



Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease

J. Massart, K. Begriche, A. Corlu, B. Fromenty

► To cite this version:

J. Massart, K. Begriche, A. Corlu, B. Fromenty. Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease. International Journal of Molecular Sciences, 2022, 23 (3), pp.1062. 10.3390/ijms23031062 . hal-03557349

HAL Id: hal-03557349

<https://hal.science/hal-03557349>

Submitted on 4 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Review

Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease

Julie Massart , Karima Begriche, Anne Corlu  and Bernard Fromenty

Institut NUMECAN (Nutrition Metabolisms and Cancer), UMR_A 1341, UMR_S 1241, INSERM, University Rennes, INRAE, F-35000 Rennes, France; karima.begriche@univ-rennes1.fr (K.B.); anne.corlu@inserm.fr (A.C.); bernard.fromenty@inserm.fr (B.F.)

* Correspondence: julie.massart@inserm.fr

Abstract: Metabolic-associated fatty liver disease (MAFLD), which is often linked to obesity, encompasses a large spectrum of hepatic lesions, including simple fatty liver, steatohepatitis, cirrhosis and hepatocellular carcinoma. Besides nutritional and genetic factors, different xenobiotics such as pharmaceuticals and environmental toxicants are suspected to aggravate MAFLD in obese individuals. More specifically, pre-existing fatty liver or steatohepatitis may worsen, or fatty liver may progress faster to steatohepatitis in treated patients, or exposed individuals. The mechanisms whereby xenobiotics can aggravate MAFLD are still poorly understood and are currently under deep investigations. Nevertheless, previous studies pointed to the role of different metabolic pathways and cellular events such as activation of de novo lipogenesis and mitochondrial dysfunction, mostly associated with reactive oxygen species overproduction. This review presents the available data gathered with some prototypic compounds with a focus on corticosteroids and rosiglitazone for pharmaceuticals as well as bisphenol A and perfluorooctanoic acid for endocrine disruptors. Although not typically considered as a xenobiotic, ethanol is also discussed because its abuse has dire consequences on obese liver.



Citation: Massart, J.; Begriche, K.; Corlu, A.; Fromenty, B. Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 1062. <https://doi.org/10.3390/ijms23031062>

Academic Editor: Cristiano Fava

Received: 14 December 2021

Accepted: 15 January 2022

Published: 19 January 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: obesity; fatty liver; NASH; drugs; environmental contaminants; endocrine disruptors; ethanol

1. Introduction

Obesity and associated diseases meet epidemic proportions in numerous countries. In particular, the hepatic tissue can rapidly suffer from the accumulation of lipids, thus leading to fatty liver and other liver lesions. The whole spectrum of hepatic lesions linked to obesity is called metabolic (dysfunction)-associated fatty liver disease (MAFLD), which is now preferred to non-alcoholic fatty liver disease (NAFLD) [1]. Obesity is associated with insulin resistance and type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia and osteoarthritic disorders. All these conditions may need the prescription of different types of pharmaceuticals, such as antidiabetic and antihypertensive drugs, lipid-lowering agents or non-steroidal anti-inflammatory drugs. Hence, obese individuals are more likely to have long-term polypharmacy [2,3]. In addition, obese people, as lean ones, can be exposed, voluntarily or accidentally, to many other xenobiotics, such as recreational drugs, plant and mushroom toxins, or industrial chemicals.

An increasing number of investigations of obese individuals and rodent models indicate or strongly suggest that some xenobiotics can further increase hepatic lipid levels (Figure 1), or accelerate the transition from fatty liver to steatohepatitis or cirrhosis (Figure 2). Unfortunately, the mechanisms of these deleterious effects are not well understood, in particular because many investigations are only observational. Nonetheless, some experimental studies allow different hypotheses to be proposed in order to explain the exacerbation of fatty liver, or the faster occurrence of steatohepatitis. In this review, we first recall the main features of MAFLD regarding its physiopathology. Next, we review

some xenobiotics which can worsen MAFLD, including pharmaceuticals and industrial chemicals. Finally, we discuss ethanol, although this molecule is not typically considered as a xenobiotic. Indeed, there is now ample evidence that ethanol abuse has dire consequences on the obese liver.

