mistakenly consumed as butter (Herzberg, 1947). In subsequent human exposure episodes such as the 1968 Yusho incident in Japan which was followed by the similar Yu Cheng incident in Taiwan (1979), the primary toxicant was identified as PCBs, but later studies found that the rice oil consumed by the victims also contained PCNs and other similar contaminants (Ryan and Masuda, 1994; Haglund et al., 1995), which were identified in the blood, milk and adipose tissue of the exposed subjects.

PCN toxicity resulting from accidental ingestion of contaminated feed was also noted in domestic animals during the 1940's and described as the mysterious “X-disease” (a severe systemic disease characterized by hyperkeratosis) which caused many cattle herds to be destroyed (Bell, 1952, 1953, 1954; Hayward, 1998; IPCS, 2001; Sikes and Bridges, 1952; US Ministry of Agriculture, 1954). Other effects included loss of hair, the generation or irregular growth of horns, anaemia, dehydration, fewer, loss of weight and severe liver damage. Experimental studies implicated higher chlorinated (mainly pentaCNs and hexaCNs) PCN congeners as the causative agents (Hayward, 1998).

The following sub-sections summarize the effects of PCN exposure in humans, generally as a result of occupational exposure, and in animals as the results of experimental studies using technical PCN mixtures, PCN homologue groups and individual congeners. The most toxic effects of PCNs have been evidenced in animal or *in vitro* studies, including binding of PCNs to the AhR. However, the pleiotropic outcomes of AhR binding and the relatively small number of studies make it difficult to identify which effects, apart from CYP induction, arise solely through this mechanism.

3.1. PCNs as aryl hydrocarbon receptor (AhR) ligands

Historical reports on the effects of PCNs were generally, a result of the occupational and accidental exposures that resulted when PCNs were in routine industrial use. The decline in the use of PCNs and studies on the effects of the legacy of earlier usage are more recent phenomena. Halogenated aromatic hydrocarbons are widely recognised as potent agonists of the AhR, with the effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) often being used as a paradigm of this class of environmental and food contaminants. In recent years, the recognition of this mode of action has been extended to other synthetic or xenobiotic ligands (as well as some naturally produced ones) that are commonly identified as environmental and food contaminants. Some of the more potent members of this class of compounds includes PCDD/Fs, PCBs, PCNs and their brominated and mixed halogenated analogues - PBDD/Fs, PXDD/Fs, PXBs, etc. (Falandysz et al., 2012, 2014; Fernandes and Falandysz, 2021; Van den Berg et al., 2006, Van den Berg et al., 2013).

In a manner that has been studied more extensively for similar compounds such as PCDD/Fs and PCBs, PCNs are able to migrate across the

cellular membrane and bind to the AhR. This predominantly cytoplasmic ligand-activated transcription factor is capable of binding to exogenous (xenobiotic) ligands such as PCDD/Fs, PCBs, PCNs, PBDD/Fs etc. with varying degrees of potency that depend on the size and configuration of the individual molecules. Ligand binding is followed by translocation of the AhR-Ligand complex to the nucleus where dimerization with the AhR nuclear translocator (ARNT) protein occurs (Dennison et al., 2002). The resulting dimer has high binding affinity for xenobiotic responsive elements (XREs) on the enhancer regions of specific target genes, up-regulating their transcription. The targeted genes include the cytochrome P-450 (CYP) family of genes. This ability to transcript cytochrome P-450 enzymes is observed in many cell types and in particular, liver cells. Thus, in many mammalian systems, this family of microsomal enzymes (generally found in hepatocytes) function as monooxygenases that process xenobiotics such as PCNs and other chlorinated hydrocarbons. In particular CYP genes such as *CYP1A1*, *CYP1A2* and others are capable of encoding for enzymes that are used to metabolise xenobiotics including PCNs. In this process, formation of mutagenic intermediates, a preliminary pre-carcinogenic or tumour initiation stage, cannot be ruled out. It has long been reported (Poland and Knutson, 1982; Kleinjans et al., 2015) that CYP1A1 induction is proportionate to the potency of these binding ligands, and hence the quantitative estimation of CYP1A1 expression has been used as a sensitive indicator for this mode of action. The up-regulation of CYP1A1 and CYP1A2 associated enzyme activity has been noted in all test animals exposed to PCN congeners, such as 1,2,3,4,6,7-H_6CN (repeated exposure: from 0.5 to 50 μg kg^{-1} bw) and 1,2,3,5,6,7-H_6CN (single exposure: 100 and 250 mg kg^{-1} bw and repeated exposure: from 0.5 μg kg^{-1} to 10 mg kg^{-1} bw) (Kilanowicz and Skrzypinska-Gawrysiak, 2010; Hooth et al., 2012).

In common with other groups of chlorinated aromatic hydrocarbons, the potency of AhR binding varies between PCN congeners. Both, *in vitro* and *in silico* studies indicate that many di-, tri- and tetraCN congeners (e.g., 1,4-D_2CN, 1,5-D_2CN 1,8-D_2CN, 2,3-D_2CN, 1,2,7-T_3CN, 1,2,3,4-T_4CN, 1,2,4,6-T_4CN, 1,2,5,6-T_4CN, etc., either did not activate the AhR or had very low activity (Blankenship et al., 2000; Puzyn et al., 2007; Falandysz et al., 2014; Suzuki et al., 2020). On the other hand, higher chlorinated congeners (penta- to heptaCNs), and in particular, many of the ten hexaCNs display strong binding potential (Behnisch et al., 2003; Falandysz et al., 2014; Kilanowicz et al., 2015; Fernandes et al., 2017). A possible determinant for maximum binding potency for AhR ligands may be an optimum molecular dimension (up to 14 × 12 × 5 Å) that can be accommodated by the AhR (Dennison et al., 2002) and this feature may be relevant to the different classes of halogenated aromatic contaminants. However, it would be simplistic to assume that molecular dimension is the only factor that influences binding, as a range of diverse synthetic and natural chemicals demonstrate this effect, and it is likely that other physical properties of these ligands such as electrostatic and dispersion-type interactions during ligand-AhR binding also influence the process. The configurations of PCN congeners that show the strongest binding potency are shown in Fig. 2 with reported potencies of 0.0002 to 0.005 relative to 2,3,7,8-TCDD (Fernandes et al., 2017; Suzuki et al., 2020).

