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Mechanisms of Environmental Contributions to Fatty Liver Disease

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Abstract

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CONFLICT OF INTEREST

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Purpose: Fatty liver disease (FLD) affects over 25% of the global population and may lead to liver-related mortality due to cirrhosis and liver cancer. FLD caused by occupational and environmental chemical exposures is termed 'toxicant associated steatohepatitis' (TASH). The current review addresses the scientific progress made in the mechanistic understanding of TASH since its initial description in 2010.

Recent Findings: Recently discovered modes of actions for volatile organic compounds and persistent organic pollutants include: (*i*) the endocrine, metabolism, and signaling disrupting chemical hypotheses; (*ii*) chemical-nutrient interactions and the two 'hit' hypothesis. These key hypotheses were then reviewed in the context of the steatosis adverse outcome pathway (AOP) proposed by the US Environmental Protection Agency.

Summary: The conceptual understanding of the contribution of environmental exposures to FLD has progressed significantly. However, because this is a new research area, more studies including mechanistic human data are required to address current knowledge gaps.

Keywords

toxicant associated steatohepatitis; TASH; signaling disruption; endocrine disruption; polychlorinated biphenyls; vinyl chloride

INTRODUCTION

Chronic liver diseases may increase mortality due to liver-related causes (e.g., cirrhosis and hepatocellular carcinoma) and also due to increased risk for cardiovascular and infectious diseases. In fact, liver-related mortality has increased world-wide. Recent data demonstrate that between 1999 and 2016, the cirrhosis annual death rate increased by 65%, and the liver cancer annual death rate doubled in the United States [1]. The most common histologic form of liver pathology is fatty liver disease (FLD). FLD encompasses a progressive pathologic spectrum ranging from steatosis, to steatohepatitis with or without fibrosis, to cirrhosis, and hepatocellular carcinoma. Steatosis results from altered lipid metabolic pathways and complex changes in overall energy metabolism [2]. FLDs are named according to the etiologic exposure associated with their development. Alcoholic fatty liver disease was initially described followed by nonalcoholic fatty liver disease (NAFLD). NAFLD has been associated with diet-induced obesity, insulin resistance, and metabolic syndrome; but not all subjects with NAFLD have obesity or diabetes [3].

FLD is common, and the global prevalence of NAFLD alone is 25.2% [3]. More recently, it was recognized that occupational and environmental chemical exposures may be associated with the development of FLD. The Cave laboratory coined the term, toxicant associated steatohepatitis (TASH), to describe FLD occurring in highly-exposed polyvinyl chloride (PVC) production workers which was associated with increased pro-inflammatory cytokines, insulin resistance, and decreased antioxidants [4]. Numerous environmental chemicals have subsequently been associated with TASH in animal and/or epidemiological studies, including volatile organic chemicals (VOCs), persistent organic pollutants (POPs), metals, particulate matter, pesticides, and others (Table 1). These studies implicate both adult and developmental chemical exposures in the pathogenesis of FLD. While the exact

number of environmental pollutants that cause fatty liver is unknown, one-third of chemicals in the National Institute for Occupational Safety and Health's (NIOSH) Pocket Guide are associated with hepatotoxicity [5]. Moreover, the liver appears to be the most common target organ for chemical toxicity; and this is probably due to liver's central role in xenobiotic detoxification [6].

The mechanistic similarities and differences between alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH), and TASH were recently reviewed [7]. While ASH, NASH, and TASH are pathologically similar, disease mechanisms vary by etiologic exposure. Since its initial description nearly a decade ago, significant progress has been made in the scientific understanding of TASH, as previously reviewed [7, 6, 8–11]. This manuscript extends these prior review articles by examining: (*i*) key hypotheses currently of interest to the field; (*ii*) newly discovered modes of action for VOCs and POPs in the context of these hypotheses; and (*iii*) current limitations and suggested future research directions.

KEY HYPOTHESES CURRENTLY OF INTEREST TO THE FIELD

Several hypotheses contextualize TASH as a part of a systemic disease and provide the framework to evaluate recently described modes of action for environmental pollutants in TASH. These hypotheses include the endocrine, metabolism, and signaling disrupting chemical hypotheses, as well as chemical-nutrient interactions impacting the two 'hit' hypothesis.