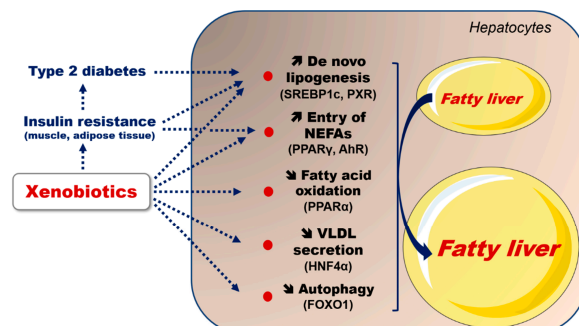


Figure 1. Mechanisms whereby xenobiotics can aggravate obesity-related fatty liver. Xenobiotics can exacerbate pre-existent lipid accumulation in hepatocytes by direct mechanisms such as stimulation of de novo lipogenesis (DNL), increased non-esterified fatty acid (NEFA) uptake, reduction in fatty acid oxidation and impairment of very low-density lipoprotein (VLDL) secretion. Stimulation of DNL results from the activation of different lipogenic nuclear receptors such as PPAR γ and PXR. Alternatively, increased DNL is secondary to insulin resistance, for instance, at the level of skeletal muscle and adipose tissue. Insulin resistance leads to hyperinsulinemia, which activates SREBP1c in hepatocytes. Insulin resistance in white adipose tissue also favors triacylglycerol lipolysis, thus leading to the unrestrained release in blood of NEFAs freely entering the liver via FAT/CD36 or other fatty acid transporters. If insulin resistance progresses to type 2 diabetes, hyperglycemia increases hepatic DNL via the activation of ChREBP. Reduced fatty acid oxidation can be attributed to different mechanisms, including reduced PPAR α activity, or direct impairment of mitochondrial enzymes. Reduced VLDL secretion can be secondary to endoplasmic reticulum stress. Finally, impairment of autophagy favors lipid accumulation by reducing the clearance of excessive lipid droplets. Some connection arrows are not mentioned for the sake of clarity. Further information is provided in the text.

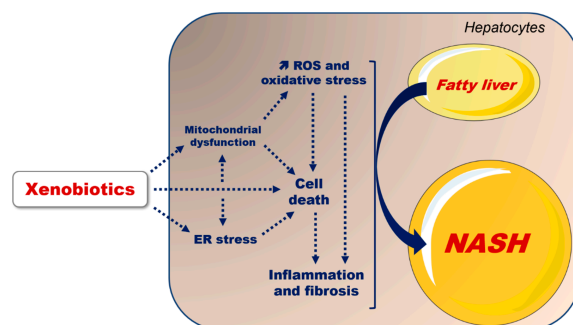


Figure 2. Mechanisms whereby xenobiotics can favor the progression of obesity-related fatty liver to NASH, characterized by necroinflammation, hepatocyte ballooning, apoptosis and fibrosis, in addition to steatosis. Mitochondrial dysfunction, in particular at the level of the respiratory chain, leads to reactive oxygen species (ROS) overproduction, which, in turn, induces oxidative stress. Mitochondrial dysfunction, ROS overproduction and oxidative stress trigger cell death by necrosis or apoptosis. Cell death can also be induced by different cytokines such as TNF- α and Fas ligand. ROS overproduction and hepatocyte cell death favor inflammation and fibrosis through the activation of Kupffer cells and stellate cells, respectively. Finally, endoplasmic reticulum (ER) stress can also lead to cell death and oxidative stress (not shown). Note that there is an interplay between mitochondrial dysfunction and ER stress. Some connection arrows are not mentioned for the sake of clarity. Further information is provided in the text.