It was reported earlier that around 20% of PCN congeners (mostly hexa-hepta-, and a few pentaCN compounds) show relative potencies that vary between 0.004 and 0.000001 (Falandysz et al., 2014; Fernandes et al., 2017). For comparative purposes (see Fig. 3), the corresponding range of toxic equivalence factors for regulated dioxin-like PCBs are 0.03 to 0.00003 (apart from the value of 0.1 for PCB 126 which is currently being re-evaluated) and 1 to 0.0003 for regulated PCDDs and PCDFs (Van den Berg et al., 2006). The REPs for the more potent PCN congeners as determined from different *in vitro* and *in silico* studies are listed in Table 1. In terms of the characteristics that influence potency, molecular co-planarity and a configurational similarity to 2,3,7,8-TCDD appear to be important structural features but as discussed earlier, molecular dimensions are also important. Thus, in the case of halogenated contaminants, binding potency appears to be influenced by molecular structures that are diaromatic, laterally substituted (e.g. with chlorine or bromine) and can assume a co-planar configuration with dimensions approximating to 3 × 10 Å (Poland and Knutson, 1982; McKinney, 1989), characteristics that bestow an isosteric relationship to 2,3,7,8-TCDD. This is probably why hexachlorinated-CNs with 2,3,6,7-Cl substitution (PCNs 66, 67 and 70 in Table 1) show the highest REP values, and similarly PCNs 73, 54 and 48 (Table 1) show the highest REP values within the other homologue groups (hepta-, penta- and tetraCNs).

The current volume of studies reporting REPs may be insufficient to establish consensus values for the studied PCN congeners, but the values reported from the various *in vitro* studies (Table 1) can be used conservatively to allow a cumulative risk assessment by estimating the toxic content associated with measured PCN congeners. The more recent human exposure studies have derived PCN TEQs through the use of these REPs, using reported values or after rationalisation of the various reported values

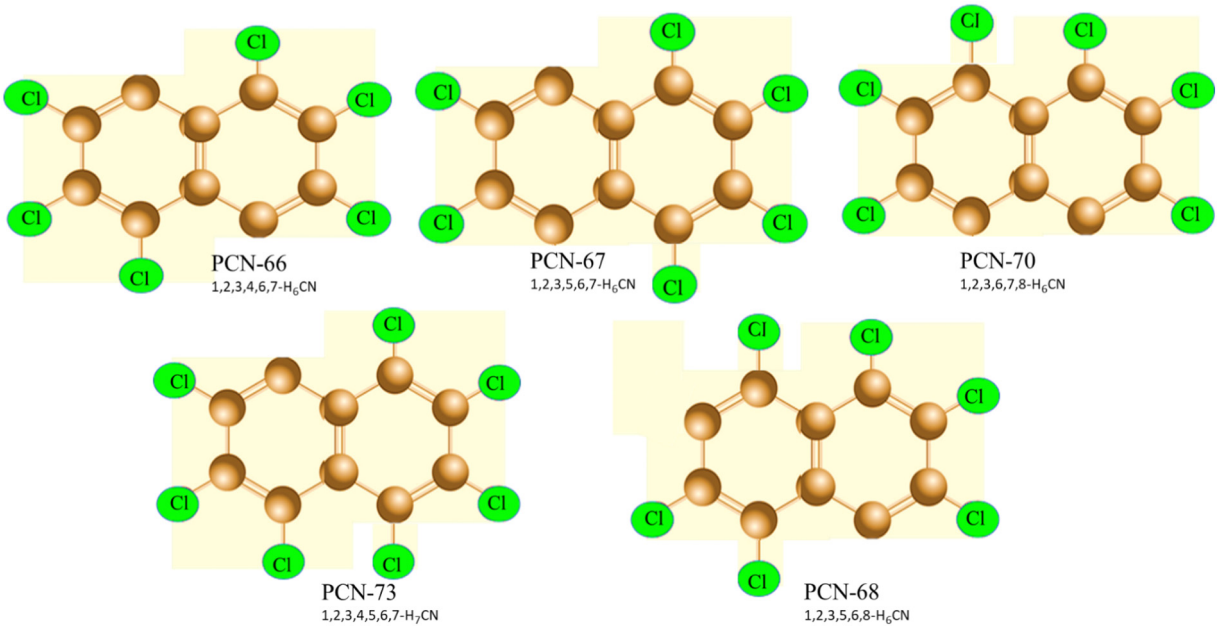

Fig. 2. Molecular configurations for PCN congeners that show potent AhR binding.

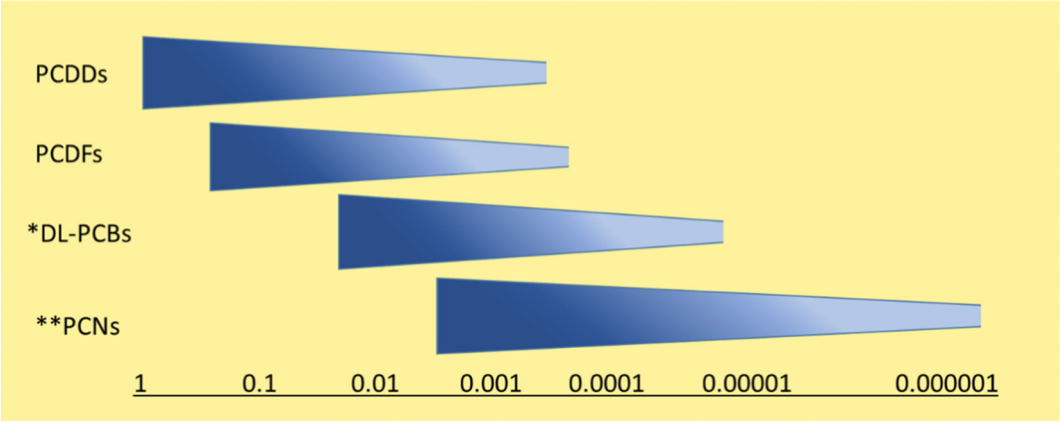

Fig. 3. Relative Potency ranges for PCNs and Toxic Equivalency Factor (TEF) ranges for related dioxin-like compounds *DL-PCBs excludes PCB-126, currently being re-evaluated. ** Penta- to HeptaCNs.

(COT, 2009; Fernandes et al., 2010). The REP values most commonly used in these and related studies (Fernandes et al., 2010, 2011, 2018; Falandysz et al., 2019; Pratt et al., 2013, Rigby et al., 2021; Zacs et al., 2021), are also listed in Table 1. Although the use of this set of REP values are more conservative, the derived TEQs may be more representative because:

- most studies to date do not measure/report all relevant PCN congeners (mostly because reliable standards were not available, although this situation is slowly improving)
- *in vitro* REP values are not available for all measured congeners.
- Consequently, reported TEQs are likely to be underestimated.