The endocrine and metabolism disrupting chemical hypotheses were recently reviewed [11]. Endocrine disrupting chemicals (EDCs) interfere with any aspect of hormone action [11]. Metabolism disrupting chemicals (MDCs) promote metabolic changes that can result in obesity, type 2 diabetes, or fatty liver in animals and humans alike [11]. These metabolic changes can be independent of chemical effects on hormone action [11]. Thus, FLD can be considered as the hepatic manifestation of systemic endocrine and metabolic disruption. However, it was recently demonstrated that chemical exposures can also alter hepatokine production, demonstrating that TASH can also be a cause, and not just an effect, of systemic endocrine disruption [12]. MDCs may also cause hormone-independent alterations in hepatic metabolism through diverse mechanisms including receptor-based modes of action [13, 11, 8] and mitochondrial toxicity [14]. In fact, nuclear receptor 'crosstalk'-based modes of action were proposed to be molecular initiating events (MIEs) in the hepatic steatosis adverse outcome pathway (AOP) proposed by the U.S. Environmental Protection Agency (EPA) [13]. These and other MIEs regulated the four identified apical key events impacting steatosis (e.g., fatty acid uptake, efflux, synthesis, and oxidative metabolism) [13]. EPA's AOP were recently validated *in vitro* [15], and expanded to demonstrate the downstream systemic impact of the receptor-based MIE's on diabetes and cardiovascular disease [16].

Signaling disrupting chemicals (SDCs) can disrupt the normal hepatic intracellular signaling that regulates metabolism, inflammation, and fibrosis. SDCs may ligand activate transcription factors implicated in TASH (such as dioxin and the aryl hydrocarbon receptor, AhR); antagonize these receptors; or indirectly impact receptor function. Recently, it was demonstrated that some POPs and pesticides may antagonize the epidermal growth factor

receptor (EGFR) reducing signal transduction leading to altered transcription factor (including nuclear receptor) phosphorylation and function in TASH [17–20]. The EDC, MDC, and SDC hypotheses provide a framework to evaluate the mechanisms responsible for the observed transcriptional reprogramming in TASH. The AOP framework appears to be a useful new tool to evaluate mechanisms of EDCs, MDCs, and SDCs in TASH.

New understanding about how interactions between environmental chemicals and nutrition impact FLD extends Day's two 'hit' hypothesis in new directions [21]. The two 'hit' hypothesis proposed that a second 'hit' is required for patients with steatosis to progress to more histologically advanced liver disease. Classically proposed second 'hits' include oxidative stress, insulin resistance, organelle dysfunction, and pro-inflammatory cytokines. Some exposures such as high-dose vinyl chloride were associated with steatohepatitis and fibrosis in humans through the simultaneous induction of multiple hit mechanisms [4, 22]. In animal models, a polychlorinated biphenyl (PCB) mixture caused steatohepatitis only in mice fed a high fat diet [23]. It was thus proposed that differential exposures to environmental chemicals could serve as a second 'hit' in the progression of diet-induced steatosis to steatohepatitis, again via upregulation of deleterious mechanisms like pro-inflammatory cytokines [23]. More recently, hepatic proteomics analysis of PCB-exposed mice demonstrated that PCB exposures were associated with the attenuation of liver's protective responses against diet-induced obesity including the antioxidant response and nuclear receptor function (e.g., the farnesoid x receptor, FXR) [20]. Likewise, a recent mouse study demonstrated that low-dose vinyl chloride exposures caused steatohepatitis only in mice fed high fat diet [14], although vinyl chloride induced mitochondrial dysfunction in mice fed either a control or high fat diet. Over-nutrition likely exceeded the reserve capacity of mitochondria damaged by reactive vinyl chloride metabolites to worsen high fat diet-induced steatosis and cause steatohepatitis. Based, in part, on these observations, it was recently proposed that environmental pollutant exposures may be the first 'hit' which compromise the liver's protective responses against over-nutrition to promote steatohepatitis following the second 'hit' of hypercaloric diets [20]. Thus, complex interactions between environmental chemicals and nutrients appear to be important determinants of liver disease. These interactions are being increasingly understood in the context of the two 'hit' hypothesis. Such exposure biology approaches take into consideration more than one biology factor in the analysis of liver disease susceptibility.

NEWLY DISCOVERED MODES OF ACTION FOR VOLATILE ORGANIC POLLUTANTS AND PERSISTENT ORGANIC POLLUTANTS IN THE CONTEXT OF KEY HYPOTHESES

Significant advances have been in the mechanistic understanding of TASH, particularly following VOC and POP exposures (Table 2).