2. Main Features of MAFLD

2.1. Clinical Features, Liver Pathology and Blood Chemistry

While the classical term NAFLD refers to fatty liver disease in absence of excessive alcohol consumption, which is quite restrictive, MAFLD more appropriately places this disease in the broader context of metabolic dysfunction [1]. In fact, hepatologists wished to follow the example of other medical specialties such as cardiology, diabetology and oncology, which have successfully distanced the disease from underlying obesity, smoking, alcohol overconsumption and drug abuse [1]. The whole spectrum of hepatic lesions in MAFLD is the same as NAFLD and includes fatty liver (also referred to as hepatic steatosis), steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma [4]. Most obese individuals present simple fatty liver but this lesion can progress, in the long term, to NASH in 10–20% of subjects. In obesity-associated fatty liver, lipids accumulate mainly as macrovacuolar steatosis, but microvesicular steatosis is also observed and seems to be linked to more severe forms of MAFLD [5], possibly due to severe impairment of mitochondrial fatty acid oxidation (FAO) [6,7]. NASH is characterized by necroinflammation, hepatocyte ballooning and some degree of fibrosis, in addition to steatosis. Apoptotic hepatocytes, megamitochondria, Mallory-Denk bodies and iron accumulation can also be observed [5,8]. At these stages of the disease, patients are often asymptomatic but some of them present non-specific symptoms, such as fatigue, right upper quadrant discomfort and hepatomegaly [9]. NASH can then progress, in some individuals, to advanced cirrhosis, which is associated with bridging fibrosis and nodularity as well as canalicular cholestasis [5]. When cirrhosis occurs, ascites can cause abdominal distention, nausea and vomiting, dyspnea and lower-extremity edema. Late complications of cirrhosis include variceal hemorrhages, hepatic encephalopathy, spontaneous bacterial peritonitis and sepsis. Accordingly, the mortality of patients with decompensated cirrhosis is high.

Blood chemistry in MAFLD can include mild elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, thus reflecting the presence of slight hepatic cytolysis, but a significant number of patients can have normal aminotransferase levels [10,11]. When the disease progresses to cirrhosis, hyperbilirubinemia, hyperammone-mia, hypoalbuminemia and abnormal prothrombin time can be observed [9,10].

2.2. Physiopathology of MAFLD

The physiopathology of MAFLD is complex and is still poorly understood. Here, we briefly review the main features of MAFLD pathogenesis, although several recent reviews are available for more details on this subject [8,12–17].

Insulin resistance in white adipose tissue (WAT) and skeletal muscle plays a major role in the pathogenesis of obesity-related fatty liver [12,14,15,17,18]. Insulin resistance in WAT favors triacylglycerol lipolysis, thus leading to a massive release, into the circulation, of glycerol and non-esterified fatty acids (NEFAs), which enter the liver in a concentration-dependent manner via transporters such as the fatty acid translocase (FAT/CD36) and different fatty acid transport proteins (FATPs). Furthermore, fatty acids are synthesized actively in the liver because insulin resistance-associated hyperinsulinemia favors *de novo* lipogenesis (DNL; i.e., the synthesis of fatty acids from carbohydrates) via the activation of sterol regulatory element-binding protein 1c (SREBP1c). Insulin resistance in skeletal muscle impairs glucose uptake and glycogen synthesis, thus favoring glucose utilization for hepatic DNL. In addition, hepatic DNL can be activated by carbohydrate response element binding protein (ChREBP) when hyperglycemia occurs [13,19]. Finally, whereas mitochondrial FAO is not reduced in the early stage of MAFLD, impaired autophagy can favor lipid droplets accumulation [16,20]. Indeed, a defect in autophagy reduces the clearance of lipid droplets, further promoting steatosis development [20].

The pathogenesis of fatty liver progression to NASH seems to involve multiple hits and targets as extensively discussed in previous reviews [8,12,14,15,17,21–23] (Figure 2). Briefly, evidence points to a major role of mitochondrial dysfunction, overproduction of reactive oxygen species (ROS), reduced ROS detoxification and endoplasmic reticulum

(ER) stress. Of note, ER stress seems to also play an important role in hepatic lipid accumulation via different mechanisms, including impairment of very low-density lipoprotein (VLDL) secretion [21,24]. ROS overproduction during MAFLD might mainly occur within mitochondria, in particular at the level of different complexes of the mitochondrial respiratory chain (MRC) and some enzymes of the FAO pathway [23,25]. However, another source of ROS in MAFLD seems to be cytochrome P450 2E1 (CYP2E1), as discussed below. Other important factors involved in MAFLD progression include increased production of pro-inflammatory and profibrogenic cytokines by parenchymal and non-parenchymal liver cells. Lastly, besides the exposure to different xenobiotics as discussed in this review, genetic polymorphisms in different genes (e.g., *PNPLA3* and *TM6SF2*) could be involved in fatty liver progression to NASH in a subset of obese subjects.