A meta-analysis of all reported PCN REP values would be useful and would facilitate harmonisation of their use for risk assessments after confirmation. It is clear from Table 1 that the penta- to heptaCNs show the most potent binding potential.

3.2. Hepatotoxicity

A number of chlorinated hydrocarbons are hepatotoxic and chlorinated aromatics in particular, such as PCNs and PCBs are known to cause potent liver damage (fatty liver changes, hepatomegaly, CYP1A1 induction) (IPCS, 2001, Barć and Gregoraszczuk, 2014; Kilanowicz et al., 2015). At higher concentrations, the resulting hepatotoxicity is seen as subacute necrosis or acute yellow atrophy of the liver (Kleinfeld et al., 1972; Ward et al., 1996; IPCS, 2001), e.g., in humans, fatal cases of yellow atrophy were reported in workers at an industrial plant where air concentrations of 1–2 mg m^{-3} (a mixture of penta- and hexaCNs) were reported (IPCS, 2001). Hepatotoxicity was one of the main reported toxic effects following occupational exposure to PCNs in the previous century. In workers, acute yellow liver atrophy, elevated levels of liver enzymes (mainly γ-glutamyltransferase) and steatosis were noted. In many cases, extensive liver damage and isolated cases of death due to cirrhosis or acute yellow liver atrophy occurred only after the end of exposure, usually from several months to a year (IPCS, 2001; Popp et al., 1997; Ward et al., 1996).

Similarly, hepatotoxicity was one of the dominant effects seen in animals following PCN exposure, regardless of the route of administration or form (single congeners or mixtures, including technical mixtures). Most of the historical animal studies used technical mixtures and reported more severe hepatotoxic effects (IPCS, 2001). However, recent studies using specific congeners, often hexaCNs, have reported more consistent effects such as hepatomegaly or steatosis (Klimczak et al., 2018; Kilanowicz et al., 2015. Repeated dose administration (0.5–50 μg kg^{-1} bw up to 14 days and 1–10 mg kg^{-1} bw up to 28 days) of 1,2,3,4,6,7-H_6CN and/or 1,2,3,5,6,7-H_6CN led to fatty changes accompanied by inflammation of hepatocytes, hepatocellular hypertrophy and focal to multifocal hepatocellular necrosis (Hooth et al., 2012; Stragierowicz et al., 2015). Subchronic exposure caused mainly hepatomegaly, and mixed micro- and macrovesicular steatosis (Klimczak et al., 2018). Additionally, 1,2,3,5,6,7- H_6CN has been shown to induce oxidative stress in hepatocytes and cause extreme induction of CYP1A (Kilanowicz and Skrzypinska-Gawrysiak, 2010; Stragierowicz et al., 2018; Klimczak et al., 2018).

3.3. Neurotoxicity

Early studies describing occupational exposure to PCNs reported fewer specific symptoms, such as weight loss due to a significantly decreased appetite, headaches, difficulty in concentrating, irritability and impotence (IPCS, 2001). In later reports, cohort studies of children whose pregnant mothers were exposed to various halogenated hydrocarbons (PCBs, PBDEs, PCDDs, but also PCNs) documented deleterious effects on neuropsychological development (Kannan et al., 2000; Gascon et al., 2013; Eskenazi et al., 2013; Ginsberg et al., 2004; Gray et al., 2005). These effects, as well as others observed in animal studies, i.e., the inhibition of the feeling of hunger and thirst despite diminished feed and water consumption (Galoch et al., 2006; Kilanowicz et al., 2009; Kilanowicz and Skrzypinska-Gawrysiak, 2010) provide an indication of the neurotoxic activity of PCNs. The disposition of different PCN congeners in the organs of male Wistar rats provides evidence of the varying affinity for the CNS and sciatic nerve (Kilanowicz et al., 2004, 2012). Higher concentrations of both 1,3,5,8-T_4CN [ring-U-^{3}H] and 1,2,3,5,6,7-H_6CN [^{14}C] were also noted in fetal brains compared to maternal blood (Kilanowicz et al., 2019b; Stragierowicz et al., 2018).

Studies (Vinitskaya et al., 2005; Stragierowicz et al., 2018) of specific regions in the rat brain (brain stem, basal ganglia and cerebellum) following repeated exposure (up to 21 days at a dose of 10 mg kg^{-1} bw of tetraCN:54%, pentaCN:8%, hexaCN: 23% and heptaCN:14%, isomers and up to 13 weeks at 0.03–0.3 mg kg^{-1} bw of 1,2,3,5,6,7-H_6CN) demonstrated the impairment of γ-aminobutyric acid (GABA) metabolism in these regions. The effect was manifested by a negative impact on the activity of almost all tested enzymes involved in this process (glutamate decarboxylase, GAMA-aminotransferase, succinic semialdehyde dehydrogenase and succinate dehydrogenase) (Vinitskaya et al., 2005). In a later study, Stragierowicz et al. (2018) examined the effects of a mixture of hexaCN congeners (0.03–0.3 mg kg^{-1} bw) in the same regions in the rat brain. The study also reported a significant decrease in the level of GABA and glutamate in all analyzed structures after subacute exposure (two and four weeks), but not after a thirteen-week sub-chronic exposure. The functioning of the CNS in Wistar rats was also reported to be affected during a range of neurobehavioral tests, after 1,2,3,5,6,7-H_6CN administration (Kilanowicz et al., 2012). The results indicated impaired motivational processes (seen as an anorectic effect connected with aphagia and adipsia), decreased motor activity (hypokinesia), disorders in long-term memory and a significantly reduced reaction to stress. Such signs are very similar to those described earlier in humans occupationally exposed to PCNs (IPCS, 2001).

Table 1
Relative potency values for individual PCN congeners as reported and as used in recent human exposure studies.