A. VOLATILE ORGANIC COMPOUNDS

VOCs are often present in household products such as paints/varnishes, cleaning supplies, gasoline, and dry-cleaned clothing [24]. VOCs also contaminate ground water and are frequently present at National Priority List (NPL) Superfund sites. As such, many VOCs

rank highly on the Agency for Toxic Substances and Disease Registry's (ATSDR) Hazardous Substance Priority List [24]. Ambient VOC levels are often higher indoors and can be significantly affected by the building's proximity to contaminated sites and its ventilation [25, 26]. The VOC, vinyl chloride, is a direct hepatotoxicant at high exposures [4]. Low-dose vinyl chloride exposures that are not hepatotoxic per se, can enhance underlying liver injury due to another factor [27, 28, 14], consistent with the 'two hit' hypothesis. The toxicity of VOCs in TASH may be mediated by reactive VOC metabolites [27].

Several VOCs have been shown to be MDCs, by disrupting normal hepatic carbohydrate and lipid metabolism to induce steatosis. While highly-exposed vinyl chloride workers had insulin resistance (IR) [4]; low-dose vinyl chloride exposures caused IR in mice fed a high fat diet [14]. A recent serum metabolomics analysis of occupationally exposed vinyl chloride workers described changes in several lipid metabolites and metabolism regulating enzymes, such as AMP-activated protein kinase (AMPK) [29]. These results were recapitulated in a mouse model of vinyl chloride metabolite exposure, demonstrating that mammalian target of rapamycin (mTOR) and AMPK, which are normally activated in opposition, were both activated causing a paradoxical state of lipid accumulation and glycogen depletion [27]. By impacting normal regulatory kinase function, vinyl chloride may also be considered to be a SDC. Repeated exposure to high levels of perchloroethylene (PCE) also induced hepatic steatosis [30]. Metabolomics analyses demonstrated that even low-dose PCE significantly altered lipid homeostasis *in vivo*, contributing to enhanced steatosis [31, 32]. This was due, at least in part, to altered activation of peroxisome proliferator-activated receptor α (PPARα) [33, 34].

The carbonyl stress imposed by reactive VOC metabolites damages organelles, thus contributing to TASH. Mitochondria are key to maintaining cellular energy homeostasis, and several VOCs have been demonstrated to impact mitochondrial integrity and function. vinyl chloride-induced mitochondrial damage serves as a canonical example of an environmental exposure limiting the capacity of mitochondria to adapt appropriately to the metabolic stress imposed by the second 'hit' of a hypercaloric diet. Vinyl chloride and its metabolites directly damage mitochondrial complex I and II, leading to uncoupling of the electron transport chain. This causes the cell to increase flux through anaerobic glycolysis to compensate for this loss of ATP yield [14], also rendering it more sensitive to cytotoxic second 'hits'. Mitochondria are also a significant source of endogenous reactive oxygen species (ROS) via electron leakage during normal oxidative respiration [35, 36]. In human subjects, vinyl chloride exposures were associated with antioxidant depletion consistent with oxidative stress [4] and increased circulating lipid peroxidation products and decreased carnitine/carnitine esters consistent with mitochondrial dysfunction [29] validating the animal studies. Active VOC metabolites are often strongly electrophilic and therefore highly reactive. Specifically, oxidative damage occurs upon covalent adduct formation on major macromolecules in the hepatocyte, including proteins, lipids, and/or DNA (i.e., carbonyl stress). For example, vinyl chloride metabolite exposure significantly increased 4-hydroxynonenal adduct formation in high fat diet-fed mice [28], likely due to increased electron leakage by damaged mitochondria [27, 14]. Similarly, major metabolites of PCE including trichloroacetic acid (TCA) and dichloroacetic acid (DCA), caused oxidative stress

through formation of lipid peroxidation adducts *in vivo* [37, 38]. Likewise, acrolein is a well-known propagator of oxidative stress by causing lipid peroxidation adducts [39, 40].

The endoplasmic reticulum (ER) is the cell's hub for protein folding and synthesis [41, 42]. Upon detection of adducted or misfolded proteins, the ER prompts the unfolded protein response (UPR) to remove these proteins. The aldehydes and ROS generated by VOCs avidly react with proteins resulting in ER stress [43]. For example, vinyl chloride and its metabolites enhanced the accumulation of oxidatively damaged proteins caused by high fat diet, accompanied by a robust dilation of the ER [27, 28, 14]. Likewise, acrolein significantly increased expression of ER stress markers, without protective UPR activation in primary human hepatocytes [39] and in intestinal epithelial cells [44]. The latter changes caused gut barrier disruption, which contributes to fatty liver pathogenesis by increasing portal venous endotoxemia [45–48]. Thus, the ER and mitochondria are examples of organelles damaged by the carbonyl stress imposed by VOC metabolism contributing to TASH.

