

The hepato-exposome axis: How endocrine disruptors hijack liver receptors to drive MASLD

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Summary

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing worldwide at a pace that cannot be fully explained by obesity, diet, or genetics alone. Emerging evidence provides mechanistic insight into how defined endocrine-disrupting chemicals (EDCs) rewire hepatic transcriptional and metabolic networks relevant to MASLD. This review focuses on the molecular interfaces through which major EDC families intersect with hepatic metabolic regulation. We propose the “hepato-exposome axis” as a receptor-centric framework that maps specific EDC classes to nuclear receptors (NRs) and key metabolic pathways involved in lipid metabolism, glucose homeostasis, mitochondrial function, and inflammatory signalling that are implicated in MASLD progression. We summarise key EDC groups linked to liver disease, including organochlorine pesticides, pyrethroids, bisphenols, phthalates, organophosphate esters, and per- and polyfluoroalkyl substances (PFAS). We then integrate current understanding of hepatic metabolic and xenobiotic pathways in homeostasis and MASLD, emphasising xenobiotic-sensing and metabolic NRs (AhR, PXR, CAR, PPARs, FXR, LXRs, RXR) as convergence points for EDC action. Drawing on *in vivo* and *in vitro* studies, we show that distinct EDC families imprint overlapping molecular signatures onto pathways that control *de novo* lipogenesis, β -oxidation, glucose handling, antioxidant defences, and inflammatory/immune signalling, collectively fostering a pro-steatotic and pro-inflammatory hepatic milieu. We further discuss vulnerable populations, critical windows of exposure, mixture effects, and sex-specific responses, positioning EDCs as environmental modifiers of the MASLD trajectory across the life course. Finally, we outline priorities for mechanistic and translational research, including mixture toxicology, multi-omics exposome profiling, and biomarker discovery, to better quantify and mitigate endocrine disruptors' contribution to the global MASLD burden.

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Introduction – the hepato-exposome axis

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most prevalent chronic liver disease worldwide, affecting more than one-third of the global adult population.¹ It is defined by excess lipid accumulation in hepatocytes, and can progress to inflammation, fibrosis, cirrhosis, and even hepatocellular carcinoma.² While excess caloric intake, sedentary lifestyle, obesity, and genetic susceptibility remain major contributors to MASLD, these factors do not fully account for the speed and breadth of MASLD's increase across populations and geographies. This gap has attracted attention to environmental determinants, particularly the chemical exposome, as additional drivers and modifiers of liver dysfunction.^{3,4}

The exposome framework, defined as the totality of exposures an individual experiences across the life course,⁴ can be divided into four main categories.⁵ Here, we focus on the

chemical exposome, specifically endocrine-disrupting chemicals (EDCs) that directly interact with hepatic metabolic regulation. Environmental chemicals can be categorised according to their origin (natural or anthropogenic), intended use (e.g. industrial pollutants, pharmaceuticals, plant protection products, and additives in consumer products and cosmetics), environmental persistence (e.g. persistent organic pollutants [POPs]), bioaccumulation (based on their half-life in organisms), and biological effects or toxicity (e.g., EDCs, carcinogens, neurotoxins, and reproductive toxins).^{6,7} EDCs are of particular interest, as they were recognised in the 1990s and have been associated with liver disease since 2015.⁸ The World Health Organization defines them as “an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny or (sub) population”.⁹ Regulatory frameworks, such as the EU Classification, Labelling and

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Keypoints

- MASLD is increasing worldwide at a pace not fully explained by genetics, diet, or obesity, suggesting additional environmental drivers.
- Endocrine-disrupting chemicals (EDCs) constitute a biologically coherent component of the chemical exposome that can actively rewire hepatic metabolic networks.
- We introduce a receptor-centric “hepato-exposome axis” framework in which the liver integrates environmental chemical sensing via nuclear receptors (NRs) and transport systems, with downstream metabolic and inflammatory outputs.
- Structurally hormone-like and lipid-like EDCs exert their effects through molecular mimicry, hijacking endogenous signalling pathways that regulate lipid flux, mitochondrial function, and redox homeostasis.
- Experimental evidence from *in vivo* and *in vitro* models reveals that EDC exposure induces reproducible alterations in hepatic genes controlling lipid metabolism, mitochondrial function, redox balance, and inflammation.
- Xenobiotic- and metabolism-sensing NRs (AhR, PXR, CAR, PPARs, FXR, LXRs) are key convergence nodes mediating EDC-driven metabolic rewiring relevant to MASLD.
- EDC exposure induces convergent transcriptional signatures involving lipid uptake and synthesis, oxidative capacity impairment, mitochondrial stress, and low-grade inflammatory activation.
- Critical windows of exposure, mixture effects, and sex-dependent receptor responses further modulate individual susceptibility to environmentally driven MASLD.
- Integrating exposome science, multi-omics approaches, and mechanistic toxicology is essential for quantifying and mitigating the environmental contribution to MASLD.

Packaging (CLP) regulation, further specify that a substance qualifies as an EDC only if it exhibits endocrine activity, produces adverse effects in an intact organism, its offspring, or future generations, and shows a biologically plausible link between the endocrine activity and the observed adverse outcome.¹⁰ Mechanistically, many EDCs act through molecular mimicry: by resembling endogenous ligands, they bind receptors and perturb downstream pathways governing metabolic regulation and cellular homeostasis.¹¹ Within this broad category, metabolism-disrupting chemicals have been defined as a subgroup of EDCs for which metabolic alterations represent the predominant adverse outcome.¹²

The liver sits at the centre of this interaction. As the body's principal metabolic hub and detoxification organ, it is continuously exposed to EDCs through diet, inhalation, and dermal absorption.¹³ Hepatic nuclear receptors (NRs) form a highly plastic regulatory network that integrates nutrient flux, hormonal signals, and chemical exposures.¹⁴ While this flexibility supports metabolic adaptation in the liver, it also increases susceptibility to disruption by EDCs that interfere with metabolic regulation.¹⁵

Unlike prior exposome-oriented reviews that broadly survey environmental determinants of liver disease, this article focuses specifically on receptor-mediated metabolic rewiring induced by defined EDC families in the context of MASLD. By integrating mechanistic evidence, including transcriptomic readouts from experimental models, we highlight convergent molecular signatures that may explain why particular chemical exposures disproportionately accelerate metabolic liver injury. We introduce the “hepato-exposome axis” as a receptor-centric framework linking environmental chemical exposures to hepatic sensing systems, downstream metabolic rewiring, and clinically relevant MASLD phenotypes. Within this framework, molecular mimicry serves as a unifying principle through which structurally diverse EDCs hijack endogenous signalling

pathways, thereby reshaping hepatic metabolic homeostasis and promoting disease progression.

Overview of major EDC classes and their molecular mimicry

EDCs arise from diverse environmental and consumer sources. Their persistence, bioaccumulation, and potential for amplified effects during critical developmental windows make them especially relevant to human metabolic health. Despite their chemical diversity, many EDCs share a unifying functional principle: they mimic, antagonise, or otherwise perturb endogenous ligands and signalling cues, including steroid hormones, thyroid hormones, fatty acids (FAs), and aromatic metabolites, thereby altering receptor engagement and downstream gene regulation.¹¹ Through this receptor-level interference, EDCs can disrupt developmental and reproductive programmes as well as metabolic homeostasis.

To illustrate the diversity and metabolic relevance of these chemicals, we summarise the major EDC classes with known or suspected roles in hepatic metabolic disruption (Table 1). We also highlight specific EDCs with established links to MASLD-related endpoints (Table 2).

Alkylphenol ethoxylates

Alkylphenol ethoxylates (APEs) are industrial chemicals used in the production of detergents, plastics, and other products. APEs can be degraded to form alkylphenols, including nonylphenol (NP), predominantly present as the isomeric mixture 4-nonylphenol.¹⁶ NP exhibits endocrine-disrupting properties largely through oestrogenic mimicry, enabling interaction with oestrogen receptors (ER/ESR).^{16,17} Functionally, NP has been linked to oxidative stress, inflammation, and dysregulation of lipid metabolism, including the promotion of adipogenesis and altered hepatic gene expression.^{16–18} In experimental models,

Table 1. Overview of the 17 representative EDCs included in this review.

Name	Short name	Chemical group	PubChem ID	An endogenous molecule mimicked	Source	Human exposure source	Ref.
Nonylphenol	NP	AP	1752	17 β -oestradiol (oestrogen)	Plastics, pesticides, paints, detergents, and cosmetics	Water sources, food packaging, cleaning products, and cosmetics	16, 17, 18
Benzo[a]pyrene	BaP	PAHs	2336	Benzene-like molecules, ligands of the AhR receptor, such as tryptophan metabolites (kynurenine, indoles)	Incomplete combustion of organic substances from natural or anthropogenetic origin	Domestic and industrial food, smoking cigarettes, smoke from fires, drinking water, and petroleum products	20, 21
Butylparaben	Bpar/BuP	Parabens	7184	Oestrogens and benzene-like molecules	Cosmetics, personal care products, food additives, pharmaceutical products, pesticides	Cosmetics, personal care products, contaminated food or water, and medication	26
Bisphenol S	BPS	Bisphenols	6626	Oestrogens-like molecules	Personal care products, nutrition, and consumables industries	Thermal papers, food packaging, baby and children's products	28, 29
Dichlorodiphenyltrichloroethane or Dichlorodiphenyl-dichloroethylene	DDT/DDE	OCPs	3035	Oestrogens-like molecules	Pesticide use as agricultural pest control and insect vectors	Contaminated food and water sources, air	52, 53
Bis(2-ethylhexyl) phthalate, and its primary degradation metabolite, Mono-2-ethylhexyl phthalate	DEHP and MEHP	Phthalate	8343 20393	Benzene-like molecules such as oestradiol	Plasticiser for PVC products, medical devices, paints, food packaging, and personal care products	Food, health, and personal care, furniture	13, 34
Diisononyl cyclohexane-1,2-dicarboxylate and its primary degradation metabolite, Mono-iso-nonyl cyclohexane-1,2-dicarboxylate	DINCH and MINCH	Alternative phthalate	11524680 166638203	Lipophilic ligand	Food packaging, paints, medical devices, children's toys, textiles	Food, health, and personal care, toys	39, 40
Permethrin	PER	Pyrethroids	40326	Thyroids-like molecules	Insecticide use in agriculture, veterinary medicine, and household products	Contaminated food, household products	53, 57, 58
Perfluorobutane sulfonic acid	PFBS	PFAS	67815	Short-chain fatty acids	Textiles, surfactants, furniture, food packaging, lubricants, firefighting foams, non-sticky cookware	Textiles, personal care products, and contaminated food, water sources, and soil	61, 62, 63
Perfluorononanoic acid	PFNA		67821	Long-chain fatty acids			
Perfluorooctanoic acid	PFOA		9554	Long-chain fatty acids			
Perfluorooctane sulfonic acid	PFOS		74483	Long-chain fatty acids			
Hexafluoropropylene oxide dimer acid	GenX		114481	Short-chain fatty acids			
Triphenyl phosphate	TPP	OPEs	8289	Phenol-like molecules	Personal care products, flame retardants, plasticisers, textiles, building materials, plastic packaging	Textiles, personal care products, contaminated food, and water sources	45, 46

AP, alkylphenols; OCPs, organochlorine pesticides; OPEs, organophosphate esters; PAHs, polycyclic aromatic hydrocarbons; PFAS, per- and polyfluoroalkyl substances; PVC, polyvinyl chloride.

Table 2. Experimental models evaluating the hepatic impact of EDCs.