Configuration	PCN congener number	*In vitro* REPs						In silico REPs		REPs used in human exposure studies
		H4II-EROD		H4II-luc		DR-CALUX (pM)	Micro-EROD (pM)	DR-CALUX (REP-EC_{5TCDD})		
Source Reference		Villeneuve et al., 2000	Hanberg et al., 1990	Blankenship et al., 1999, 2000		Behnisch et al., 2003		Suzuki et al., 2020	Puzyn et al., 2007	Falandysz et al., 2019, 2020; Fernandes et al., 2010, 2011, 2017, 2019 Pratt et al., 2013; Zacs et al., 2021; Zhihua et al., 2019
1,2,3,4-TeCN	27							2.3×10^{-7}	9.1×10^{-7} 2.3×10^{-6}	2.3×10^{-7}
1,2,4,7-TeCN	34							5.8×10^{-7}	4.7×10^{-7} 1.3×10^{-6}	
1,2,5,6-TeCN	36							2.1×10^{-7}	1.1×10^{-6} 2.7×10^{-6}	2.1×10^{-7}
1,2,6,7-TeCN	39							5.6×10^{-6}	3.3×10^{-7} 7.4×10^{-7}	
1,2,6,8-TeCN	40								1.2×10^{-7} 0.000014	
1,3,5,7-TeCN	42					7.5×10^{-6}	1.9×10^{-6}		1.2×10^{-6} 3.2×10^{-6}	
2,3,6,7-TeCN	48					0.000041		2.4×10^{-5}	0.00023 0.00001	0.000024
1,2,3,4,5-PeCN	49							3.3×10^{-5}		0.000033
1,2,3,4,6-PeCN	50					0.000068	0.000043		0.000042 0.00003	0.0001
1,2,3,5,7-PeCN	52					$< 3.4 \times 10^{-6}$	$< 1.8 \times 10^{-6}$	2.5×10^{-6}	8.5×10^{-6} 3.8×10^{-5}	0.000025
1,2,3,5,8-PeCN	53					$< 1.8 \times 10^{-6}$	$< 1.2 \times 10^{-6}$	4.6×10^{-7}	1.3×10^{-8} 5.2×10^{-6}	1.8×10^{-6}
1,2,3,6,7-PeCN	54	7.6×10^{-5}		< 0.00069	0.00017	0.00058		0.00061	2.8×10^{-5} 5.5×10^{-5}	
1,2,3,7,8-PeCN	56	2.2×10^{-5}		0.00049					2.3×10^{-5} 5.6×10^{-5}	
1,2,4,5,6-PeCN	57	1.6×10^{-6}						0.000025	1.5×10^{-6} 1.5×10^{-6}	
1,2,4,6,7-PeCN	60	$< 4.2 \times 10^{-7}$			$< 2.8 \times 10^{-5}$			0.0001	1.3×10^{-6} 2.8×10^{-5}	0.0001
1,2,3,4,5,6-HxCN	63		0.002					0.00017	2.2×10^{-5} 2.2×10^{-5}	0.00017
1,2,3,4,5,7-HxCN	64		2×10^{-5}					0.000044	0.00011 1.0×10^{-5}	0.0028
1,2,3,4,6,7-HxCN	66	0.00063		0.0024	0.0039	0.0012	0.00054	0.0018	0.00069 0.0029	0.004
1,2,3,5,6,7-HxCN	67	0.00029	0.002		0.001	0.00048		0.00027	0.001 0.0017	0.004[a]
1,2,3,5,6,8-HxCN	68		0.002		0.00015	0.00049		0.00021	0.00027 0.00011	0.0028
1,2,3,5,7,8-HxCN	69		0.002			0.00011	6.4×10^{-6}	0.000065	8.3×10^{-7} 0.00015	0.002
1,2,3,6,7,8-HxCN	70	0.0021		0.0095	0.00059	0.0028		0.0051	0.0028 0.00071	0.0051
1,2,4,5,6,8-HxCN	71					$< 1.1 \times 10^{-6}$			4.3×10^{-5} 1.6×10^{-7}	0.00009
1,2,4,5,7,8-HxCN	72					6.0×10^{-5}	7.1×10^{-6}	0.00002	0.0001 8.9×10^{-8}	0.00009
1,2,3,4,5,6,7-HpCN	73	0.00046	0.003	0.0006	0.001	0.00052		0.00067	0.00038 0.0018	0.0031
1,2,3,4,5,6,8-HpCN	74					4.1×10^{-6}		0.000003	1.0×10^{-7}	4.1×10^{-6}
1,2,3,4,5,6,7,8-OCN	75					1.0×10^{-5}	$< 4.3 \times 10^{-6}$	7.8×10^{-7}		0.00001

[a] Reported REPs for PCN 67 are lower, but as it is chromatographically inseparable from PCN 66 by most conventional GC methods, the REP for PCN 66 is used for the combined concentration during TEQ estimation.

Recent *in vitro* studies using differentiated PC12 cells and primary hippocampal neurons have shown that 1,2,3,5,6,7-H_6CN leads to neuron loss via a mitochondrial-dependent mechanisms. Impaired function of mitochondria and neurite damage may be connected with cognitive defects or even some diseases such as schizophrenia and Alzheimer's disease (Lisek et al., 2020). PC12 cells were also used to investigate the effects of a 1,2,3,5,6,7-H_6CN (0.025 to 0.35 μg mL^{-1}) on the dopamine biosynthesis and secretion pathway (Lisek et al., 2022). This *in vitro* study showed that 1,2,3,5,6,7-H_6CN dosing resulted in diminished dopamine content and lower dopamine release while also affecting the expression of tyrosine hydroxylase. Based on the findings the study hypothesised that 1,2,3,5,6,7-H_6CN caused dopamine deficiency and contributed to neuronal death by affecting cellular antioxidant potency (Lisek et al., 2022).