Metabolic “flexibility” or “adaptation” is an important feature of MAFLD, at least in the early stages of the disease. For instance, higher hepatic secretion of VLDL is observed in patients with obesity-related fatty liver [13,23,26]. Increased mitochondrial FAO and tricarboxylic acid cycle activity also occurs in simple fatty liver [15,23,27]. However, these metabolic adaptations are still not sufficient to avoid hepatic lipid accumulation. Furthermore, mitochondrial flexibility appears to play a major role in oxidative stress and inflammatory processes [23,27]. Notably, mitochondrial adaptations are apparently lost during NASH, which might further favor ROS overproduction [23,28]. The occurrence of mitochondrial “inflexibility” could involve a progressive reduction in MRC activity and a loss of peroxisome proliferator-activated receptor alpha (PPAR α) expression and activity [23,28,29].

2.3. MAFLD and Changes in Xenobiotic Metabolism

Another metabolic feature of MAFLD and obesity is the altered hepatic expression and activity of numerous xenobiotic metabolizing enzymes (XMEs), extensively discussed in several previous reviews [30–34]. XME activity is also altered in the intestine and kidneys of obese individuals, further impacting drug pharmacokinetics [33]. In addition to metabolism, the alteration in drug absorption, distribution and elimination is observed in obesity due to altered gastric emptying and gut permeability, higher cardiac output and increased volume of distribution and glomerular filtration [33,35,36]. Although the impact of obesity and associated diseases (e.g., MAFLD and diabetes) on drug pharmacokinetics have been explored in many studies [32–35,37], much less is known regarding other xenobiotics such as industrial chemicals. Nevertheless, it is conceivable that several molecules present altered pharmacokinetics in obese people, which might change their toxicological profile.

MAFLD is associated with changes in the activity of some CYPs. For instance, human MAFLD is frequently associated with reduced CYP3A4 activity and increased CYP2E1 activity [32–35,37,38]. Thus, the metabolism of drugs, such as troglitazone metabolized by CYP3A4 or acetaminophen by CYP2E1, as well as their hepatotoxicity profile, may be altered [39,40]. The mechanism of reduced CYP3A4 activity in MAFLD is still poorly understood, although two hypotheses can be put forward. Inflammation might be involved, since CYP3A4 expression and activity were found to be markedly reduced by different pro-inflammatory cytokines, such as IL1 β and IL6 [41,42]. Whether decreased CYP3A4 activity plays a role in MAFLD progression remains unclear. Some investigations also pointed to a role of the fibroblast growth factor 21-pregnane X receptor (PXR) pathway, but others failed to demonstrate any involvement of PXR [38]. Likewise, the mechanism of MAFLD-associated CYP2E1 induction is still unclear. Previous investigations pointed to a role of some fatty acids such as stearic acid [43,44]. In addition, insulin resistance-associated hyperinsulinemia and increased glycemia might also play a role in some obese individuals [45]. Lastly, MAFLD is associated with changes in the activity of XMEs other than CYPs, such as uridine diphosphate glucuronosyltransferases (UGTs), which can be associated with higher glucuronide formation, at least with some drugs, including lorazepam, oxazepam and acetaminophen [35,38].

Increased CYP2E1 activity in MAFLD might explain why some drugs such as acetaminophen and halothane induce more severe hepatic liver injury in obese patients, as discussed in previous reviews [40,46,47]. Besides its effect on drug-induced liver injury, higher CYP2E1 activity seems to play a significant role in the progression of fatty liver to NASH [43,48–50]. Indeed, the induction of CYP2E1 could favor oxidative stress, because this enzyme produces significant amounts of superoxide anion during its catalytic cycle [43,48]. Noteworthy, CYP2E1 is located within the ER and the mitochondria, thus producing ROS and inducing oxidative stress in both compartments [51,52]. Thus, endogenous or exogenous compounds able to enhance hepatic CYP2E1 activity are expected to promote the transition from fatty liver to NASH. Finally, some investigations suggested that CYP2E1 induction exacerbates hepatic lipid accumulation, possibly via an ROS-mediated reduction in PPAR α activity [47,53].