Short name	Model (<i>in vivo</i> & <i>in vitro</i>)	Dose & way of administration	Exposure duration	Target genes	MASLD association	Other effects	References
NP	Sprague-Dawley rats (age not specified)	0.02, 0.2, and 2 µg of NP/kg/day and fed with a high-sucrose/high-fat diet. Daily oral gavage	90 days	↑ FAS, UCP2, PPAR _γ , C/EBP _α	Effects observed at the highest dose. An increase in BW was detected without changes in the LW/BW ratio. Hepatic steatosis was significantly increased, along with significant elevations in TG, TC, LDL, ALT, and AST levels.	A significant increase in food and water intake was observed.	19
	Adult male zebrafish	50 and 100 µg/L. Tank water	21 days	AMPK _α , Bax, caspases, Cat, ER (esr1, esr2), Fasn, GPx1a, GST _α 1, IL-6, IL-1 _β , NF-κB, NOS2, NOX4, PGC1 _α , Sirt1, SOD1, SOD2, Srebf1, TLR-4, TNF- _α	Increased liver ROS levels, upregulation of the antioxidant enzymes, macrovesicular steatosis in 100 µg/L doses, increased liver/BW ratio, lipogenesis and energy sensors upregulation, liver inflammation, and upregulation of pro-apoptotic proteins	No BW alteration. Activation of the ER.	17
	6-week-old Swiss male and C57BL/6 male and female mice	0.5 and 2.5 mg/kg/day. Drinking water	14 weeks	Esr1, Esr2, Adipoq, Fabp4, Leptin	Increase in serum AST levels	Reduction of liver TG, BW decrease, but adiposity increases with differential expression in target genes	16
	4-month-old zebrafish	45.38 and 453.8 nM. Tank water	28 days	See RNA seq results (e.g. ↑ Cpt1, Cyp27, Fabp1 _α , Me1, Pdk1 _α , etc)	Observed changes in the morphology of liver subcellular structures; notable impact on the liver steroid, fatty acid, and sphingolipid metabolism	Variability in SOD, GSH, and MDA during the different time-points of exposure (not always significant)	18
BaP	6–7-week-old male C57BL/6 WT mice + primary hepatocytes	Mice: 0.5, 5, and 50 µg/kg. Oral. Primary hepatocytes: 0.001–1 mmol/L. Culture medium	Mice: 70 days Primary hepatocytes: 72h	Primary hepatocytes. ↑ Cpt1 _α , Cpt2, p62, LC3-I, LC3-II. ↓ Atg5	Mice. LW/BW ratio decreased significantly; increased liver TG content was observed on histology. Primary hepatocytes. Increased TG content, impaired fusion of autophagosomes and lysosomes.	Mice. No BW alteration, no hair alteration, no food or water intake alterations, serum liver parameters not affected	22
	6-week-old female C57BL/6J mice	50 µg/kg. Food. Low-fat (LFD) or high-fat diet (HFD) groups.	8 weeks	↑ CYP1A1 and SREBP-1c. No significant changes in ER _α mRNA, but a reduction in the protein levels.	Increased levels of serum hepatic transaminase, serum and liver TG and TC, liver steatosis increased in BaP supplemented groups compared to the control groups, activation of AhR, and changes in protein regulators of lipid and oestrogen metabolism	The combination of HFD with BaP worsened the phenotype compared to the LFD-BaP group.	23
	Male BALB/c mice	2 mg/kg. Daily oral gavage	10 weeks	↑ CD36, FATP2, GPAT, PPAR _γ , SREBP1, and VWF. ↓ STAT1, STAT2, STAT3, JAK2, CD274, CXCL1, CXCL9, CXCL10, IRF1, SG15, and IFIT1. Additionally, see transcriptomics results	Hepatic steatosis, increased TG levels in serum and liver tissue, increased serum ALT, FFA, and TBA, increased hepatic MDA, and altered pathways revealed by transcriptomics related to immune and inflammatory response	No BW alteration. No serum TC, LDL, and HDL alteration. Faecal microbiota dysbiosis, with a notable decrease in the <i>Lactobacillus</i> genus	24
Bpar/BuP	6-week-old male CD-1 (ICR) mice	5 and 25 mg/kg/day. Oral	9 weeks	↑ FASN, IL-6, IRS1, JNK, TNF- _α , P38, PEPCCK, and SREBP1. ↓ CYP7A1, CYP27A1, FXR, PPAR _α , and SHP	Increased serum TG, TC, LDL, and glucose, increased hepatic TG, TC, LDL, and decreased hepatic TBA, hepatic steatosis seen by histology, alteration in genes associated with lipid, BA, and inflammatory metabolic pathway	Reduced expression of MUC2 and occludin in the colon, microbiota alteration by the reduction in the Bacteroidetes phylum, and the <i>Lactobacillus</i> and <i>Streptococcus</i> genus	27
BPS	7-week-old male C57BL/6 mice + <i>in vitro</i> model	Mice. 0.1 mg/kg/day & 1 mg/kg/day. Oral gavage. AML12 cell line & primary hepatocytes. 100 µM. Culture medium	Mice: 12 weeks AML12 cell line & primary hepatocytes: 24h	Only <i>in vitro</i> data. ↑ Acot2, Acox2, Acaa1, Atf3, Cpt1. ↓ Elovl6 and Scd1.	Mice. Increase in liver TG, serum LDL, ALT, and NEFA; dysregulation of genes related to steroid and cholesterol metabolism. AML12 cell line & primary hepatocytes. Lipid deposition in BPS-treated cells, dysregulation in genes related to steroid and fatty acid metabolism.	No BW and LW alteration. Changes in chromatin accessibility in cells due to BPS exposure.	31
	3-week-old male Wistar rats	50 µg BPS/kg of body/day. Drinking water	38 weeks	↑ Drp-1 (mitochondrial fission)	Increase of serum TG after 38 weeks, increase of BW from week 21 to week 35, impairment of glucose homeostasis, reduction in the citrate synthase activity, increase in protein carbonyls, and higher rates of H ₂ O ₂ generation.	No LW alterations. No oxygen consumption alterations in liver biopsies.	30

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Table 2. (continued)

Short name	Model (<i>in vivo</i> & <i>in vitro</i>)	Dose & way of administration	Exposure duration	Target genes	MASLD association	Other effects	References
DDT/DDE	7-week-old male SPRET/EiJ mice	112.5 µg/g BW/day of DDE. Food	30 days	↑ Adh1, Cyp2b10, cyp2b13, Gstm1, Gstm2, Gstm3, Gstt1, Gstt2, Por, Ifitm2, Vnn1, Nfkbib, Rarres1, Ccni2, Lmnb2, Abcc3 ↓ Apob, Elovl3, Fabp3, Ifi47, Irs2, Rdh12, Cldn7, Scara5, Cox8b, Cpb1, Ogdh	Liver histological analysis revealed dilated central veins. Gene expression alterations were observed in pathways related to biotransformation, lipid metabolism, immune response, transport, cell signalling, apoptosis, tumour progression, and other processes.	BW remained unchanged. Steatosis was not described in the histological analysis.	56
	Primary hepatocytes isolated from 5-week-old Sprague-Dawley rats	150 µM of DDT. Culture medium	24h	↑ top 5: Slc25a4, Pla2g7, Scd2, Hmg2, Cxcl10 ↓ top 5: Bdh1, Cyp3a5/7, Pemt, Cyp17a1	Changes in transcriptomics (cells) and metabolomics (culture medium). 127 downregulated and 139 upregulated genes, some of which are associated with liver steatosis (ucp1), liver inflammation (Srebf1, Ifnb1), and liver necrosis (Insig1).	Enhanced effect when combined with 150 µM PER.	55
DEHP/MEHP	4-week-old male C57BL/6 mice + <i>in vitro</i> model in HepG2 cell line	Mice. 1000 mg/kg of DEHP. Intraperitoneal injection HepG2 cell line. 200 µmol/L of DEHP. Culture medium	Mice. 16 weeks HepG2 cell line. 24h	↑ PD-L1, JAK2, and STAT3 in mice and cells are associated with tumour immune escape.	Mice. Significant increase in the liver weight, but significant decrease in the BW. Significant increase in serum AST, ALT, AFP, TNF-α, and IL-6 levels. Considerable increase in expression of PD-L1, JAK2, and STAT3 proteins. HepG2 cell line. Significant increase in PD-L1 mRNA.	1,000 mg/kg of DEHP, in combination with DEN + CCl4, increases the number of liver tumours. 200 µmol/L of DEHP in cells did not affect the cell viability.	37
	6-week-old male and female Sprague-Dawley rats	3 g/kg of DEHP; 0.1 g/kg of MEHP. Oral gavage	60 days	No expression analysis available.	DEHP effects. Dilated congestion in the male's liver, a significant decrease in serum ALT, and a considerable increase in serum cholesterol, LDL, and triglyceride. MEHP effects. Dilated congestion in the male's liver; significant decrease in serum ALT only in males; substantial reduction in serum cholesterol and triglyceride only in females; significant increase in serum LDL only in males.	DEHP and MEHP reduced gut microbiota diversity, altered faecal SCFA content, and changed serum BA, amino acids, and lipidomic data. In addition, all these variances differed between male and female rats.	38
DINCH/MINCH	8-week-old female and 10-week-old male Long-Evans rats, and male and female offspring	30 or 300 mg/kg/BW. Animals were exposed to food containing DINCH during premating, pregnancy, and lactation	Premating (2 weeks), mating (10 days), pregnancy (23 days), lactation (6 days)	Dams. ↑ IL-1β, TNF-α, NF-κB, PUMA, Caspase-3, APAF-1. ↓ PGC-1α, SOD, Bcl-2, Bcl-xL. Postnatal day 6 offspring. ↑ TNF-α, cytochrome c, NK-kβ, APAF-1. ↓ PGC-1α, PPAR-γ, CAT, Bcl-2, AIF.	General increase in inflammatory and apoptotic markers in the liver of dams (IL-1β, TNF-α, NK-kβ, PUMA, Caspase-3, APAF-1). General increase in inflammatory and apoptotic markers in the liver of postnatal day 6 offspring (TNF-α, NK-kβ, cytochrome c, APAF-1). Reduction of antioxidant enzyme activities in dams (SOD) and postnatal day 6 offspring (CAT)	LW or BW were not measured.	42
GenX	9-11-week-old male and female WT C57BL/6J mice	0.3 mg/kg/day. Drinking water	20 weeks	↑ CD36, Cyp4a14, Ehhadh, Lpl, and Fgf21	Decrease in the BW, insulin tolerance was slightly improved, liver triglycerides were significantly increased, and there was a general alteration in gene sets related to lipid metabolism (e.g. PPARα target genes)	LW/BW ratio was not altered.	69
PER	Primary hepatocytes isolated from 5-week-old Sprague-Dawley rats	150 µM. Culture medium	24 h	↑ top 5: Cyp4a11, Pck1, Hmg2, Ehhadh and Slc34a2. ↓ top 5: Diaph3, Akr1b10, Defb1, Cyp17a1, Cyp3a5/7	Changes in transcriptomics (cells) and metabolomics (culture medium). 164 downregulated and 92 upregulated genes, including some associated with liver steatosis (ucp1), cirrhosis (Rxrg), xenobiotic or lipid metabolism (Srebf1, Ppara, Mxipl).	Enhanced effect when combined with 150 µM DDT.	55

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Table 2. (continued)