3.4. Prenatal and developmental toxicity

Although there are no specific studies confirming toxic effects following environmental exposure to PCNs on pregnant women or the developing fetus, such effects cannot be excluded based on reported studies for similar compounds such as PCBs, PBDEs, PCDDs or PCDFs (Herbstman et al., 2008; Tsukimori et al., 2013; Kim et al., 2015). Evidence for this exposure is clear from the results of neonatal cord blood analysis performed as part of environmental pollution monitoring (EWG, 2009). The total concentration of PCNs (640 pg g^{-1}) determined in the umbilical cord blood of new-borns was about 12 times higher than PCDDs (52.6 pg g^{-1}) and almost 40 times higher than PCDFs (16.3 pg g^{-1}) (EWG, 2009). Similar results were also published by Kim et al. (2015) who noted that the concentrations of individual PCNs (n.d. to 571 pg g^{-1} lipid) in the umbilical cord blood of new-borns was at a comparable level to PCDDs and PCDFs (n.d. to 295 pg g^{-1} lipid). PCNs contributed significantly to the total TEQ, reaching about 25% of its value (Kim et al., 2015). In comparison to other similar halogenated pollutants such as PCBs, PBDEs and PCDD/Fs for which harmful effects on the fetus (growth restriction, nervous and immune system development disorders, reproductive organ abnormalities, decreased levels of thyroid hormones in pregnant mothers) (Herbstman et al., 2008; Tsukimori et al., 2013), have been widely studied, similar information for PCNs is scarce. There are only single cohort studies which show for example, that children whose mothers consumed fish from the Great Lakes during pregnancy were more likely to experience psychomotor retardation, problems with concentration and significantly lower IQ levels (Rodier, 2004; Ginsberg et al., 2004). Interestingly, most fish species caught in these lakes showed high concentrations of not only PCBs, PBDEs, PCDDs, but also PCNs (Kannan et al., 2000; Hanari et al., 2004; Helm et al., 2008) and continue to do so to the present time, even if the trend is to lower concentrations (Pagano and Garner, 2021). Similarly, Pereg et al. (2002), in a study conducted on a population of woman from North Quebec whose diet consisted of large amounts of fish and meat from marine mammals contaminated with various organochlorine compounds, reported a correlation between significantly increased CYP1A1 activity in the placenta (which is considered to be a marker of prenatal toxicity) and an increased number of miscarriages and low birth weight. It is believed that compounds that are inducers of CYP1A1 can reach relatively high concentrations in fetal tissues and organs compared to the mothers (Lagueux et al., 1999; Pereg et al., 2002). The prenatal period, especially the time of organogenesis, is critical in the event of exposure to toxic compounds, because in addition to the maternal organs that are normally responsible for the metabolism of these xenobiotics, the placenta is also metabolically active during this period. The induction of placental enzymes related to cytochrome P450, i.e., CYP1A, 2C and 3A, is believed to be one of the mechanisms involved not only in the embryotoxic, but also fetotoxic and probably, teratogenic effects of xenobiotics.

Studies on the effects of PCNs on reproduction are limited to only a few animal studies using PCN mixtures or a few individual congeners (Kilanowicz et al., 2011), tetra-CN (Kilanowicz et al., 2019a), 1,2,3,4,6-P_5CN (Şişman and Geyikoğlu, 2008), and hexaCN (Omura et al., 2000; Kilanowicz et al., 2015; Şişman and Geyikoğlu, 2008). Zebrafish embryos exposed to 1,2,3,4,6-P_5CN or 1,2,3,4,6,7-H_6CN (at 30 and 50 μg L^{-1}) showed a significant reduction in survival rate as well as developmental abnormalities (abnormal hatching, disrupted axial body, kyphosis, lordosis, reduced heartbeat and tail defect). 1,2,3,4,6,7-H_6CN was seen to be more embryotoxic and teratogenic than 1,2,3,4,6-P_5CN, because some of these effects were observed at a lower concentration of 20 μg L^{-1} (Şişman and Geyikoğlu, 2008).

Omura et al. (2000) reported toxicity of 1,2,3,4,6,7-H_6CN in rat offspring after prenatal exposure (day 14–16 of gestation) of the dams to a non-toxic dose (1 μg kg^{-1} bw) The results indicated early reproductive effects in male offspring (females were not studied), such as the accelerated onset of spermatogenesis as well as the onset of LH and FSH secretions from the pituitary gland (Omura et al., 2000).

More recently, a series of three prenatal toxicity studies were carried out by exposing pregnant Wistar rats during the period of organogenesis (days 6–15 of gestation) to a 0.3–9.0 mg kg^{-1} bw mixture of PCNs (Kilanowicz et al., 2011), 0.3–3.0 mg kg^{-1} bw 1,3,5,8-T_4CN (Kilanowicz et al., 2019a) and 0.1–1.0 mg kg^{-1} bw 1,2,3,5,6,7-H_6CN (Kilanowicz et al., 2015). The results of these studies confirmed different toxic effects of various PCN congeners. The maternal toxicity and LOAEL determinations showed that 1,3,5,8-T_4CN was the least toxic because none of the doses (0.3–3.0 mg kg^{-1} bw) used in the study showed toxicity to the dams. In comparison, a PCN mixture (similar to a mix of Halowax 1013 and 1014) showed a LOAEL of 1 mg kg^{-1} bw. The most toxic effect was observed for 1,2,3,5,6,7-H_6CN with the lowest LOAEL value of 0.3 mg kg^{-1} bw (Kilanowicz et al., 2011, 2015, 2019b). In these studies, maternal toxicity was characterized by decreased body weight and gain, and a reduction in the daily consumption of water and food during pregnancy. Absolute and relative organ weights were also diminished. All of the tested PCNs were fetotoxic, often dose-dependently, although the dams did not appear to be affected at the lower dose of 0.3 mg kg^{-1} bw. The most commonly observed fetotoxic effects included delayed ossification, manifested by the absence of one or two ossification centres of the sternum, renal pelvis enlargement (induced by the PCN mixture and 1,3,5,8-T_4CN) and short supernumerary ribs (caused only by 1,2,3,5,6,7-H_6CN) (Kilanowicz et al., 2011, 2015, 2019b). Other effects, noted only when the PCN mixture was administered, were reduced body weight and length of fetuses, enlargement of lateral brain ventricules and retardation of the development of internal organs (Kilanowicz et al., 2011).

Embryotoxic effects measured by the number of postimplantation losses were documented for all tested doses of 1,2,3,5,6,7-H_6CN (Kilanowicz et al., 2015) and the PCN mixture (Kilanowicz et al., 2011), but not for 1,3,5,8-T_4CN at any of the applied doses (Kilanowicz et al., 2019a), whereas teratogenic effects were characteristic only after administration with the PCN mixture. Congenital effects such as cleft palate and hydronephrosis were also noted (Kilanowicz et al., 2011).

3.5. PCNs as endocrine disrupting chemicals (EDCs)

A number of halogenated aromatic contaminants such as PCDD/Fs, PCBs, and PBDEs can initiate abnormalities in the endocrine system causing mainly reproductive system disorders such as lack of ovulation, premature ovarian failure or polycystic ovarian syndrome (Gregoraszczuk and Ptak, 2013). The results of studies on mass produced halogenated aromatic chemicals such as PCBs and PBDEs, showed significant differences between individual congeners in inducing changes characteristic of EDCs, which were dependent on the degree of ring chlorination, concentration and also configuration (Plíškova et al., 2005; Roszko et al., 2018a, 2018b). Similar differences in inducing endocrine disrupting effects were also noted for PCNs, although the existing literature shows that few *in vitro* or *in vivo* studies have been conducted for individual PCNs in order to evaluate their specific effects on the hormonal balance, and in particular, sex and thyroid hormones.