The transition from steatosis to the more severe steatohepatitis requires the development of superimposed hepatic inflammation. High-dose vinyl chloride exposures were associated with increased liver inflammatory infiltrate and increased serum pro-inflammatory cytokines in PVC production workers [4]. In mice, chronic vinyl chloride exposures (sub-OSHA dose) increased the hepatic neutrophil accumulation caused by high fat diet-feeding [14]. As was the case with vinyl chloride-induced organelle toxicity, vinyl chloride-induced inflammation appears to be due, at least in part, to vinyl chloride metabolites. In a mouse model, treatment with vinyl chloride metabolites significantly increased neutrophil infiltration, inflammasome activation, and pro-inflammatory cytokine expression in mice fed a diet enriched with saturated fat (the second 'hit') [28]. Interestingly, mice fed a diet rich in unsaturated fat were protected from liver injury and inflammasome activation [28]. This specific diet-dependence observed in mice was surprising because vinyl chloride exposures in humans were associated with marked upregulation of oxidized linoleic metabolites known to active the inflammasome while inducing liver mitochondrial dysfunction and apoptosis [29, 49]. In addition to inflammasome activation, the local and systemic inflammatory responses associated with VOC exposures can be induced and propagated by VOC-induced oxidative and ER stress [50]. Carbon tetrachloride has also been shown to enhance monocyte recruitment to the liver [51]. Regarding the developmental origins of FLD, trichloroethylene exposures during lactation and gestation increased expression of pro-inflammatory chemokines in offspring of mice [52]. A new field in the study of mechanisms of inflammation is the formation and release of neutrophil extracellular traps (NETs). NETs are an extensive meshwork of decondensed chromatin and hydrolytic enzymes, contributing to injury and necrosis [53]. The VOC, acrolein, has recently been shown to increase hepatic tissue damage after ischemia reperfusion. Increased expression of pro-inflammatory cytokines and enhanced NET formation were observed in isolated neutrophils [54]. Thus, VOCs induce hepatic inflammation though mechanisms including inflammasome activation, organelle stress, and enhanced NET formation.

B. PERSISTENT ORGANIC POLLUTANTS

Dioxins and dioxin-like PCBs—Dioxins (e.g., 2,3,7,8-tetrachlorodibenzodioxin, TCDD) and dioxin-like PCBs (e.g., PCB 126) activate the aryl hydrocarbon receptor (AhR), and that is their proposed mode of action. Exposures to dioxins have long been associated with wasting syndrome, steatosis, and hypoglycemia. Following PCB 126 exposures in rats, specific hepatic fatty acids incorporated into triglycerides were increased in a dose-response with adrenic acid (22:4) showing the greatest maximal increase [55]. Likewise, mice exposed to PCB 126 had increased hepatic triglycerides and free fatty acids [12]. In rodent models, PCB 126-induced steatosis was reproducibly associated with increased lipid influx (via upregulation of AhR target genes including CD36 and fatty acid binding protein-1); variably decreased fatty acid oxidation (via downregulation of PPARα); and variably decreased lipid efflux (via downregulation of apolipoprotein B100); despite decreased lipogenesis (via downregulation of fatty acid synthase) [12, 56–59]. In some cases, the increased liver lipids were associated with reduced serum lipids and trend toward reduced adiposity, consistent with the central redistribution of fat to the liver [12]. PCB 126 reduced hepatic gluconeogenesis and increased insulin sensitivity to promote fasting hypoglycemia despite decreased insulin production [12, 56–58].

New mechanisms for PCB 126 in FLD were recently identified. In mice, PCB 126 decreased production of the hepatokine, fibroblast growth factor-21 (FGF-21) [58, 12], and the enterokine, glucagon-like peptide-1 (GLP-1) [60]. Because FGF-21 and GLP-1 protect against metabolic syndrome, these data implicate liver and intestinal disease as a cause of PCB 126-mediated endocrine disruption. The reduction in GLP-1 was associated with PCB 126-induced dysbiosis including a reduction in bifidobacteria and a significantly increased Firmicutes to Bacteroidetes ratio [60]. Following PCB 126 exposures, the development of more severe liver injury, inflammation, and fibrosis (e.g., steatohepatitis) may require a nutritional second ‘hit’ [59, 58]. A recent liver metabolomics analysis of PCB 126 treated mice demonstrated that compared to mice fed a control diet, mice fed a methionine-choline deficient (MCD) diet had more metabolites associated with dysfunctional pathways and increased hepatic lipid peroxidation, mitochondrial dysfunction, and thiol depletion [61]. Regarding signaling disruption, PCB 126 was the most potent EGFR inhibitor tested [18], and it also inhibited protective hepatic AMPK and cyclic AMP responsive element binding protein 1 (CREB-1) signaling [57]. TCDD exposures also increased hepatic steatosis via fatty acid uptake [62] and appeared to require high fat diet co-exposures in order to increase fibrosis [63]. Metabolic reprogramming by TCDD in FLD was recently reviewed [64]. The endocrine and metabolic disruption accounting for TCDD-induced steatosis shares many similarities with PCB 126-induced steatosis, strongly implicating AhR’s role in TASH [64].