Short name	Model (<i>in vivo</i> & <i>in vitro</i>)	Dose & way of administration	Exposure duration	Target genes	MASLD association	Other effects	References
PFBS	6-week-old male C57BL/6 mice	30 and 300 mg PFBS/kg/day. Daily via oral gavage	28 days	↑ TNF- α , IL-6, PPAR- α , and Acox1 ↓ Nr2f2, SOD1, SOD2, Ho-1, Cyp7a1 and Cyp27a1	An increase in the LW/BW ratio and hepatic AST levels was observed at high doses of PFBS. Histological analysis revealed immune cell infiltration, along with alterations in hepatic gene expression of detoxification systems, lipid metabolism, and inflammation.	Changes in microbial composition.	73
PFNA	8-week-old male C57BL/6 WT mice	Unique dose of 5 ml/kg of body weight. Intraperitoneal injection	1 week	↑ PPAR α , CAR, FXR, Lrh1, Abcg isoforms, HMGCoAR, Abca1, SR-B1, S1AR ↓ Cyp7b1, Shp	LW/BW ratio was altered. Serum ALT and BA profiles were significantly changed in the PFNA-treated group. Liver cholesterol was increased substantially in the PFNA-treated group—alteration in sterol-associated enzymes, BA transporters, and BA biosynthesis enzymes genes.	Serum cholesterol was not altered.	72
PFOA	9–11-week-old male and female WT C57BL/6J	0.05 and 0.3 mg/kg BW/day. Drinking water	20 weeks	↑ CD36, Cyp4a14, Ehhadh, and Lpl. ↓ of genes related to cholesterol synthesis.	Effects under 0.3 mg/kg/day: Significant decrease in the BW (from w5 to w20). Significant increase in the LW/BW ratio. The glucose and insulin tolerance tests were improved. Plasma triglycerides, NEFA, and glycerol were significantly decreased. Liver glycogen was significantly reduced, while liver triglycerides were increased considerably. General alteration in gene sets related to lipid metabolism (e.g. PPAR α target genes).	Most effects below 0.3 mg/kg/day were not observed at the lower PFOA dose of 0.05 mg/kg/day.	69
	8–12-week-old male and female C57BL/6J	50 and 300 μ g/kg BW/day. Drinking water	28 days	↑ Ehhadh, Fatp1, Cyp4a10, Cyp2b10, Cyp3a11, Acot1, Hmgcr ↓ Cyp7a1	A significant increase in the LW/BW ratio was observed in both males and females at the high dose. Plasma cholesterol and triglyceride levels were elevated, with sex-specific effects. A significant increase in hepatic triglycerides was observed only in males exposed to the highest dose. Changes were also noted in PPAR α target genes, CAR/PXR target genes, and selected genes involved in cholesterol metabolism.	No changes in BW. Glucose tolerance was not affected by PFOA.	70
PFOS	6-week-old male C57BL/6N mice	0.36 mg of PFOS/kg/day. Food. Mice received either a standard or an HFD diet	10 weeks	Similar hepatic effects were consistently observed in PFOS-treated groups. ↑ Cyp4a10, Cyp4a12, Cyp4a14, Acs11, Cyp2b10, Cyp3a11, Ehhadh, Acot2, Cpt1b, Slc27a1, Slc27a2, Por, Aldh3a2, Ces1g, Ces2c, Ugt1a1, Nqo-1, Gstm3, Ephx1	Decreased BW was observed following PFOS exposure. A significant increase in the LW/BW ratio was found in animals supplemented with PFOS. Histological liver alterations were more pronounced in the HFD+PFOS group compared to the standard diet. Change in gene expression related to lipid and xenobiotic metabolism.	No clear effect was detected on serum parameters. Gonadal white adipose tissue (WAT) was reduced in PFOS-treated groups.	71

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Table 2. (continued)

Short name	Model (<i>in vivo</i> & <i>in vitro</i>)	Dose & way of administration	Exposure duration	Target genes	MASLD association	Other effects	References
TPP	5-month-old zebrafish	0.05 and 0.300 mg TPP/L. Tank water	7 days	Some of the genes identified were as follows: ↑ Cyp1a2, Cyp2b ↓ Sdhda, FABP1, Elovl6, Elovl7, Ppt, Fmo5, Cyp11a, Cyp7a1, Cyp17a1, p53R2	Significant changes in blood were observed, including elevated glucose, TG, TC, and HDL levels, with the most potent effects at the 0.3 mg/L dose. Alterations were detected in metabolites related to carbohydrate, lipid, amino acid, and TMAO metabolism. Liver histology revealed signs of hepatic inflammation. Differentially expressed genes were associated with PPAR signalling, the TCA cycle, steroid hormone biosynthesis, FA and xenobiotic metabolism, or p53 signalling pathways, among others.	No changes were reported in BW or LW	48
	4-week-old male C57BL/6J mice	Low TPP dose (TPP-L) of 10 µg/kg BW/day or high TPP dose (TPP-H) of 1,000 µg/kg BW/day. TPP mixed into the mouse feed, normal or HFF diet	12 weeks	Protein expression in TPP-H, control diet: ↑ MHCII/MHCI related protein, ACOT3, ACOT4, ACAA1B, SCD1, FABP5, CYP4A14, FHHADH, ME1. ↓ HSD3B5, CYP1A2, CYP2C39, CYP7B1, SCD4. Protein expression in TPP-H, HFF diet: ↑ CPA1, CYP4A14, CYP4A10, CYP2C50. ↓ PRSS2, SCD1, SCD4, CYP2C39. TPP-R on liver mRNA levels. ↑ Fasn, Acot3, GRP146, and Hmgcs1. ↓ Ocln, Cldn5, Tph1, Jam3	TPP dose-dependent increase in BW observed in HFF diet groups. Significant increases in serum parameters of TG, TC, LDL, HDL, and AST in TPP-L and TPP-H groups vs. controls. ALT increased only in TPP-L and TPP-H of the control diet groups. TG and total cholesterol were significantly elevated in the liver, especially in the TPP-H groups. Altered expression in proteins related to antigen processing/presentation, unsaturated FA biosynthesis, PPAR signalling, steroid hormone biosynthesis, and lipid metabolism. Main effects observed in TPP-R-exposed mice. Significant increase in liver TC, TG, and MDA. Metabolomics results showed alterations in PPAR signalling, arachidonic acid, BA secretion, and carbohydrate metabolism, which were also confirmed by mRNA analysis.	No significant changes in BW in control diet groups, regardless of TPP exposure dose. Optical density of ORO staining increased in TPP-H and inflammatory infiltration, but no clear steatosis was observed histologically in the livers.	49
	8-week-old male C57BL/6J mice	Subchronic exposure to TPP. 0.1 or 7 µg/kg BW/day (TPP-E and TPP-R, respectively). Food	12 weeks			No changes were observed in BW, basal glycaemia, or the glycaemic response following either a GTT or ITT. At the histological level, cell infiltration and a slight increase in the ORO-positive area were observed, but no clear steatosis was detected. TPP exposure altered caecal microbial composition.	50

ABC, ATP-binding cassette; Acca, acetyl-CoA acyltransferase; Acot, acyl-CoA thioesterase; Acox, acyl-CoA oxidase; ACSL, acyl-CoA synthetase long-chain; Adh, alcohol dehydrogenase; AFP, alpha-fetoprotein; AIF, apoptosis-inducing factor; ALT, alanine aminotransferase; ALDH, aldehyde dehydrogenase; AMPK, AMP-activated protein kinase alpha subunit; APAF, apoptotic protease activating factor; Apob, apolipoprotein B; ATF, activating transcription factor; Atg, autophagy-related gene; BaP, benzo[a]pyrene; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; Bdh, 3-hydroxybutyrate dehydrogenase; Bpar/BuP, butylparabene; BPS, bisphenol S; BW, body weight; CAR, constitutive androstane receptor; CAT, catalase; CCl₄, carbon tetrachloride; Ccnl2, cyclin L2; CD36, cluster of differentiation 36; CD274, cluster of differentiation 274; CES, carboxylesterase; C/EBP α , CCAAT enhancer-binding protein α ; CLDN, claudin; Cox, cytochrome c oxidase; CPA1, carboxypeptidase A1; Cpb1, carboxypeptidase B1; Cpt, carnitine palmitoyltransferase; CXCL, C-X-C motif chemokine ligand; CYP, cytochrome P450; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, bis(2-ethylhexyl) phthalate; DEN, diethylnitrosamine; DINCH, diisononyl cyclohexane-1,2-dicarboxylate; Drp-1, dynamin-related protein 1; Ehhadh, enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase; Elovl, elongation of very long chain fatty acids protein; EPHX1, epoxide hydrolase 1 (microsomal); ER/ Esr, estrogen receptor; FA, fatty acid; FABP, fatty acid-binding protein; FHHADH, 3-hydroxyacyl-CoA dehydrogenase type II; Fatp, fatty acid transport protein; Fasn, fatty acid synthase; FFA, free fatty acids; Fgf21, fibroblast growth factor 21; FMO, flavin monooxygenase; FXR, farnesoid X receptor; GenX, hexafluoropropylene oxide dimer acid; GPAT, glycerol-3-phosphate acyltransferase; GPx, glutathione peroxidase; GRP146, G-protein coupled receptor 146; GSH, glutathione; GST, glutathione S-transferase; GTT, glucose tolerance test; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HFD, high-fat diet; HFF, high fructose and high fat diet; HMGCOR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; Hmgn, high mobility group nucleosome binding domain; HO, heme oxygenase; HSD3B5, hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 5; Ifi, interferon gamma-inducible protein; Ifnb, interferon beta; IL-1 β , interleukin-1 beta; IL-6, interleukin 6; Insig, insulin-induced gene; IRF, interferon regulatory factor; IRS, insulin receptor substrate; ITT, insulin tolerance test; LFD, low-fat diet; JAM, junctional adhesion molecule; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LC3, microtubule-associated protein 1A/1B-light chain 3; LDL, low-density lipoprotein; Lpl, lipoprotein lipase; Lmnb2, lamin B2; LRH, liver receptor homolog; LW, liver weight; MDA, malondialdehyde; Me1, malic enzyme 1; MEHP, mono-2-ethylhexyl phthalate; MHCII/ I, major histocompatibility complex class I or II; MINCH, mono-iso-nonyl cyclohexane-1,2-dicarboxylate; Mixlpl, MLX interacting protein like (ChREBP); MUC, mucin protein; NEFA, non-esterified fatty acids; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, nitric oxide synthase; NOX, NADPH (nicotinamide adenine dinucleotide phosphate) oxidase; NP, nonylphenol; NQO, NAD(P)H quinone dehydrogenase; OCLN, occludin; Ogdh, oxoglutarate dehydrogenase; PAHs, polycyclic aromatic hydrocarbons; Pck1, phosphoenolpyruvate carboxykinase 1; Pdk, pyruvate dehydrogenase kinase; PD-L1, programmed death ligand 1; Pemt, phosphatidylethanolamine N-methyltransferase; PEPCK, phosphoenolpyruvate carboxykinase; PER, permethrin; PFBS, perfluorobutane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PGC, peroxisome proliferator-activated receptor gamma coactivator; Pla2g7, phospholipase A2 group VII; Por, P450 oxidoreductase; PPAR, peroxisome proliferator-activated receptor; PPT, palmitoyl-protein thioesterase; PRSS2, protease serine 2 (trypsinogen 2); PUMA, p53 upregulated modulator of apoptosis; P53R2, ribonucleoside-diphosphate reductase subunit M2; Scara, scavenger receptor class A; Scd, stearoyl-CoA desaturase; Sdh, succinate dehydrogenase; SHP, small heterodimer partner; Sirt, sirtuin; Slc, solute carrier family; Soat, sterol O-acyltransferase; SOD, superoxide dismutase; SR-B1, scavenger receptor class B type 1; SREBF, sterol regulatory element-binding transcription factor; SREBP, sterol regulatory element-binding protein; StAR, steroidogenic acute regulatory protein; STAT, signal transducer and activator of transcription; Rarres, retinoic acid receptor responder; Rdh, retinol dehydrogenase; ROS, reactive oxygen species; RXR, retinoid X receptor; TBA, total bile acids; TC, total cholesterol; TG, triglycerides; TLR, Toll-like receptor; TNF- α , tumour necrosis factor alpha; TPH, tryptophan hydroxylase; TPP, triphenyl phosphite; Ucp1, uncoupling protein 1; UGT, UDP-glucuronosyltransferase; VWF, von Willebrand factor; Vnn, vanin; WAT, white adipose tissue; WT, wild-type.