3.5.1. Sex hormones

Recent studies using various *in vitro* models have shown the disruptive effects of commercial PCN mixtures and some congeners on both, the levels

of sex hormones and the expression of genes associated with these hormones.

The anti-estrogenic activity of Halowax 1051 (technical chloronaphthalene mixture dominated by individual heptaCNs, 1,2,3,4,5,6,7-H_7CN and 1,2,3,4,5,6,8-H_7CN, and octachloronaphthalene) was examined in a porcine ovarian follicle model (Barć and Gregoraszczuk, 2014). The study demonstrated that all three congeners reduced estradiol secretion and also decreased gene and protein expression of ERa/b (Estrogen Receptor) (Barć and Gregoraszczuk, 2014 and Barć and Gregoraszczuk, 2016; Rak et al., 2017). The same anti-estrogenic effect was documented in an *in vitro* yeast model (YES assay) for 1,2,3,5,6,7-H_6CN but was not noticed for 1,3,5,8-T_4CN (Stragierowicz et al., 2021). An *in vivo* study of hexaCNs, (Stragierowicz et al., 2018) showed a non-linear dose-response curve of the tested compounds. Sub-acute toxicity (over two and four weeks) was manifested in an increase in estradiol and progesterone concentration in the uterus and in the serum, which indicated estrogenic activity (Stragierowicz et al., 2018). On the other hand, a sub-chronic toxicity study (dosing over 13 weeks with the same hexaCN), showed an anti-estrogenic effect, expressed by both, reduced uterine estradiol concentration and decrease in uterine weight (Stragierowicz et al., 2018). Other potent AhR ligands, e.g. TCDD have been shown to exhibit different responses: estrogenic (Meerts et al., 2004; Yang et al., 2005), as well as anti-estrogenic (Kharat and Saatcioglu, 1996). Disruption of sex hormone expression may also be a causative agent for irregularities in the oestrous cycle. A prolonged oestrous cycle, connected with the extension of the oestrus phase were observed in female rats dosed with a 1,2,3,5,6,7-H_6CN (Stragierowicz et al., 2018).

In another *in vivo* study (Omura et al., 2000), using a single hexaCN congener, (1,2,3,4,6,7-H_6CN administered at 1 μg kg^{-1} bw day^{-1} on days 14–16 of gestation), a negative effect was observed on the hypothalamic-pituitary-testes axis in the male offspring of Wistar dams exposed during pregnancy. A maxima was observed in the serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by postnatal day 31 indicating early and accelerated onset of the secretions of these hormones from the pituitary gland, causing an earlier onset of spermatogenesis.

Single *in vitro* studies using porcine ovarian follicles showed the androgenic effect of the technical PCN mixture Halowax 1015, expressed by increased testosterone secretion (Gregoraszczuk et al., 2011; Rak et al., 2017) and increased gene and protein expression of the Androgen Receptor (AR) (Barć and Gregoraszczuk, 2016). On the other hand, the latest studies applying the yeast model (YAS assay) have noted anti-androgenic activity of both 1,2,3,5,6,7-H_6CN and 1,3,5,8-T_4CN (Stragierowicz et al., 2021). The results of the latter study are consistent with the observations made for other similar halogenated aromatics such as TCDD, PCBs and PBDEs (Ciftci et al., 2012; Goncharov et al., 2009; Gupta et al., 2006; Karman et al., 2012; Leong et al., 2019; Stoker et al., 2005).

3.5.2. Thyroid hormones

The effects of PCNs on thyroid hormones and their receptors have only been investigated in a few independent studies. Individual congeners (mono-, di- and tetraCNs) and technical Halowax mixtures (Halowaxes-, 1000, 1001, 1013, 1014 and 1099) showed antagonistic activity on the thyroid hormone receptor β (TRβ) in an *in vitro* yeast model (Li et al., 2008). PCNs were investigated as part of a wider series of halogenated aromatics and the results were in line with those previously obtained for PCBs, PBBs and PBDEs.

An *in vivo* study (Stragierowicz et al., 2018) on female Wistar rats over 2 to 13 weeks showed that the effects of 1,2,3,5,6,7-H_6CN on thyroid functioning appear to be analogous to those observed for TCDD and other dioxin-like compounds (Sewall et al., 1995). Exposure to 1,2,3,5,6,7-H_6CN resulted in a statistically significant and dose-dependent (doses range, 30–300 μg kg^{-1}) increase in thyroid stimulating hormone (TSH) concentrations in serum, which was correlated with a concomitant decrease of thyroxine (T_4) concentration (Stragierowicz et al., 2018). The direction of these changes may lead not only to a condition similar to hypothyroidism, but also (especially at elevated concentrations of TSH) to ovulatory disorders, and even impaired fertility (Hiraoka et al., 2016).

3.6. Other toxic effects

The thymus is another organ impacted by chlorinated aromatic hydrocarbons, including PCNs (McConnell, 1989). Both acute and chronic exposure have resulted in histopathological changes including significant reduction of thymic size in young animals (McConnell and Moore, 1979; Nishizumi, 1978). This effect, caused by a loss of cortical lymphocytes, is referred to as thymic atrophy, but may actually involve necrosis of the lymphocytes, a condition that was observed more markedly in young offspring of dams that were exposed during lactation and gestation. A more recent study (Hooth et al., 2012) reported a significant increase in thymic atrophy in female Harlan Sprague-Dawley rats exposed to high doses (500 g kg^{-1}) of 1,2,3,4,6,7-H_6CN and 1,2,3,5,6,7-H_6CN, with the severity of the atrophy exceeding that of rats exposed to 2,3,7,8-TCDD. Lower levels of atrophy were seen in animals exposed to a 10-fold lower dose.

Polyhalogenated aromatic hydrocarbons (PAHs) are known to affect hepatic heme biosynthesis (Smith and Chernova, 2009), an effect observed in female Wistar rats following exposure to hexachloronaphthalenes (Klimczak et al., 2018). It was manifested by diminished activity of hepatic aminolevulinic acid dehydratase (ALAD) and uroporphyrinogen decarboxylase (UROD), hepatic uroporphyria and decreased concentration of porphyrins in urine with a simultaneous increase in ALA concentration The proposed mechanism of URO-D inhibition by halogenated aromatics, including PCNs, is associated with the expressions of the gene connected with the AhR (as noted earlier, higher chlorinated PCNs cause rapid activation of this receptor) as has been discussed in relation to the porphyrogenic action of halogenated aromatics (Smith and Chernova, 2009).