Non-dioxin-like PCBs—Non-dioxin-like PCBs (NDL PCBs) disrupt hepatic energy metabolism through other receptor-based mechanisms including constitutive androstane receptor (CAR) and pregnane X receptor (PXR) [8]. In diet-induced obesity mouse models, exposures to the NDL PCB 153 increased steatosis [65]; while Aroclor 1260 exposures caused steatohepatitis [23]. The latter data were recently confirmed in a cross-sectional analysis of the Anniston Community Health Survey (ACHS) [66]. Using serologic biomarkers, a high prevalence of TASH was observed in this cohort with increased PCB

exposures and overweight/obesity. TASH was associated with increased PCB exposures, insulin resistance, dyslipidemia, pro-inflammatory cytokines, and liver necrosis. ΣPCBs was inversely associated with leptin and pancreatic insulin production. EPA's steatosis AOP proposed pollutant-induced PXR/CAR activation to be MIEs for FLD [13, 16]. Thus, we hypothesized that PXR or CAR knockout mice would be protected against the steatohepatitis associated with Aroclor 1260 in a diet-induced obesity model [67]. While PXR and CAR clearly modulated several mechanisms implicated in FLD, knocking out these receptors did not prevent steatohepatitis [67]; thus implicating additional mechanisms.

CAR can either be directly activated by ligand binding or indirectly activated via altered receptor phosphorylation. Direct CAR ligands, such as TCPOBOP, protect against FLD [68], suggesting that the indirect activators may cause TASH. PCBs are indirect murine CAR activators, but may activate human CAR both directly and indirectly [69, 18, 17]. Recently, the mechanism for PCB-induced indirect CAR activation was elucidated. PCBs antagonized EGFR via high-affinity hydrophobic binding at the ligand binding domain to prevent ligand-induced endocytosis and tyrosine kinase activation leading to downstream CAR de-phosphorylation and consequently increased CAR activity [18, 17]. Perhaps because it shares similarities with the insulin receptor, the EGFR also regulates numerous pathways involved in metabolism, regeneration, and gene expression [70, 71]. Disruption of these pathways may promote TASH.

A recent *in vivo* hepatic phosphoproteomics analysis revealed that PCB-induced signaling disruption impacted many pathways and interacted with diet [19]. Aroclor 1260 reduced hepatic phosphoprotein levels by nearly 25%. Consistent with ACHS, PCBs impacted leptin and insulin signaling pathways while liver necrosis was a pathologic ontology: increased by the interaction between PCBs and high fat diet. Casein kinase 2 (CK2), extracellular regulated kinase, protein kinase B, and cyclin dependent kinase activities were downregulated by PCBs, and this downregulation was worsened by diet-induced obesity. PCB-induced alterations in CK2 subunit expression negatively regulated caspase-3 to promote secondary liver necrosis. More recently, it was demonstrated that nuclear factor erythroid 2-related factor (NRF2) and hepatocyte nuclear factor 4-alpha (HNF4α) were epidermal growth factor sensitive targets whose functions were reduced by NDL PCBs [20]. PCB-induced NRF2 down-regulation decreased hepatic glutathione levels, rendering the liver more susceptible to the oxidative stress imposed by the diet-induced obesity second 'hit' [20]. HNF4α is a critical identity gene regulating the expression of the liver's specific metabolic genes [72] as well as pancreatic insulin production. Other recently described novel modes of action for PCBs in FLD include: (*i*) reduced expression of signal transducer and activator of transcription 3 (STAT3, a transcription factor implicated in interleukin-6 and leptin signaling) [17]; (*ii*) reduced function of protective nuclear receptors [e.g., PPARα, β, γ and FXR)] [20]; (*iii*) altered hepatokine expression impacting the liver:pancreas axis [12]; (*iv*) gene:environment interactions [e.g., patatin-like phospholipase domain-containing protein (PNPLA3)] [12]; and (*v*) increased production of pro-fibrotic cytokines like transforming growth factor β (TGF-β) [20]. Thus, NDL PCBs impact multiple FLD mechanisms including nuclear receptors, signaling molecules and pathways, cell death pathways and antioxidant defenses.