NP exposure exacerbates diet-induced MASLD by promoting steatosis and activation of lipogenic genes.¹⁹

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are generated during incomplete combustion and are commonly encountered through diet and inhalation. Benzo[a]pyrene (BaP) is one of the most common PAH molecules. It is mainly found in processed grilled food and tobacco smoke.²⁰ BaP binds and activates the aryl hydrocarbon receptor (AhR), a cytosolic transcription factor. While AhR can be engaged by endogenous ligands derived from host or microbial metabolism, BaP and related PAHs can mimic these interactions, driving AhR activation and nuclear translocation.²¹ Once activated, AhR binds to xenobiotic response elements and regulates the expression of genes involved in detoxification pathways.²¹ This enhances the production of reactive oxygen species (ROS), which promote lipid peroxidation and result in tissue damage.²⁰ *In vivo* evidence further indicates that exposure to BaP can alter the expression of genes associated with lipid metabolism in the liver, such as peroxisome proliferator-activated receptors (PPARs), sterol regulatory element-binding proteins (SREBPs), and carnitine palmitoyltransferases (CPTs), as well as genes involved in lipid transport (e.g. CD36) and xenobiotic metabolism (e.g. cytochrome P450 enzymes).^{22–24}

Parabens

Parabens are widely used as preservatives in consumer products and some pesticides. They share a hydroxybenzoate core with variable alkyl chain lengths (methyl, ethyl, propyl, butyl, heptyl). Butylparaben (BuP) is among the most commonly used.²⁵ In recent years, parabens have been classified as EDCs due to their ability to interact with cellular receptors and promote adipogenesis, inflammation, and other metabolic disturbances such as insulin resistance (IR).²⁶ Additionally, their structure resembles that of oestrogens, with consequences for the endocrine system.²⁵ Mechanistically, BuP has been reported to impair lipid and glucose homeostasis by inhibiting farnesoid X receptor (FXR) signalling, leading to steatosis, inflammation, gluconeogenesis, IR, and gut microbiota dysbiosis.²⁷

Bisphenols

Bisphenols are primarily used in the production of plastics and resins. These substances are commonly found in a variety of consumer products, including food cans, packaging materials, and baby bottles. Bisphenol A (BPA) is the most extensively studied and exhibits oestrogen-like activity, leading to regulatory restriction in multiple jurisdictions. Consequently, structural analogues such as bisphenol S (BPS) and bisphenol F have emerged as alternatives, with their use steadily increasing to replace BPA.^{28,29} Recently, attention has shifted towards the potential effects of these analogues, particularly BPS.^{28,29} Experimental evidence indicates that BPS promotes hepatic lipid accumulation and dysregulates genes involved in fatty acid and steroid metabolism.^{30,31} Newer alternatives (e.g. Pergafast 201) have been introduced with claims of reduced toxicity, but limited mechanistic data are available, underscoring the need for further research.^{32,33}

Phthalates

Phthalates are widely used plasticizers present in consumer and medical products.^{34,35} They resemble oestradiol, allowing them to interact with the oestrogen receptor.¹³ They have also been associated with various cardiovascular outcomes and other diseases, classifying them as EDCs. Bis(2-ethylhexyl) phthalate (DEHP) is one of the most extensively studied high-molecular-weight phthalates, and its primary degradation metabolite is mono(2-ethylhexyl) phthalate (MEHP).³⁵ Both have been strongly linked to the development of diabetes and obesity, as they both act as ligands for PPARs.^{13,36} *In vivo* experiments have shown that exposure to these compounds increases serum ALT and interleukin levels, leading to an increased number of liver tumours³⁷ and inducing changes in the gut microbiota.³⁸ Emerging alternatives, such as diisononyl cyclohexane-1,2-dicarboxylate (DINCH) and its metabolite mono-isononyl cyclohexane-1,2-dicarboxylate (MINCH), are structurally more similar to FAs.^{36,39,40} Initially considered safer, current evidence suggests that DINCH induces oxidative stress and triggers pro-inflammatory signalling pathways.³⁹ Dietary DINCH exposure in mice was shown to induce proteomic alterations in different white adipose tissue depots and the liver, including changes in FA metabolism, upregulation of hepatic xenobiotic metabolism pathways, and sex-specific metabolic effects.⁴¹ Moreover, DINCH exposure in pregnant female animals upregulated proinflammatory genes, including IL-1 β , TNF- α , and NF- κ B, as well as proapoptotic genes in the livers of their offspring, indicating transgenerational effects.⁴²

Organophosphate esters

Organophosphate esters (OPEs) are a group of synthetic organic compounds, containing phosphorus in their structures, that are widely used as flame retardants and plasticisers.^{43,44} OPEs have been associated with metabolic disruption, causing IR, fat accumulation, and interference with thyroid and sex hormone functions.⁴⁴ However, they have also been linked to various health outcomes during pregnancy and childhood.⁴³ One of the most common OPE is triphenyl phosphate (TPP or TPHP), and its primary metabolite is diphenyl phosphate (DPP or DPHP). TPP is used in personal care products (primarily nail polish), textiles, building materials, and plastic packaging.^{45,46} It is classified as an organophosphate with oestrogenic and thyroid-disrupting properties and is suspected to cause metabolic disorders.^{45,47} In zebrafish, short-term TPP exposure disrupts hepatic carbohydrate and lipid metabolism, alters PPAR-related pathways, and impairs DNA damage repair, consistent with hepatotoxic stress responses.⁴⁸ Recent studies in mice, whether on a control or high-fructose high-fat diet, have shown that TPP can disrupt proteins involved in antigen processing, the biosynthesis of unsaturated FAs, PPAR signalling, steroid hormones biosynthesis, and lipid metabolism.⁴⁹ Furthermore, exposure to TPP disrupts gut–liver axis metabolism and alters the composition of the caecal microbiota.⁵⁰

Organochlorine pesticides

Organochlorine pesticides (OCPs) are a class of synthetic pesticides that were widely used throughout the mid-20th century

for agricultural pest control and to reduce the transmission of vector-borne diseases⁵¹. Their strong carbon–chlorine bonds confer high stability and hydrophobicity, driving persistence and bioaccumulation, thereby classifying them as POPs.^{51,52} Despite regulatory restrictions, exposure persists through contaminated food and the environment.⁵¹ Moreover, these compounds can cross the placenta and be transferred via breast milk, with higher burdens in children.⁵² OCPs can be categorised into different groups, with the most well-known being the diphenyl aliphatics.⁵² Within this subgroup, dichlorodiphenyltrichloroethane (DDT) and its primary metabolite, dichlorodiphenyldichloroethylene (DDE), are of particular concern. Historically, DDT has been one of the most effective pesticides for malaria control, and it continues to be used for this purpose in some countries today.^{51,52} However, DDT and DDE exhibit oestrogenic and anti-androgenic activity and interact with NRs, including pregnane X receptor (PXR), classifying them as EDCs.^{52,53} DDT has also been shown to interact with the nervous system and to interfere with thyroid hormone signalling.⁵¹ Furthermore, they have been linked to MASLD and induce transcriptional changes in pathways related to lipid metabolism, inflammation, and xenobiotic processing.^{54–56}

Pyrethroids

Pyrethroids are synthetic insecticides chemically derived from natural pyrethrins.⁵⁷ To improve their stability and effectiveness, pyrethrins were chemically modified to yield pyrethroids, making them more resistant to degradation and more persistent in the environment.⁵⁸ They are widely used in agriculture, veterinary applications, and household insect control.⁵⁸ They are classified into two main groups based on their neurotoxic mechanisms, including compounds such as permethrin (PER or PMT), deltamethrin, and cypermethrin.⁵⁷ Their structural similarity to thyroid hormones underlies their endocrine-disrupting potential.⁵³ Although primarily studied for neurotoxicity, they also induce hepatic metabolic changes, including gene expression patterns associated with steatosis and xenobiotic metabolism.^{55,59}

Per- and polyfluoroalkyl substances

Per- and polyfluoroalkyl substances (PFAS), often referred to as “forever chemicals”, are highly persistent synthetic compounds widely used in industrial and consumer applications.^{60–62} PFAS are generally categorised as either short-chain (4–7 carbon atoms) or long-chain compounds (8 or more carbon atoms).^{63,64} To date, more than 5,000–10,000 PFAS congeners have been identified.⁶¹ The most studied members include perfluorobutane sulfonic acid (PFBS), perfluorononanoic acid (PFNA), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and, more recently, hexafluoropropylene oxide dimer acid (GenX), which is used as a perfluorooctanoic acid substitute. Notably, several countries have banned or strictly regulated certain PFAS, such as PFOA and PFOS, because of their documented toxicity and environmental persistence.⁶² However, these compounds remain present in drinking water, leading to continuous human exposure.⁶⁰ Their structural similarity to FAs enables them to interact with lipid-sensing pathways, particularly PPAR α signalling. PFAS exposure is consistently associated with hepatic steatosis, altered bile acid (BA) metabolism, and liver injury biomarkers.^{63,65–68}

Mechanistically, they promote oxidative stress, mitochondrial dysfunction, and widespread metabolic rewiring across lipid and energy pathways, with evidence of sex-specific effects.^{69–73} Additionally, PFAS may act extrahepatically via the Nrf2/ARE pathways in adipocytes, influencing systemic metabolism.⁷⁴

Key concept: molecular mimicry as a unifying mechanism

Despite their chemical heterogeneity, many EDCs converge on shared mechanisms by mimicking key endogenous ligands. By resembling FAs, steroid hormones, thyroid hormones, or canonical xenobiotic ligands, distinct EDC families can engage overlapping sensing systems and transcriptional programmes. These include activation of PPARs, modulation of ER-dependent signalling, and engagement of xenobiotic-sensing NRs, with downstream rewiring of lipid handling, BA metabolism, and inflammatory tone. In parallel, EDC-driven induction of cytochrome P450 (CYP) enzymes can increase ROS generation and oxidative burden, thereby perturbing redox homeostasis (including Nrf2/ARE-linked responses), promoting mitochondrial stress, and amplifying hepatocellular injury. Collectively, these receptor- and stress-axis perturbations can erode metabolic flexibility and detoxification capacity, creating conditions that favour steatosis and progression along the MASLD spectrum. However, understanding how EDCs are absorbed, metabolised, and bioactivated in the liver remains essential to elucidate their hepatotoxic potential. The following section introduces the liver’s fundamental metabolic architecture and outlines the features that make it intrinsically vulnerable to EDCs.