Other effects, i.e., perturbation of haematological parameters have also been noted (Klimczak et al., 2018). Female Wistar rats exposed to the 1,2,3,5,6,7-H_6CN for up to 4 and 12 weeks, showed significant thrombocytopenia as well as other haematological disturbances at a dose of 0.3 mg kg^{-1}). These included a decreased in platelet count with a concomitant increase in mean platelet volume, indicating increased platelet production (Klimczak et al., 2018; Kilanowicz et al., 2019b). In addition, 1,2,3,5,6,7-H_6CN was seen to alter both coagulation and fibrinolysis processes (as observed by the reduction of selected coagulation parameters) and decreases in the fibrinogen concentration (Kilanowicz et al., 2019b). Other similar polyhalogenated aromatics, such as PCBs or PCDD/Fs may disturbs haemostasis and seemed to contribute to the late haemorrhagic disease of the new-born (Koppe et al., 1989), but the mechanism behind this effect remains to be elucidated.

4. Discussion

Much of the early work on the toxicity of PCNs was stimulated by the overt signs of ill-health in workers that were occupationally exposed to technical PCN mixtures or products containing PCNs. The effects ranged from chloracne (which was observed for PCN exposure as well as other chlorinated aromatic chemicals such as PCBs) to fatality (most often through liver disease, variously recorded as hepatic jaundice, acute yellow atrophy, cirrhosis, liver necrosis, etc.) in the most extreme cases. Workers suffering these symptoms were exposed to PCN mixtures or products that contained these mixtures, with little or no modification of the composition of the mixtures. These inhalatory or dermal exposures were associated with the elevated temperatures required to improve the handling of the waxy products (the effects were noted for higher chlorinated, penta- and hexaCN mixtures rather than the more mobile triCN products) which resulted in inhalation of the fumes or vapours condensing on the skin of workers and which was reported to act more quickly than direct skin contact. Almost half a century following the end of widescale PCN production and use, the emphasis of more recent studies has moved from investigating the effects of the occupationally exposed (to high concentrations of PCNs) to more subtle effects that may arise through non-occupational pathways,

e.g., environmental and dietary. Of these (and in common with other similar contaminants such as PCDD/Fs and PCB), dietary intake is likely to be the dominant exposure route and to account for the vast majority of general population exposure. Assisted by the improvements in analytical techniques (Fernandes et al., 2017) that allow greater characterisation of the occurrences, the more recent toxicological studies are able to target specific PCN congeners or homologue groups and more subtle effects. However, as discussed in Section 1.2, dietary intake also results in exposure to an integral mix of congeners that originated from commercial mixtures and combustion sources but was subjected to a range of removal mechanisms (evaporation, environmental degradation, metabolism, etc.). A more modern assessment of risk to non-occupationally exposed populations may be better served if studies targeted PCN congeners that occurred more abundantly and frequently in the diet (e.g., 1,3,5,7-T_4CN, 1,2,3,5,7-P_5CN/1,2,4,6,7-P_5CN, 1,2,3,4,6,7-H_6CN/1,2,3,5,6,7-H_6CN, 1,2,3,4,5,6,7-H_7CN, etc.).

PCNs have been detected in human tissues in more recent times (Schiavone et al., 2010; Kunisue et al., 2009; Park et al., 2010; Pratt et al., 2013; Fernandes et al., 2017; Fromme et al., 2015; Jin et al., 2019) which confirms the exposure of general populations to these environmental contaminants. As seen in studies on test animals, PCNs accumulate mainly in the adipose tissue and liver with greater retention seen for the higher chlorinated (≥ 4 chlorines) congeners and homologue groups. The higher levels in adipose tissue and liver are consistent with the lipophilicity and lower tendency of the higher chlorinated PCN congeners to undergo hydroxylation, as observed in test animals (Section 2.1). Physiologically, in most species the liver is responsible for fatty acid synthesis and lipid circulation through lipoprotein synthesis, although CYP associated sequestration of PCNs is also likely as reported in some species for other chemically similar contaminants such as PCBs and PCDD/Fs (Kunisue et al., 2006; Holma-Suutari et al., 2016). However, recent studies from industrialised settings in China have reported that lower chlorinated (mono- to tri-) PCNs were the dominant congeners in human serum (Jin et al., 2019; Wang et al., 2022).

Despite confirmation that PCNs bind potently to the AhR (Table 1), it is difficult to distinguish between this mechanism and other forms of toxicity because of the pleiotropic outcomes of AhR binding and activation, and the limited number of PCN-specific studies on this mode of action. Similarly, although 1,2,3,4,6,7-H_6CN has been reported (Omura et al., 2000) to accelerate the onset of spermatogenesis in male offspring of rats (dosed at 1 μg kg $^{-1}$ day^{-1} on days 14–16 of gestation), this potentially endocrine disruptive effect raises obvious questions such as: do other PCN congeners that feature prominently in exposure studies (1,2,3,5,7-P_5CN, 1,2,3,5,6,7-H_6CN, 1,2,3,4,5,6,7-H_7CN, etc.) also elicit this effect? Are there other similar or more sensitive end-points? (e.g., a delay in reproductive development, i.e. BPS, was reported as a very sensitive effect of maternal TCDD toxicity in Wistar rats – Bell et al., 2007, 2010) These deficits in our knowledge indicate that more in-depth investigations are needed to support a more refined risk assessment for dietary and environmental exposure. The studies of the AhR mediated effects in humans and test animals, although relatively few, provide a strong indication that exposure to some PCN congeners (particularly hexaCNs) elicit responses that are similar to, and occur at a similar range of potency as the more toxic dioxin-like contaminants. However, other aspect of PCN toxicity such as prenatal, developmental toxicity, neurotoxicity, etc. should also be further investigated.

The historical observations of anorectic behaviour in occupationally exposed workers and in later animal studies have not been fully explored, but some of the most recent neurotoxicity studies (Lisek et al., 2020, 2022) suggest that some PCN congeners (e.g. 1,2,3,5,6,7-H_6CN) appear to affect dopaminergic transmission (dopamine is associated in the regulation of food intake) by altering tyrosine hydroxylation, reducing VMAT1 expression and impairing antioxidant protection. However, the proposed role (Lisek et al., 2022) of this and other PCN congeners in promoting dopamine deficiency and neuronal death by affecting cellular antioxidant potency needs to be further clarified. Another target of more recent investigation is the developmental toxicity of PCNs (embryotoxicity, fetotoxicity and even teratogenicity) that has been studied in animals (Omura et al., 2000; Gregoraszczuk and Ptak, 2013; Kilanowicz et al., 2011, 2015, 2019a; Stragierowicz et al., 2018). The results demonstrate the ability of PCNs to cross the placental barrier, affecting the fetus which showed the highest concentrations of tetra- and hexaCNs in the brain and kidneys. In addition, PCNs mainly affect the liver, but also induce other adverse endocrine effects, which are a major concern due to the widespread PCN contamination of the environment and dietary products. These effects are summarised in Fig. 4.