Perfluoroalkyl substances—PFAS disrupt hepatic lipid metabolism by interacting with PPARs and other receptors due to their structural similarities with fatty acids [73]. PFAS appear to cause steatosis by upregulating lipogenesis and lipid influx, while downregulating lipid efflux [74–81]. PFAS are potent immunotoxic chemicals suppressing innate immune function, partly through PPARα-dependent mechanisms [82]. In the C8 Health Study, blood PFAS levels were positively associated with liver enzymes, a liver apoptosis biomarker, and sex differences in adipocytokine levels; but were inversely associated with serum tumor necrosis factor α [83–85]. In the National Health and Nutrition Examination Survey, low-level PFAS exposures were associated with elevated liver enzymes only in obese participants [86], consistent with the FLD two 'hit' hypothesis. Thus, PFAS exposures seem to uniquely regulate liver lipid metabolism, cell death, and inflammation in diet-induced obesity.

CURRENT LIMITATIONS AND SUGGESTED FUTURE RESEARCH DIRECTIONS

Because TASH is a recently described disease, important knowledge gaps remain in the understanding of TASH mechanisms. These data gaps inform future research directions. Most importantly, more mechanistic human data are required. Although pathology is the gold standard for the diagnosis of steatohepatitis and fibrosis; the liver biopsy procedure is often associated with risk. Moreover, FLD is asymptomatic or has nonspecific symptoms until it has progressed to decompensated cirrhosis or liver cancer; and standard serologic biomarkers for liver injury, such as alanine aminotransferase (ALT) may be insensitive for the diagnosis of TASH [4]. Therefore, liver biopsy is not justified or available in most environmental exposure cohorts, because even subjects with liver disease may be asymptomatic or have normal liver enzymes. The lack of human liver tissue paired with exposure assessment data remains a major barrier to the field. Several alternative strategies could alleviate this research barrier. First, exposure assessment could be performed in previously biopsied NAFLD cohorts. Second, novel blood [(e.g., cytokeratin 18 [4, 66, 85] or "liquid liver biopsy" [87]] or imaging-based biomarkers (e.g., fibroscan) for FLD could be applied to existing exposure cohorts. These studies could potentially (*i*) identify environmental chemicals associated with TASH, (*ii*) determine dose responses for these chemicals, and (*iii*) determine mechanisms. NAFLD mortality is associated with fibrosis [88], and more studies evaluating fibrosis in TASH are required. Some studies (Table 1) suggest a role for environmental exposures in the developmental origins of FLD. This along with the possible contribution of epigenetic mechanisms require further investigation. Polymorphisms in several genes including PNPLA3 have been associated with NAFLD, and some animal studies suggest that environmental exposures may regulate PNPLA3 expression [12]. More data are needed on gene:environment interactions in TASH. The potential reversibility of TASH is unknown, and therapy studies are required. The gut:liver axis has become increasingly important in the pathogenesis of FLD; and it is profoundly impacted by the gut microbiome. The microbiome may have a role in TASH [60], but more data are required. Likewise, environmental exposures may influence the genesis and progression of alcoholic liver disease [89], but more data are needed to better understand the potential role of exposures in alcoholic liver disease. Finally, some POPs disrupt sex hormone signaling. For instance, some low molecular weight PCBs are known to activate estrogen receptors and

to antagonize androgen receptor, whereas higher molecular weight PCB congeners may be anti-estrogenic [90, 91]. More data are needed to identify potential sex differences in TASH.

CONCLUSIONS

The conceptual understanding of the contribution of environmental exposures, particularly POPs and VOCs, to fatty liver disease has progressed significantly. Increasing numbers of environmental health studies now include liver endpoints, allowing for the further identification of chemicals implicated in TASH and their mechanisms. Several key hypothesis and the EPA's proposed steatosis adverse outcome pathway have provided a better framework for understanding TASH mechanisms. Such key hypotheses include: the endocrine, metabolism, and signaling disrupting chemical hypotheses; and the chemical-nutrition interactions impacting the two "hit" hypothesis. Environmental exposures (first 'hit') may compromise the liver's protective responses against over-nutrition (summarized in Figure 1) to promote steatohepatitis from hypercaloric diets (second 'hit'). Finally, because this is a new research area, more studies are required to address current knowledge gaps.