Liver metabolic architecture and vulnerability to EDCs

The liver sits at the intersection of nutrient metabolism, hormonal regulation, and xenobiotic processing. While these features confer metabolic flexibility, they also increase susceptibility to EDC disruption. Three principles shape hepatic vulnerability to EDCs. First, *metabolic openness*: hepatocytes are continuously exposed to dietary compounds and portal blood-borne xenobiotics, making the liver the primary interface for biotransformation. Second, *receptor plasticity*: hepatic NRs exhibit broad ligand promiscuity (e.g. PPARs, PXR, AhR, ER), enabling diverse EDCs to hijack transcriptional programmes normally tuned to endogenous metabolites. Third, *energetic centrality*: reliance on mitochondrial function, redox cycling, and high lipid flux renders the liver highly sensitive to oxidative imbalance and perturbations in metabolic signalling. Together, these features create a physiological setting in which EDCs can readily interfere with essential hepatic pathways. Table 2 summarises the exposure to the previously mentioned EDCs and their primary effects associated with MASLD. Below, we outline the core hepatic metabolic processes that are particularly vulnerable to EDC-driven rewiring.

Carbohydrate metabolism: a network sensitive to hormonal and xenobiotic signals

The liver maintains systemic glucose homeostasis through glycolysis, gluconeogenesis, glycogenesis/glycogenolysis, and the pentose phosphate pathway, which supports

antioxidant defence via NADPH production and nucleotide biosynthesis.⁷⁵ The integration of insulin, glucagon, thyroid hormone, and nutrient signalling makes carbohydrate metabolism highly sensitive to endocrine and xenobiotic disruption.^{76,77} EDCs such as NP, BuP, and PER modulate key gluconeogenic and insulin signalling nodes, including phosphoenolpyruvate carboxykinase 1 (PEPCK1), pyruvate dehydrogenase kinase 1 (PDK1), malic enzyme 1, and insulin receptor substrate (IRS) family members.^{18,27,55} Other EDC classes (e.g. DDT/DDE, DINCH/MINCH) have been associated with reduced IRS signalling and impaired peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC1 α) expression, potentially attenuating insulin responsiveness and mitochondrial-metabolic coordination.^{42,56} Overall, these effects converge on hepatic IR, a central driver of MASLD progression.^{78–80}

Lipid metabolism: The central target of EDC-induced rewiring

Lipid metabolism is the most extensively disrupted domain in MASLD and a primary target of EDCs. The liver coordinates FA oxidation, *de novo* lipogenesis (DNL), triglyceride (TG) synthesis, very low-density lipoprotein secretion, phospholipid and sphingolipid synthesis, cholesterol homeostasis, and BA metabolism.^{81–84} EDCs can interfere at multiple levels, underscoring their critical role in MASLD pathogenesis. First, they can disrupt mitochondrial β -oxidation via PPAR α modulation,⁶⁷ and induce DNL by upregulating acyl-CoA thioesterase, acyl-CoA oxidase, FA synthase (FASN), SREBP, and CPT pathways.^{27,31,50,69,73} Third, they can perturb the BA-lipid axis by affecting FXR signalling and BA transporters, thereby altering BA biosynthesis, cholesterol catabolism, and enterohepatic communication.^{27,72} Finally, many EDCs influence hepatic lipid influx. Free FA uptake is mediated by CD36 and FA transport proteins (SLC27 family), and its upregulation is a recognised feature of MASLD.^{85,86} Transcriptomic datasets reveal that multiple EDCs upregulate hepatic CD36 expression, promoting free FA uptake and lipid droplet expansion.^{24,69}

Nitrogen and protein metabolism: A hidden mediator of xenobiotic sensitivity

The liver regulates nitrogen disposal, amino acid metabolism, and plasma protein synthesis and clearance. Amino acid catabolism generates key mitochondrial tricarboxylic acid intermediates and regulates the NAD⁺/NADH and NADP⁺/NADPH balance.^{87–89} Although direct evidence remains limited, several plausible mechanisms suggest that vulnerability exists. EDC-driven oxidative stress and mitochondrial dysfunction could compromise urea cycle capacity, impair ammonia clearance, and shift amino acid profiles. Downstream consequences may include altered synthesis of albumin and clotting factors, disruption of transferrin/hepcidin regulation, and activation of hepatocellular stress responses such as the unfolded protein response.

Xenobiotic metabolism: The critical interface exploited by EDCs

Xenobiotic metabolism is the domain most directly engaged by environmental exposures. The liver coordinates this via the

Phase 0–III system (influx, oxidation, conjugation, efflux)^{90–94} (Fig. 1). While the canonical Phase 0–III framework of xenobiotic metabolism has been comprehensively reviewed elsewhere, MASLD creates a context in which detoxification pathways become dysregulated, resulting in the accumulation of reactive intermediates rather than their efficient clearance.

EDCs act as both substrates and inducers of xenobiotic pathways via NR activation (AhR, CAR, PXR), thereby increasing oxidative stress and metabolic rewiring. Importantly, efficient detoxification is not always achieved, as several EDCs (e.g. PFAS) are poorly metabolised and persist in the liver.⁶⁴ Although hepatocytes are the primary site of xenobiotic metabolism (Fig. 1), emerging evidence indicates that cholangiocytes and immune cells may also contribute to xenobiotic sensing and metabolic responses via shared transporter and receptor systems.^{95,96}

The hepatic xenobiotic-sensing NR network: Targets of EDCs

Upon xenobiotic exposure, hepatocytes activate a network of NRs that integrate environmental signals with metabolic regulation. Key sensors include AhR, PXR, and the constitutive androstane receptor (CAR), which directly induce Phase I–III detoxification pathways,^{90,97} whereas PPARs, FXR, and liver X receptor (LXR) modulate xenobiotic responses through their roles in lipid and BA metabolism.^{97,98}

Rather than acting as isolated pathways, these receptors form a highly interconnected regulatory network characterised by ligand promiscuity and extensive crosstalk. This architecture enables diverse EDCs to engage overlapping signalling circuits and reprogramme transcriptional outputs relevant to metabolism and detoxification. AhR is primarily activated by environmental pollutants such as PAHs and drives CYP-dependent biotransformation and oxidative stress responses.⁹⁹ PXR and CAR function as broad-spectrum xenobiotic sensors that regulate Phase I/II enzymes (e.g. CYP2B, CYP2C, CYP3A, UDP-glucuronosyltransferases, sulfotransferases) and transporters (e.g. multidrug resistance protein 1), while simultaneously influencing lipid, glucose, and BA metabolism.^{97,100–103} Upon heterodimerisation with retinoid X receptor (RXR), PXR and CAR couple detoxification responses to metabolic rewiring. PXR activation induces: i) lipogenesis via the activation of CD36 and stearoyl-CoA desaturase 1 (SCD1); ii) inhibition of β -oxidation via blockade of Forkhead box protein A2 (FOX A2); iii) regulation of glucose metabolism via repression of Forkhead box protein O1 (FOX O1), hepatocyte nuclear factor 4, cAMP response element-binding protein, and PGC1 α ; iv) activation of cholesterol synthesis through SREBP2; and v) its connection with BA metabolism via FXR.^{97,101,103,104} CAR controls BA entry into cells by reducing the expression of the solute carrier organic anion transport protein 1a1 (OATP1A1) and appears to regulate liver TG and circulating low-density lipoprotein levels.¹⁰⁵ PPARs (PPAR α , PPAR β/δ , and PPAR γ), FXR, and LXR link metabolic and xenobiotic signalling by coordinating FA oxidation, lipogenesis, and BA homeostasis.^{84,106} These receptors are highly sensitive to both endogenous metabolites and exogenous ligands, making them key entry points for EDC-induced metabolic perturbation.¹⁰² Through shared co-regulators and RXR-dependent heterodimerisation, these receptors integrate

nutrient and xenobiotic cues into unified transcriptional programmes. RXR acts as a central hub within this network, enabling signal integration across multiple NR pathways (e.g. PXR, CAR, PPAR, and LXR) and amplifying context-dependent transcriptional responses.¹⁰⁷

To integrate these receptor-specific mechanisms across chemical EDC classes, Fig. 2 summarises the current evidence linking major EDC groups with NR activation patterns and stages along the MASLD disease spectrum. While hepatocellular carcinoma is not directly addressed in this review, emerging integrative multi-omics evidence suggests that chronic exposure to EDCs may contribute to hepatocarcinogenesis, although causal relationships remain to be fully established.¹⁰⁸

Why the liver is especially susceptible to EDCs in MASLD

MASLD involves progressive disruption of hepatic metabolic homeostasis, with early steatosis arising from lipid imbalance and IR.¹ With progression, lipotoxicity and immune-metabolic

interactions intensify oxidative stress, mitochondrial dysfunction, and inflammation, promoting fibrogenesis.^{109,110} MASLD is also associated with remodelling of xenobiotic metabolism (including CYP activity) and reduced detoxification capacity.^{89,111,112} These changes increase vulnerability through interconnected mechanisms: impaired mitochondrial function, redox imbalance, increased oxidative burden, altered transporters, and chronic inflammation. Importantly, EDC exposure interacts with the liver's metabolic state, potentially accelerating injury trajectories. This helps explain heightened susceptibility in obesity, metabolic syndrome, alcohol use, and high-fat diets.

Moreover, the liver is uniquely susceptible to EDCs due to its anatomical position and central role in systemic detoxification. EDCs enter the body via oral, inhalational, or dermal routes; compounds absorbed in the gastrointestinal tract reach the liver directly through the portal circulation, whereas those absorbed via inhalational or dermal routes enter the systemic circulation before being cleared by the liver. In MASLD, this susceptibility is further amplified by alterations in