The studies reviewed and discussed here confirm the hazard to human health that is associated with PCN exposure. In general, the results of most studies suggest that the higher chlorinated naphthalenes (≥ 4 chlorines) and particularly hexaCNs, are of greater concern but apart from the effects observed for 1,2,3,4,6,7-H_6CN and 1,2,3,5,6,7-H_6CN, similar information on the other congeners is scarce. One of the biggest gaps in our knowledge is reconciling the observed effects with current levels of PCN intake. Most of the current PCN exposure to general populations is dietary (no

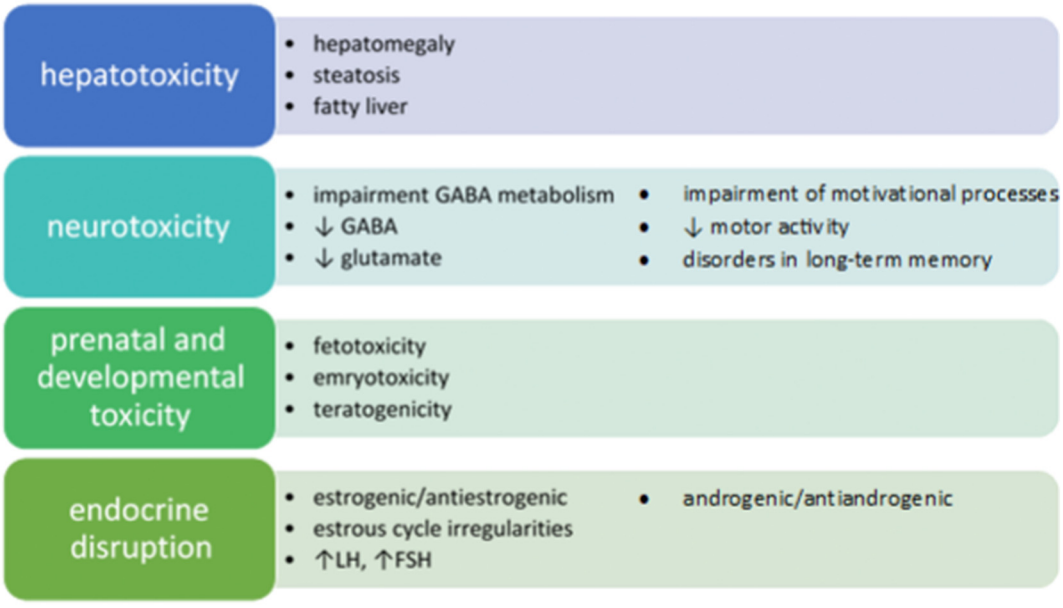

Fig. 4. Summary of toxic targets documented by *in vivo* and *in vitro* studies.

exclusively occupational exposure has been reported in recent years, but the presence of PCNs in older switchgear, cables, and older electronic/electrical items and communication equipment that has been phased out, suggest that exposure during disposal cannot be entirely ruled out; similarly, in heavily industrialised settings with poor air quality, inhalatory intake of lower chlorinated PCNs may be significant as seen by the higher blood serum levels of these congeners in the working population in such areas (Jin et al., 2019)). Future toxicological studies should consider the range of exposures seen in the diet (Section 1.2) as well as predominantly occurring congeners, in order to provide a more realistic view of the hazard posed by dietary intake. These studies should be complemented by structured monitoring programmes that assess current dietary intake, as much of the existing food occurrence data is the result of isolated individual investigations that only provide a temporal snapshot. Additionally, most of the toxicological information to date is based on a range of doses in acute, subacute and subchronic studies, so chronic studies would allow for a more relevant approximation to the way in which most populations are currently exposed. Chronic exposure studies may be additionally relevant as demonstrated by the greater potency of closely related compounds such as TCDD to induce developmental effects after chronic dosing, in comparison to acute dosing (Bell et al., 2010). Finally, in view of the similarity of response to other halogenated aromatic contaminants (PCBs, PCDD/F, PBDD/Fs, etc.) and similar routes of exposure, a holistic consideration which includes combined dosing of these contaminants in a range that reflects current exposure levels may be relevant.

5. Summary

PCNs are high-volume industrial chemicals that were manufactured during the last century. Their production and use is now restricted but the legacy of their use has resulted in global environmental contamination and they are reported to occur in a wide variety of food products. Dietary intake is likely to be the most significant route of current human exposure. The available animal and *in vitro* studies reviewed here indicate that a number of adverse effects are associated with this exposure, some of the more sensitive of which may arise through the binding of PCNs to the AhR. Thus, PCNs contribute to the toxic effects of other halogenated aromatic hydrocarbons such as PCDD/Fs, PBDD/Fs, PCBs, etc., which are also potent inducers of AhR mediated toxicity and are also known food contaminants. However, PCN toxicity has not been investigated to the same extent as seen for PCBs or PCDD/Fs, in particular, a number of the more relevant congeners (with ≥ 4 chlorines) have yet to be studied, even through *in vitro* assessments (thus far *in vivo* REP data is limited to two PCNs congeners - 1,2,3,4,6,7-H_6CN and 1,2,3,5,6,7-H_6CN). An important reason for this limitation is the non-availability of a wide range of good quality, pure, PCN reference standards at the time of the reviewed studies, although this situation is slowly improving. A number of other effects on the functioning of the liver, as well as on the nervous, endocrine and reproductive systems are also apparent from recent studies, but it is difficult to disassociate these from AhR binding due to the pleiotropic nature of the response. Some PCNs particularly the higher chlorinated congeners are reported to elicit more potent effects and some of these also bio-accumulate to a greater extent in the tissues of higher order animals and humans. Most studies carried out to date involved doses at part per billion levels or higher but as most current and future PCN exposure is likely to be gradually cumulative through the diet, the effects of chronic dosing at lower levels need to be investigated.

CRediT authorship contribution statement

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Declaration of competing interest

The authors of this manuscript certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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