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LIST OF ABBREVIATIONS:

ACHS	Anniston Community Health Survey
AhR	aryl hyodrocarbon receptor
ALT	alanine aminotransferase
AMPK	AMP-activated protein kinase
AOP	adverse outcome pathway
ASH	alcoholic steatohepatitis
ATSDR	Agency for Toxic Substances and Disease Registry
CAR	constitutive androstane receptor
CK2	casein kinase 2
CREB-1	cyclic AMP responsive element binding protein 1
EDCs	endocrine disrupting chemicals
EGFR	epidermal growth factor receptor
EPA	Environmental Protection Agency
ER	endoplasmic reticulum

FLD	fatty liver disease
FXR	farnesoid x receptor
FGF-21	fibroblast growth factor-21
GLP-1	glucagon-like peptide-1
HNF4α	hepatocyte nuclear factor 4-alpha
IR	insulin resistance
MCD	methionine-choline deficient
MDCs	metabolism disrupting chemicals
MIEs	molecular initiating events
mTOR	mammalian target of rapamycin
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NDL	non-dioxin like
NIOSH	National Institute for Occupational Safety and Health
NAFLD	nonalcoholic fatty liver disease
NPL	National Priority List
NRF2	nuclear factor erythroid 2-related factor
PCBs	polychlorinated biphenyls
PCE	perchloroethylene
PFAS	perfluoroalkyl substances
POPs	persistent organic pollutants
PNPLA3	patatin-like phospholipase domain-containing protein 3
PPARα	peroxisome proliferator-activated receptor α
PVC	polyvinyl chloride
PXR	pregnane X receptor
ROS	reactive oxygen species
SDCs	signaling disrupting chemicals
STAT3	signal transducer and activator of transcription 3
TASH	toxicant associated steatohepatitis

TCDD	2,3,7,8-tetrachlorodibenzodioxin
TGF-β	transforming growth factor β
UPR	unfolded protein response
VOCs	volatile organic compounds

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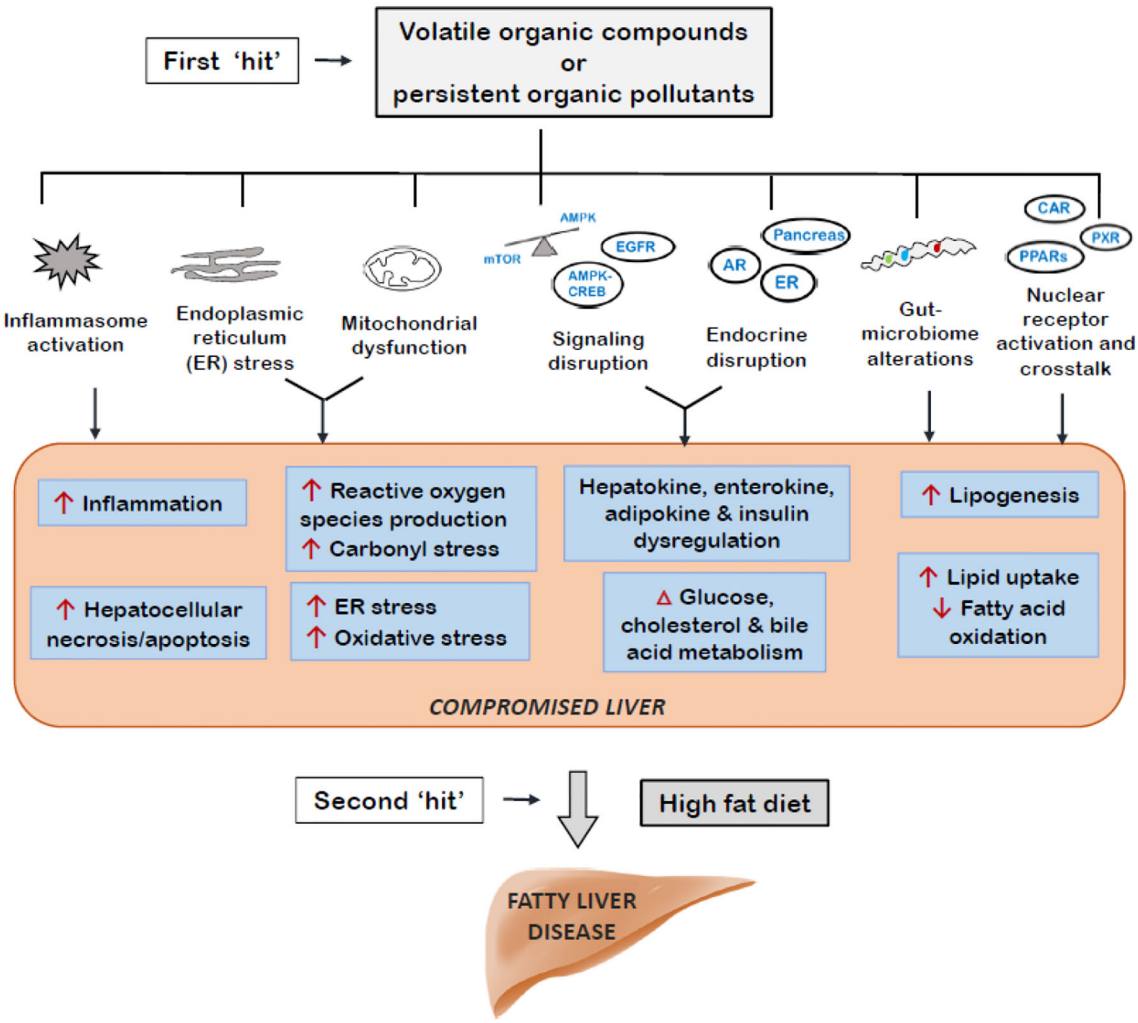