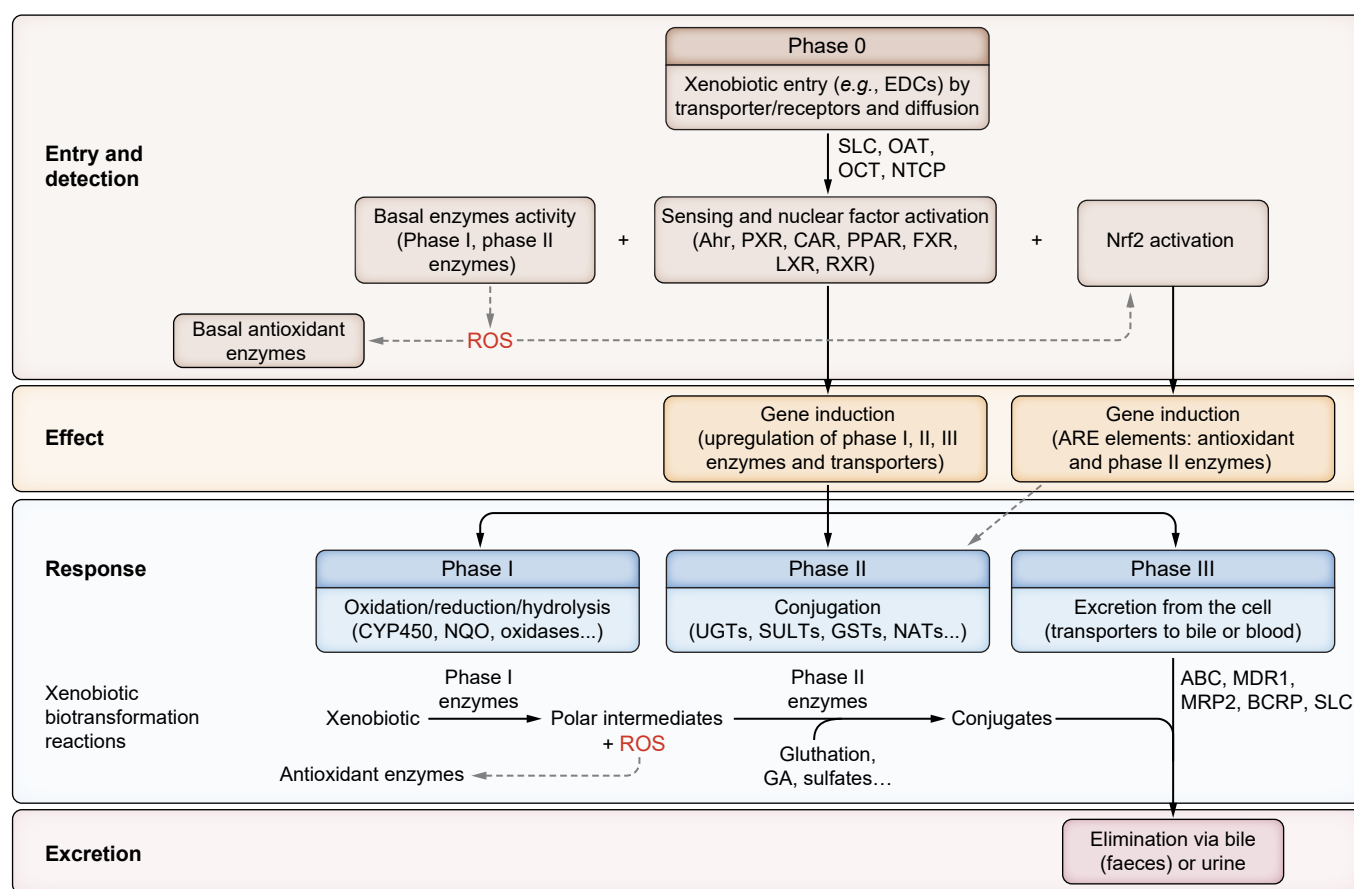


Fig. 1. Xenobiotic metabolism in hepatocytes. Xenobiotics enter hepatocytes via passive diffusion or via uptake transporters (e.g. SLC family). Biotransformation proceeds through Phase I (mainly CYP-mediated oxidation/reduction), generating reactive intermediates and ROS, followed by Phase II conjugation (UGTs, SULTs, GSTs, NATs) to increase solubility. Phase III transporters mediate efflux into bile or blood for elimination. Xenobiotic sensing is coordinated by nuclear receptors (AhR, PXR, CAR, PPAR, FXR, LXR, RXR) and redox-sensitive pathways (e.g. Nrf2), which regulate detoxification enzymes, transporters, and antioxidant responses. ABC, ATP-binding cassette; AhR, aryl hydrocarbon receptor; ARE, antioxidant response elements; BCRP, breast cancer resistance protein; CAR, constitutive androstane receptor; CYP, cytochrome P450; EDCs, endocrine-disrupting chemicals; FXR, farnesoid X receptor; GA, glucuronic acid; GST, glutathione S-transferase; LXR, liver X receptor; MDR1, multidrug resistance protein 1; MRP2, multidrug resistance-associated protein 2; NAT, N-acetyltransferase; Nrf2, nuclear factor erythroid 2-related factor 2; NQO, NAD(P)H quinone oxidoreductase; NTCP, sodium-taurocholate co-transporting polypeptide; OATs, organic anion transporters; OCTs, organic cation transporters; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; SLC, solute carrier; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

the gut–liver axis. Increased intestinal permeability and microbiota dysbiosis facilitate the translocation of luminal compounds and microbial products into the portal blood, thereby increasing hepatic exposure to EDCs and their metabolites.¹¹³ In parallel, emerging evidence suggests that certain EDCs can directly impair intestinal barrier integrity and reshape microbiota composition, thereby reinforcing a feed-forward loop that exacerbates hepatic toxic burden.^{114,115}

Mechanistic pathways: How EDCs rewire hepatic metabolism

Building on this susceptibility framework, EDC exposure engages a limited set of core hepatic control systems that regulate nutrient handling, xenobiotic defence, mitochondrial function, and inflammatory signalling.^{14,116} Here, we synthesise five mechanistic pillars that unify the ways in which EDCs promote metabolic dysfunction and bias the liver toward MASLD progression (Fig. 3).

NR hijacking: The central integrator of EDC action

Hepatic NR hijacking is a primary entry point for EDC-driven metabolic rewiring.¹⁴ Because NRs evolved to sense endogenous ligands and xenobiotics, their ligand promiscuity confers intrinsic vulnerability to EDC-mediated molecular mimicry.

Multiple receptors are engaged, including PPARs, FXR, LXR, CAR, PXR, AhR, and ER α/β .¹⁴ Aberrant activation or inhibition of these receptors disrupts lipid, glucose, and BA homeostasis, driving sex-dependent transcriptional shifts and MASLD-relevant phenotypes.

NR dysregulation is tightly coupled to xenobiotic stress. Many EDCs induce CYP isoforms via AhR-, CAR-, and PXR-dependent pathways, increasing ROS and lipid peroxidation.^{23,70,72} In parallel, competition for Phase II pathways reduces detoxification of endogenous substrates (e.g. bilirubin, BAs, and steroid hormones).^{17,56,71} These pressures are compounded by alterations in Phase III efflux transporters, particularly ABC family members, which can impair BA clearance and promote cholestatic stress.^{56,72} Together, NR hijacking, together with maladaptive detoxification responses, can produce a toxic-metabolic phenotype characterised by oxidative burden, impaired homeostatic clearance, and heightened sensitivity to inflammatory activation and hepatocellular injury.

Lipid metabolic rewiring: A steatogenic signature

Across EDC classes, hepatic lipid metabolism is repeatedly shifted toward a steatogenic phenotype, although gene-level responses vary by compound and context. EDCs frequently upregulate DNL enzymes (e.g. acetyl-CoA carboxylase, FASN,

	AhR	CAR	PXR	FXR	LXR	RXR	PPARs	ER α/β	Nrf2		Steatosis	MASH	Fibrosis
Alkylphenols (NP)	0	0	+	0	0	0	0	+	++	0	+	+	0
PAHs (BaP)	++	0	0	0	0	0	0	+	+	+	+	0	0
Parabens (Bpar/ BuP)	0	0	0	–	0	0	–	0	+	0	+	+	0
Bisphenols (BPS)	0	0	0	0	0	0	0	+	++	0	+	0	0
DDT/DDE	0	++	+	0	0	0	0	0	++	0	+	+	0
Phthalates (DEHP/MEHP)	0	++	+	0	+	+	0	+	+	0	+	0	0
Alternatives phthalates (DINCH/ MINCH)	0	0	0	0	0	0	0	–	0	0	0	+	0
Pyrethroids (PER)	0	0	0	0	0	0	0	0	0	0	+	+	+
PFAS (PFOA/PFOS/ PFBS/PFNA/GenX)	0	+	0	+	+	+	+	~	0	~	+	+	0
OPEs (TPP)	0	0	0	0	+	+	0	+	++	0	+	+	0
										++	Strong evidence		
										+	Moderate evidence/context-dependent		
										0	No clear evidence		
										–	Inhibitory		
										~	Mixed/bidirectional		

Fig. 2. Integrative matrix of EDC classes, receptor pathways, and MASLD-related phenotypes. The matrix summarises current evidence linking major EDC classes with activation or modulation of nuclear receptors (AhR, PXR, CAR, PPAR α , PPAR γ , FXR, LXR, RXR, ER) and the redox-sensitive transcription factor Nrf2, alongside key MASLD phenotypes (including the representing stages along the disease spectrum: steatosis, MASH, fibrosis). Evidence strength is indicated as follows: ++ strong; + moderate or context-dependent; 0 no clear evidence; – inhibitory; ~ mixed or bidirectional. Importantly, the lack of clear evidence for specific phenotypes does not imply a lack of effect, but instead reflects limited or insufficient data for those outcomes. Moreover, MASLD-related phenotypes should be interpreted as part of a dynamic continuum, in which steatosis often represents an early event that may progress to MASH and fibrosis under additional metabolic or environmental stressors. Nrf2 is included as a functionally relevant regulator of oxidative stress responses intersecting with metabolic and nuclear receptor signalling. The matrix provides a simplified, integrative overview and does not capture all context-specific or tissue-dependent effects. AhR, aryl hydrocarbon receptor; BaP, benzo[a]pyrene; Bpar/BuP, butylparabene; BPS, bisphenol S; CAR, constitutive androstane receptor; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, bis(2-ethylhexyl) phthalate; DINCH, diisononyl cyclohexane-1,2-dicarboxylate; ER, oestrogen receptor; FXR, farnesoid X receptor; GenX, hexafluoropropylene oxide dimer acid; LXR, liver X receptor; MASH, MASH, metabolic-associated steatohepatitis; MEHP, mono-2-ethylhexyl phthalate; NP, nonylphenol; Nrf2, nuclear factor erythroid 2 related factor 2; OPEs, organophosphate esters; PAHs, polycyclic aromatic hydrocarbons; PER, permethrin; PFAS, per- and polyfluoroalkyl substances; PFBS, perfluorobutane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PPARs, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; RXR, retinoid X receptor; TPP, triphenyl phosphate.

and SCD1), increasing endogenous FA synthesis.^{22,27,31,49,50} Several also enhance FA uptake via transporters such as CD36 and FA transport protein, exceeding oxidative capacity.²⁴ This imbalance is further exacerbated by impaired mitochondrial and peroxisomal β -oxidation through modulation of PPAR α , CPT1A, PGC1 α , and acyl-CoA oxidase 1,^{22,31,73} reducing metabolic flexibility. Importantly, emerging evidence suggests that EDCs may also impair very low-density lipoprotein assembly and secretion by downregulating MTP (microsomal triglyceride transfer protein), a critical pathway involved in hepatic lipid export.¹¹⁷ Together, these alterations converge on the fundamental processes that govern lipid handling: FA uptake, oxidation, TG synthesis, and export, collectively favouring lipid retention, TG accumulation, and steatosis.^{78,83,118,119} Functionally, disruption at these nodes drives lipid droplet expansion, insulin resistance, and hepatocellular stress, supporting a central role for EDCs in MASLD progression.

Mitochondrial dysfunction and redox stress

Mitochondrial dysfunction is a central feature of EDC-associated hepatotoxicity.¹¹⁶ EDCs alter regulators of mitochondrial biogenesis and antioxidant defence (PGC1 α , Nrf2, SOD, CAT), increasing ROS and oxidative injury.^{17,42,73} In parallel, several pro-apoptotic genes, such as p53-upregulated modulator of apoptosis (PUMA), apoptotic protease-activating factor 1 (APAF-1), and caspase-3, are upregulated, facilitating mitochondrial outer membrane permeabilization, apoptosome formation, and executioner caspase activation.⁴² The concomitant downregulation of antiapoptotic proteins B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xL) further destabilises mitochondrial integrity, lowering the threshold for cytochrome c release and the initiation of apoptosis.⁴² EDCs have also been linked to enhanced mitochondrial fission through the overexpression of dynamin-related protein 1, a shift that impairs bioenergetics and enhances vulnerability in hepatocytes.³⁰ As previously noted, excessive induction of CYP450 isoforms and Phase II detoxification enzymes can inadvertently exacerbate mitochondrial dysfunction by increasing ROS production, further reducing mitochondrial resilience in the presence of EDCs. Together, these changes induce mitochondrial fragility, amplifying hepatocellular injury in MASLD.