3. Xenobiotics Able to Aggravate MAFLD

In this section, we discuss selected drugs and environmental toxicants which could worsen MAFLD through different mechanisms (Figure 1). The molecules described in this section were chosen based on sufficient supporting clinical investigations and experimental data. However, readers are invited to peruse previous reviews in order to know more about xenobiotics that are not discussed in detail below. This concerns drugs such as irinotecan, methotrexate, nucleoside reverse transcriptase inhibitors, phenobarbital and tamoxifen (Table 1) [40,47]. Although not typically considered as a xenobiotic, we also discuss ethanol because there are now numerous studies reporting that its abuse has harmful consequences on the liver of obese alcoholics.

Table 1. Drugs and environmental toxicants shown or suspected to worsen obesity-related fatty liver disease ¹.

Drugs	Environmental Contaminants
Corticosteroids (Corticosterone, Dexamethasone)	Bisphenol A (BPA)
Irinotecan ²	Diesel exhaust particles
Methotrexate ²	Hexabromocyclododecane (HBCD)
Nucleoside reverse transcriptase inhibitors (didanosine, stavudine) ²	Nonylphenol
Pentoxifylline ²	Perchloroethylene
Phenobarbital ²	Perfluorooctanoic acid (PFOA)
Tamoxifen ²	Tetrabromodiphenyl ether (BDE-47)
Tetracycline ²	2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin (TCDD)
Thiazolidinediones (rosiglitazone, troglitazone, pioglitazone)	

¹ See text for details. ² Refer to previous reviews [40,47] for more information. Compounds in bold letters are discussed in detail in the manuscript, in particular regarding the involved mechanism(s). Ethanol is not mentioned in this table because this molecule is not typically considered as a xenobiotic.

3.1. Drugs

3.1.1. Corticosteroids

Corticosteroids (also referred to as glucocorticoids) are potent anti-inflammatory molecules used to treat lupus, rheumatoid arthritis, asthma, Crohn disease and different types of allergies. Inflammatory liver diseases such as alcoholic hepatitis are routinely treated with corticosteroids [54], while their use is not recommended for MAFLD [55]. Corticosteroids include natural hormones, such as cortisol and corticosterone, and synthetic agents, including dexamethasone, prednisone and triamcinolone. Corticosteroids can induce, in some patients, different types of liver lesions, such as hepatic cytolysis, steatosis, steatohepatitis and benign liver tumors [40,56]. Moreover, these drugs can favor abdominal obesity, hyperlipidemia, insulin resistance and T2DM, even after topical administration [47,57,58].

Despite numerous studies on corticosteroid-induced effects on lipid metabolism [59,60], the mechanisms whereby these molecules can induce hepatic steatosis only in a subset of patients are poorly understood and sometimes controversial [61]. For instance, some studies reported that corticosteroids directly induce triglyceride accumulation in cultured hepatocytes, in particular through increased uptake and synthesis of fatty acids [62,63]. In contrast, other investigations failed to report dexamethasone-induced triglyceride accumulation in cultured hepatocytes, thus leading to the proposal that corticosteroid-induced steatosis in vivo requires some systemic factors such as NEFAs or periostin [61,64]. Hence, corticosteroids may favor lipid accumulation in the liver through different mechanisms depending on substrate availability, systemic factors or binding partners [55,62,63]. Indeed, the glucocorticoid receptor (GR) interacts with numerous hepatocyte-expressed transcription factors playing a major role in lipid metabolism, such as PPAR α , Forkhead box protein O1 (FOXO1), Hepatocyte Nuclear Factor 4 α (HNF4 α) and Liver X Receptor (LXR) [60]. Obviously, further investigations are required to decipher the molecular mechanisms involved in corticosteroid-induced steatosis.

Given the extensive effects on lipid homeostasis, corticosteroids may worsen pre-existing metabolic disturbances and MAFLD (Table 1) [40,47]. Although not reported in obese individuals yet, long-term treatment with dexamethasone worsened hepatic triglyceride accumulation in diet-induced obese mice [65,66]. Importantly, liver triglycerides were not increased in mice fed a standard diet, thus indicating a synergistic effect of high-fat diet (HFD) and dexamethasone on steatosis [65,66]. However, in rats, an additive effect between corticosterone and HFD on hepatic lipid deposition was found, as corticosteroid-treated animals fed a standard diet developed hepatic steatosis [67,68]. In one of these studies, plasma bilirubin and ALT levels, and liver collagen content were significantly increased in HFD rats treated with corticosterone compared to untreated HFD rats [67]. Accordingly, these results suggest that corticosteroids might not only exacerbate liver lipid accumulation but might also favor the transition from simple fatty liver to NASH.