Figure 1. Selected Modes of Action for Volatile Organic Compounds and Persistent Organic Pollutants in Fatty Liver Disease.

These modes of action are related to the endocrine, metabolism, and signaling disrupting hypotheses as well as nutritional interactions and the two 'hit' hypothesis.

Table 1.

Selected examples of chemicals associated with fatty liver disease.

Category	Chemical / Chemical Group	Laboratory animals	Epidemiology/Clinical Evidence
POPs	Dioxins	Adult Exposure [92–95, 62, 96, 63]	[97–99]
	Polychlorinated biphenyls	Adult Exposure [12, 23, 56, 65, 92, 59, 58, 67].	[66, 97, 98,100–104]
	Perfluorooctanoic acid	Adult Exposure [80, 105, 74, 106]	[83–85, 107–109].
	Perfluorooctanesulfonic acid	Adult Exposure [110–112, 78]	[108, 109, 84, 107]
		Developmental Exposure [113]	
	Polybrominated diphenyl ethers	Adult Exposure [114]	
	Diethylhexyl phthalate	Adult Exposure [115, 116]	
		Developmental Exposure [117]	
	Organochlorine Insecticides	[118–120]	[101, 97, 99]
	Atrazine	Adult Exposure [121–123]	
VOCs	Vinyl Chloride/Metabolites	Adult Exposure [27, 28, 14]	[4, 29].
	Smoking/nicotine	Adult Exposure [124, 125]	[126, 127]
	Tributyltin	Adult Exposure [128]	
		Developmental Exposure [129–131]	
	Air Pollution / Particulate Matter	Adult Exposure [132–135]	[136]
	Benzo[a]pyrene	Adult Exposure [137]	
		Developmental Exposure [138]	
Metals	Arsenic	Adult Exposure [139–143]	[145]
		Developmental Exposure [144]	
	Lead		[100, 146]
	Mercury	Adult Exposure [147, 148]	[100]
	Cadmium	Adult Exposure [149–151]	[152, 153]
Others	Bisphenol A	Developmental Exposure [154–157]	
	Fungicides	Adult Exposure [92, 158]	
		Developmental Exposure [92]	
	Glyphosate-based herbicides	Adult Exposure [159]	[160]
	Dinoseb	Adult Exposure [161]	

Table 2.

Main targets and modes of action for volatile organic compounds and persistent organic pollutants in fatty liver disease.

Target Category	Target/Receptor	Outcomes/Processes	Chemical Group	References
Hepatic Nuclear Receptors	PPARs	-steatosis -immuno-toxicity -apoptosis	PFOA/PFOS VOCs	[73, 162, 163] [33]
	PXR, CAR, FXR	-lipogenesis & decreased fatty acid oxidation -decreased gluconeogenesis -hepatokine dysregulation -altered cholesterol/bile acid metabolism	PCBs	[23, 67, 12]
Sex Steroid Receptors	ERα, ERβ, AR	-endocrine-metabolic disruption	PCBs, PFAS	[164, 165]
Other Receptors	AhR	-lipid accumulation -inflammation and oxidative stress -hepatokine dysregulation -gut microbiome alterations	PCBs, TCDD	[62, 12, 166, 93, 167, 63, 60]
	EGFR	-EGFR signaling disruption -diminished HNF4A -altered insulin production	PCBs, OCPs	[19, 17]
Energy Sensors/ Regulators	CREB	-disruption of hepatic energy ‘sensing’	Dioxin-like PCBs	[57, 168]
	AMPK, mTOR,	-glycogen depletion -lipid accumulation	VOCs	[27, 29]
Organelles/Protein Complex	Endoplasmic reticulum, Mitochondria, Inflammasome	-ER and oxidative stress -carbonyl stress -inflammation -enhanced neutrophil extracellular trap formation	VOCs	[4, 14, 28, 43, 44, 54].
Antioxidant Responses	NRF2	-Reactive oxygen species generation -oxidative stress	PCBs, VOCs	[4, 20]