Immunometabolic activation and fibrogenic pathways

EDCs induce sustained immunometabolic activation, a key driver of MASLD progression.^{109,110} Activation of NF- κ B signalling increases pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , thereby amplifying inflammatory loops.⁴² In parallel, EDCs enhance antigen-presenting capacity by upregulating major histocompatibility complex class I and II molecules, promoting immune recognition and crosstalk with infiltrating immune cells.⁴⁹ Interferon-responsive genes, including interferon gamma-inducible protein 47, are also induced, contributing to an antiviral-like inflammatory state that further perturbs hepatocellular homeostasis.⁵⁶ Immune perturbation may be further shaped indirectly through EDC-driven remodelling of NR signalling. NR dysregulation further contributes to immune imbalance by altering regulatory T-cell/T helper 17 cell polarisation, dendritic cell maturation, and B-cell function in experimental systems¹²⁰. Additionally, reduced

expression of JAK2 and several C-X-C motif chemokine ligands have been reported, indicating suppression of key signalling pathways involved in cytokine signal transduction and immune cell recruitment, ultimately limiting the liver's capacity to coordinate effective tissue repair processes.²⁴ Collectively, these effects promote inflammation, fibrogenesis, and disease progression.

Endocrine mimicry: Hormonal perturbations with metabolic consequences

Many EDCs exert endocrine-mimetic or antagonistic effects, disrupting hormonal regulation of metabolism. Oestrogenic EDCs (e.g. bisphenols, parabens, OCPs) alter ER signalling, impairing FA oxidation and mitochondrial function.^{16,17} Others (e.g. DDT/DDE) act as androgen antagonists, interfering with steroid receptor signalling that influences lipid partitioning, glucose homeostasis, and hepatocellular growth pathways.⁵³ However, among the transcriptomic studies summarised in Table 2, clear evidence of thyroid receptor activation or canonical thyroid receptor target gene induction is not consistently reported. Given that many EDCs interfere with thyroid hormone signalling or interact with components of thyroid hormone regulatory pathways, thyroid-like EDCs may influence glucose and FA metabolism, initially modulating sirtuins and NR, and subsequently affecting specific target genes. These endocrine disturbances collectively lead to reduced hepatic β -oxidation, impaired adaptive thermogenesis, and altered insulin sensitivity.^{121,122} Recently, the mechanisms by which specific EDCs interfere with the activities of glucocorticoid receptors (GR) and mineralocorticoid receptors have been identified. DDT/DDE have been shown to exhibit GR-antagonistic effects and to attenuate the expression of glucocorticoid-responsive genes. In contrast, BPA may activate GR signalling, thereby mimicking the action of endogenous glucocorticoids.¹²³ Chronic activation of GR signalling has been associated with impaired glucose homeostasis, enhanced adipogenesis, and hepatic steatosis.¹²⁴ These hormonal perturbations contribute to sustained metabolic rewiring and increased susceptibility to MASLD.

Vulnerable populations and critical windows of exposure

The health impact of EDCs is not uniformly distributed across populations.⁶⁰ Exposure is often higher in socioeconomically disadvantaged groups due to environmental, occupational, and healthcare inequalities.¹²⁵ Susceptibility varies across the lifespan, with critical windows reflecting developmental, hormonal, and metabolic transitions. Individuals at the foetal and early postnatal stages are particularly vulnerable because of immature detoxification systems and high endocrine and epigenetic plasticity, while puberty represents an additional sensitivity window driven by hormonal remodelling.¹²⁶ In adulthood, pre-existing metabolic states (e.g. obesity, IR, and MASLD itself) may amplify the impact of EDC exposure by increasing inflammatory tone, mitochondrial stress, and baseline metabolic fragility. Intergenerational and transgenerational effects further extend EDC impact, as these compounds can disrupt reproductive function and induce epigenetic changes that alter metabolic programming

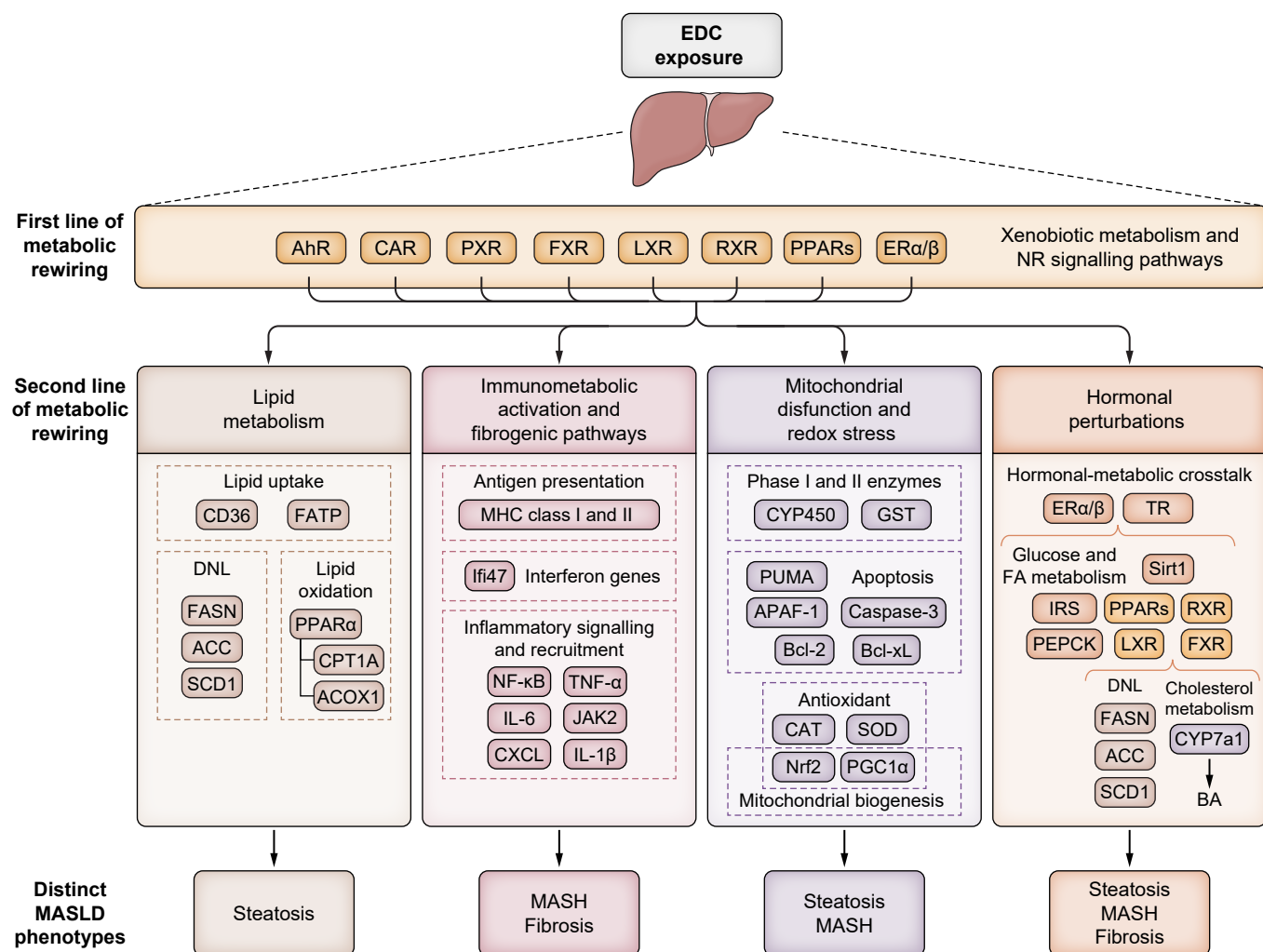


Fig. 3. Key hepatic control nodes targeted by EDC exposure. Schematic summary of the principal metabolic and signalling pathways through which endocrine-disrupting chemicals (EDCs) perturb liver physiology. Following exposure, EDCs engage xenobiotic metabolism and nuclear receptor (NR) signalling as proximal sensing layers, which subsequently propagate to downstream control modules regulating lipid and glucose metabolism, hormonal homeostasis, mitochondrial function and redox balance, and immunometabolic and pro-fibrogenic pathways. The combined disruption of these interconnected nodes rewires hepatic function and increases susceptibility to metabolic dysfunction, contributing to MASLD phenotypes ranging from steatosis and steatohepatitis (MASH) to fibrosis. Representative mediators are shown within each module. Colours denote functional categories, and overlap between modules highlights pathway cross-talk. ACOX1, acyl-CoA oxidase 1; ACC, acetyl-CoA carboxylase; AhR, aryl hydrocarbon receptor; APAF-1, apoptotic protease activating factor 1; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra-large; CAR, constitutive androstane receptor; CAT, catalase; Caspase-3, cysteine-aspartic protease 3; CD36, cluster of differentiation 36; CPT1A, carnitine palmitoyltransferase 1A; CXCL, C-X-C motif chemokine ligand; CYP450, cytochrome P450; CYP7A1, cholesterol 7 α -hydroxylase; ER α / β , oestrogen receptor alpha/beta; FASN, fatty acid synthase; FATP, fatty acid transport protein; FXR, farnesoid X receptor; GST, glutathione-S-transferase; Ifi47, interferon-inducible protein 47; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; IRS, insulin receptor substrate; JAK2, Janus kinase 2; LXR, liver X receptor; MHC class I and II, major histocompatibility complex class I and II; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; PEPCCK, phosphoenolpyruvate carboxykinase; PGC1 α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR α , peroxisome proliferator-activated receptor alpha; PPARs, peroxisome proliferator-activated receptors; PUMA, p53-upregulated modulator of apoptosis; PXR, pregnane X receptor; RXR, retinoid X receptor; SCD1, stearoyl-CoA desaturase 1; Sirt1, sirtuin 1; SOD, superoxide dismutase; TNF- α , tumor necrosis factor alpha; TR, thyroid hormone receptor.

in offspring.^{127–129} During pregnancy, maternal exposure leads to direct foetal transfer of EDCs, contributing to early-life metabolic disruption.¹³⁰ Consistently, prenatal exposure to PFAS and bisphenols has been associated with altered neonatal metabolomic and lipid profiles, immune dysregulation, and early-life growth alterations, supporting a role for developmental metabolic programming.^{131–133} Finally, sex differences add further variability, with females often showing greater sensitivity to oestrogenic EDCs, particularly in lipid and BA metabolism and mitochondrial responses.^{129,134}

To contextualise these vulnerability patterns in human populations, Table 3 integrates current epidemiological evidence linking major EDC classes to MASLD-related outcomes, alongside their mechanistic basis and regulatory status.^{135–138} Most studies rely on the measurement of EDCs in biological samples, while only a subset examines associations with inflammatory parameters or metabolic outcomes (e.g. obesity, type 2 diabetes mellitus).^{136,137} Direct epidemiological evidence linking EDC exposure to clinically defined MASLD remains limited and virtually absent. Furthermore, the existing

literature has predominantly focused on a limited set of compounds, such as PFAS, phthalates, and bisphenols, whereas a much broader spectrum of EDCs warrants systematic investigation. From a translational perspective, integrating epidemiological and regulatory data enables identification of compounds for which preventive action may be warranted. Within the European Union, regulation under the REACH framework has, in some cases, preceded full mechanistic understanding, reflecting application of the precautionary principle.¹³⁵ While direct links between regulatory actions and reduced MASLD incidence remain limited, reductions in exposure levels following restrictions suggest potential long-term health benefits.