The mechanisms whereby corticosteroids worsen obesity-related fatty liver in rodents remain largely unknown. A first suspected mechanism is insulin resistance, associated with increased [67,68] or decreased [66] body fat mass. In the latter study, the reduction in adiposity was correlated with an upregulation of the lipolytic enzyme adipose triglyceride lipase (ATGL), although increased energy expenditure might also be involved [66]. However, these investigations did not unveil how corticosteroids and obesity could synergistically activate ATGL expression [66]. In addition to insulin resistance and increased flux of NEFAs to the liver, indirect evidence also suggests that corticosteroids and obesity might favor hepatic steatosis via enhanced circulating levels of periostin, an extracellular matrix protein expressed in most tissues, including WAT [61] and liver [69]. Dexamethasone-induced steatosis in mice was almost fully prevented by the administration of a periostin-neutralizing antibody or in periostin-knockout mice [61]. In this study, the prevention of dexamethasone-induced steatosis was associated with a restoration of hepatic PPAR α expression [61]. Besides, obese patients with MAFLD present high circulating levels of periostin [69–71]. Moreover, increased hepatic expression of periostin associated with MAFLD negatively regulates PPAR α expression via a mechanism dependent on c-Jun N-terminal kinase (JNK) [69]. Nevertheless, it remains to be determined whether corticosteroids and obesity exert synergistic effects on periostin-induced PPAR α downregulation and alteration in lipid metabolism in the liver.

3.1.2. Thiazolidinediones

Thiazolidinediones are synthetic antidiabetic agents whose beneficial effect on insulin sensitivity is mediated via PPAR γ activation. This drug class includes different molecules, such as rosiglitazone, troglitazone and pioglitazone.

Rosiglitazone is an analogue of troglitazone, the first derivative of the thiazolidinedione family withdrawn from the market in 2000. Indeed, troglitazone induced several cases of fatal acute liver injury with massive hepatic cytolysis, cholestasis and microvesic-

ular steatosis [40,72,73]. Rosiglitazone is much safer than troglitazone, although several cases of hepatic cytolysis and cholestasis, sometimes severe, were reported in treated individuals [74]. In contrast, to our knowledge, rosiglitazone has not been reported to induce microvesicular steatosis in patients. Noteworthy, rosiglitazone therapy is associated with body weight gain, peripheral edema and heart failure, so that this antidiabetic is prescribed as a second-line agent for T2DM. Rosiglitazone-induced cardiovascular side effects led different countries to withdraw this drug from the market. The second thiazolidinedione derivative currently approved by the Food and Drug Administration (FDA) is pioglitazone.

Both rosiglitazone and pioglitazone have been tested in the treatment of NASH [40]. Although pioglitazone therapy showed consistent beneficial effects on NASH progression, rosiglitazone use was overall less effective than pioglitazone or found to be without significant benefit in some investigations [75,76]. In addition, rosiglitazone-induced worsening of steatosis, necroinflammation and perisinusoidal fibrosis were observed in some patients (Table 1) [47,77]. In keeping with these observations, patients treated for 12 months with rosiglitazone showed increased hepatic mRNA expression of Toll-like receptor 4 (*TLR4*), interleukin-8 (*IL8*) and C-C motif chemokine ligand 2 (*CCL2*, also known as MCP-1), thus suggesting a pro-inflammatory state [78].