Emerging tools to decode the hepato-exposome axis

Advances in omics and computational toxicology provide unprecedented opportunities to map EDC–liver interactions with greater resolution and human relevance. Exposomics comprises the analytical platforms and computational approaches used to measure and interpret the exposome.¹³⁹ Beyond exposure detection, emerging platforms now enable functional mapping of chemical–metabolic interactions in MASLD-relevant contexts. Rather than merely cataloguing environmental chemicals, recent studies have begun integrating untargeted exposure profiling with hepatic transcriptomic and lipidomic signatures, revealing coordinated perturbations in NR signalling, mitochondrial function, and lipid flux. Untargeted metabolomics, including mass spectrometry-based approaches, can capture internal biochemical signatures of exposure and effect, including EDC-associated metabolic fingerprints.¹⁴⁰ Integrating these datasets with exposome-informed statistical methods such as exposome-wide association studies or multivariate modelling allows researchers to analyse both individual chemicals and mixtures, providing insights into how EDCs influence hepatic metabolism and enabling the identification of molecular signatures and early biomarkers predictive of MASLD.¹³⁹

Complementary transcriptomic, epigenomic, and single-cell approaches enable cell type-specific resolution of EDC responses, identify NR-driven transcriptional networks, and detect developmental programming signatures that bulk analyses may miss.^{128,141} Applying these methods within well-phenotyped MASLD cohorts, while accounting for disease stage and sex, may reveal exposure–disease interactions that remain masked in metabolically healthy populations.

Adverse outcome pathways provide a structured framework linking molecular initiating events to downstream hepatic outcomes. Integration of adverse outcome pathways with public toxicology databases (e.g. Tox21, ToxCast) and computational tools such as genome-scale metabolic models and flux balance analysis allows for mapping of molecular perturbations onto higher-order phenotypes and identification of network vulnerabilities.^{142,143}

Rodent models remain essential for evaluating long-term metabolic and hepatic outcomes, including chronic exposure and diet-induced conditions.¹⁴⁴ Alternative vertebrate systems, such as zebrafish, offer complementary advantages for high-throughput screening and developmental exposure studies.¹⁴⁵ However, their translational relevance is limited by

species-specific differences in xenobiotic metabolism, NR activation, and lipid handling, which may not fully recapitulate human MASLD.

In this context, new approach methodologies, including 3D hepatic cultures, co-culture systems, organoids, and micro-physiological “organ-on-chip” platforms, offer improved mechanistic control and potential gains in human relevance while reducing reliance on animal testing.^{146,147} Compared with animal models, new approach methodologies offer advantages in experimental control, scalability, and throughput, enabling higher replication, systematic testing of mixtures and dose ranges, and reduced inter-individual variability, while also facilitating human-specific mechanistic insights. However, unlike *in vivo* models, they do not fully recapitulate systemic physiology, including inter-organ communication, endocrine signalling, immune interactions, and whole-body toxicokinetics, which are critical determinants of EDC distribution and long-term metabolic outcomes.

Together, these integrated platforms provide a complementary framework linking mechanistic insight to human translation, supporting biomarker discovery and improved risk assessment in MASLD.

Outstanding questions and future directions

Despite growing progress in defining EDC–liver interactions, several key questions remain unresolved.¹⁴⁸ Establishing the acute vs. chronic impacts of EDC exposure on liver metabolism and MASLD is challenging, in part because real-world exposures involve complex chemical mixtures, low doses, and variable timing across the life course. It remains unclear how low-dose EDC mixtures interact with baseline metabolic state, which combinations of NRs and co-regulatory circuits drive transitions from adaptive responses to pathology, and which biomarkers best capture early EDC-induced rewiring before clinical disease is established.

A major priority is to move beyond association toward causal, longitudinal validation – linking EDC exposures to molecular signatures and, in turn, to specific MASLD phenotypes (steatosis, steatohepatitis, fibrosis) with temporal resolution. This will require better-designed chronic exposure studies, especially mammalian paradigms combined with high-caloric or obesogenic diets, to model cumulative burden and progressive injury. Additional gaps include understanding how sex hormones and chromatin architecture shape differential susceptibility, whether exposome signatures can stratify MASLD subtypes, and how exposomics data can be translated into clinically actionable tools in hepatology practice. An additional emerging question is whether chronic exposure to EDCs may influence therapeutic responses in MASLD. Given that several NRs targeted by EDCs (e.g. PPAR, FXR) are also pharmacological targets,^{149,150} environmental exposures can act as background modulators of receptor signalling, potentially affecting drug efficacy or treatment response variability. However, direct clinical evidence supporting such interactions is currently lacking, highlighting an important area for future investigation. Addressing these challenges will require cross-disciplinary collaboration spanning environmental health, metabolism, hepatology, and computational biology, with shared standards for exposure measurement, mixture modelling, and mechanistic anchoring of omics readouts.

Table 3. Integrated evidence, clinical relevance, and regulatory status of major EDCs associated with MASLD.

EDC	<i>In vitro</i> or <i>In vivo</i> evidence ^a	Human evidence ^b	Clinical relevance ^c	Overall evidence in MASLD ^d	EU regulation (CAS number; ECHA/REACH decision reference)* ¹³⁵	EU priority
NP	Strong	Limited	Limited	Low–moderate	Candidate list of SVHC (104-40-5; ED/71/2019)	Very high
BaP	Strong (AhR activation)	Moderate	T2DM, obesity, CVD, hypertension ¹³⁷	Moderate	Candidate list of SVHC (50-32-8; ED/21/2016)	Very high
Bpar/BuP	Moderate	Moderate	Alteration in inflammation biomarkers ¹³⁶	Moderate	Candidate list of SVHC (94-26-8; D(2020)4578-DC)	Very high
BPS	Moderate	Moderate (emerging epidemiology)	Alteration in inflammation biomarkers, increased adiposity ^{136,138}	Moderate	Candidate list of SVHC (80-09-1; D(2022)9120-DC) and European positive list	Very high
DDT	Strong	Moderate	Increased adiposity, T2DM ¹³⁸	Moderate	POP regulation (50-29-3; 2019/1021)	High
DEHP/MEHP	Moderate	Moderate	Obesity ^{130,137}	Moderate	DEHP: Candidate list of SVHC (117-81-7; ED767/2008) and European positive list. MEHP: Registered (1276197-22-8).	Very high
DINCH/MINCH	Limited	Limited	Limited	Low	DINCH: Registered not regulated (166412-78-8; -). MINCH: not registered, primary degradation metabolite from DINCH.	Emerging
PER	Limited	Limited	Limited	Low	Registered, regulation ongoing (52645-53-1; -)	Medium
PFAS						
PFBS	Strong	Limited	Limited	Low–moderate	Candidate list of SVHC (-; ECHA/01/2020)	Very high
PFNA		Moderate–strong	T2DM, altered liver parameters (AST, ALT, GGT, CK-18, lipid and BA profiles), positive or negative correlations with MASLD stages, and increased adiposity ^{66,132,137,138}	Strong	Restricted under EU chemicals legislation (375-95-1; 32021R1297)	High
PFOA		Moderate–strong			POP regulation (335-67-1; 32022R2400)	High
PFOS		Moderate–strong			POP regulation (1763-23-1; 32025R0718)	High
GenX	Limited	Limited	Limited	Low	Candidate list of SVHC (13252-13-6; ED/71/2019) and European positive list	Emerging
TPP	Moderate	Limited	Limited	Low–moderate	Candidate list of SVHC (115-86-6; D(2024)6225-DC)	Very high

^aLimited/moderate/strong refers to both the number of available *in vitro/in vivo* studies linking each EDC to MASLD and the consistency/relevance of the reported effects. This assessment was primarily based on the evidence summarised in Table 2 and Fig. 2.

^bLimited/moderate/strong in the human evidence column reflects the amount of available epidemiological or clinical studies investigating associations between each EDC and metabolic or liver-related outcomes in humans.

^cClinical relevance includes reported associations with metabolic disease-related factors, as direct links with MASLD were not always available in the literature. Limited indicates that no specific studies assessing the clinical relevance of that EDC in relation to MASLD were identified.

^dOverall evidence in MASLD was determined by integrating the previous categories. Low/Moderate/Strong reflects the overall level of evidence supporting the involvement of each EDC in MASLD.

*In reference to European Union (EU) regulation based on European Chemical Agency (ECHA) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), there are different categories. The Candidate List comprises substances of very high concern (SVHCs), whose effects are still under investigation. Some of these substances also appear on the European positive list, which includes compounds that may be present in drinking water. We also find compounds regulated under the POP Regulation or the Restriction Regulation. These substances are prohibited or highly restricted in use. However, their priority remains high because they can still be found in drinking water or in contaminated areas with potential human exposure. Finally, there are registered substances that are not subject to specific regulatory restrictions. Compared to the other groups, they are considered medium priority; however, this does not imply that they are less harmful than the others. For ease of identification on the ECHA website, we have included the CAS number of each compound, as well as the reference document code under which it was published. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BaP, benzo[a]pyrene; Bpar/BuP, butylparaben; BPS, bisphenol S; CK-18, cytokeratin 18; CVD, cardiovascular disease; DDT, dichlorodiphenyltrichloroethane; DEHP/MEHP, bis(2-ethylhexyl) phthalate and mono-2-ethylhexyl phthalate respectively; DINCH/MINCH, diisononyl cyclohexane-1,2-dicarboxylate and mono-iso-nonyl cyclohexane-1,2-dicarboxylate respectively; EDC, endocrine-disrupting chemical; GenX, hexafluoropropylene oxide dimer acid; GGT, gamma-glutamyl transferase; MASLD, metabolic dysfunction-associated steatotic liver disease; NP, nonylphenol; PER, permethrin; PFBS, perfluorobutane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; POP, persistent organic pollutant; SVHC, substance of very high concern; T2DM, type 2 diabetes mellitus; TPP, triphenyl phosphate.

Conclusions

MASLD arises from the intersection of genetic susceptibility, lifestyle, metabolic stress and increasingly the chemical exposome. Mechanistic evidence supports the view that EDCs can rewire hepatic networks by engaging nuclear and

hormonal receptors, perturbing detoxification systems, altering lipid and carbohydrate flux, disrupting mitochondrial and redox homeostasis, and activating immunometabolic pathways that favour progression along the MASLD spectrum. Embedding the hepato-exposome axis into metabolic disease research will be essential for identifying at-risk populations,

developing early biomarkers, and informing prevention strategies and public health interventions that reduce environmental contributions to liver disease. As MASLD prevalence

continues to rise globally, clarifying and ultimately mitigating the role of environmental chemicals should be treated as a priority for both mechanistic science and population health.

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Abbreviations

AhR, aryl hydrocarbon receptor; Bpar/BuP, butylparabene; BPA, bisphenol A; BPS, bisphenol S; CAR, constitutive androstane receptor; CYP, cytochrome P450; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DINCH, diisononyl cyclohexane-1,2-dicarboxylate; DNL, *de novo* lipogenesis; EDC, endocrine-disrupting compound; ER, oestrogen receptor; FA, fatty acid; FXR, farnesoid X receptor; IR, insulin resistance; LXR, liver X receptor; MASLD, metabolic-associated steatotic liver disease; MINCH, mono-iso-nonyl cyclohexane-1,2-dicarboxylate; NP, nonylphenol; NR, nuclear receptor; OCPs, organochlorine pesticides; OPEs, organophosphate esters; PAHs, polycyclic aromatic hydrocarbons; PER, permethrin; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; POP, persistent organic pollutants; PPARs, peroxisome proliferator-activated receptors; PXR, pregnane X receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; TG, triglycerides; TPP, triphenyl phosphate.

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Conflict of interest

The authors declare no conflicts of interest pertaining to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed to the writing and critical revision of the manuscript.

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Supplementary data

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Author names in bold designate shared co-first authors

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