Several investigations performed on different murine models of obesity and T2DM reported that rosiglitazone worsened liver triglyceride accumulation and hepatic steatosis [79–86]. However, only a few studies compared rosiglitazone effects between lean and obese mice. In such investigations, rosiglitazone did not induce steatosis in lean animals, whereas it exacerbated hepatic fat accumulation in obese mice, demonstrating a synergistic effect of rosiglitazone and obesity on fatty liver [82,86]. In two aforementioned studies, rosiglitazone-induced aggravation of fatty liver was associated with increased circulating ALT activity, thus suggesting that necroinflammation could be also exacerbated [80,83]. In contrast to these studies, others showed that rosiglitazone alleviates hepatic steatosis in obese rodents [87–89]. The exact reasons of these discrepancies are still unknown but might be explained by several experimental parameters, such as differences in rodent models of obesity and protocols of rosiglitazone treatment, including duration and dose.

Rosiglitazone-induced worsening of hepatic triglyceride accumulation in obese mice was associated, in most investigations, with an improvement of insulin resistance, in keeping with its pharmacological action [80–82,84,85]. Yet, effects on body weight were not consistent, being either increased [80–82], unchanged [84] or reduced [85]. Unfortunately, these studies did not determine whether body fat mass was affected. Hence, further investigations are warranted to determine the relationship between the worsening of hepatic steatosis and adiposity.

Several studies attempted to decipher the mechanisms underlying the synergistic effect of obesity and rosiglitazone on fatty liver. Some investigations suggested an exacerbation of hepatic DNL [80], which might have been favored by the high basal expression of PPAR γ in obese liver [83,86]. This hypothesis was reinforced by in vitro investigations of mouse hepatocytes overexpressing PPAR γ 2 [90]. Indeed, although troglitazone was used as PPAR γ agonist in this study, intracellular lipid accumulation induced by PPAR γ 2 overexpression was further enhanced by this thiazolidinedione derivative [90]. In addition to exacerbated DNL, rosiglitazone could also favor uptake of NEFAs by the fatty liver, presumably via an increased expression of *FAT/CD36* [81].

Greater hepatotoxicity of rosiglitazone in some obese patients might also be secondary to an alteration in its pharmacokinetics, which might favor higher plasma concentrations and PPAR γ overactivation in the liver. In keeping with this hypothesis, the plasma half-life of rosiglitazone was nearly tripled in a mouse model of diet-induced obesity [91]. Rosiglitazone mainly undergoes CYP2C8-mediated *p*-hydroxylation and N-demethylation, followed by sulfate and glucuronide conjugation [92], metabolic pathways that might be affected in obesity. A previous study suggested reduced CYP2C8 activity in obese individuals [93], but this was not confirmed by other investigators [94]. Hence, further

investigations are required for a better understanding of rosiglitazone pharmacokinetics in obesity.

The mechanisms involved in rosiglitazone-induced hepatic necroinflammation in some subjects with MAFLD remain unknown. Rosiglitazone might exacerbate MAFLD-associated mitochondrial dysfunction, which, in turn, might cause overproduction of ROS and proinflammatory cytokines [23,27,83]. In keeping with this assumption, relatively low concentrations (25 and 50 μ M) of rosiglitazone were shown to inhibit the activity of MRC complexes I–IV in differentiated HepaRG cells, which was associated with ROS overproduction [95]. More recent investigations of MDA-MB-231 cells confirmed that rosiglitazone could induce mitochondrial dysfunction, but ROS were not assessed in this study [96].

In contrast to rosiglitazone, pioglitazone showed consistent beneficial effects on NASH progression in patients [75,76], as previously mentioned. Nevertheless, investigations of obese mice showed that pioglitazone worsened fatty liver [97,98]. In one of these studies, pioglitazone increased the mRNA expression of several genes involved in lipid synthesis, such as fatty acid synthase (*Fasn*), stearyl-CoA desaturase (*Scd1*) and enzymes involved in fatty acid elongation (*Elovl3*, -5 and -7) [98]. However, pioglitazone concomitantly decreased the expression of different genes involved in the inflammatory response [98]. Interestingly, pioglitazone but not rosiglitazone might elicit anti-inflammatory effects via PPAR α activation [99]. Hence, the anti-inflammatory property of pioglitazone might explain why this thiazolidinedione derivative presents more favorable effects on NASH progression than rosiglitazone. In addition, it is noteworthy that pioglitazone is a weaker human PPAR γ activator than rosiglitazone [100,101], which could explain the differential steatogenic effect on patients.

3.1.3. Other Drugs

MAFLD may be worsened, in obese patients, by other pharmaceuticals, such as irinotecan, methotrexate and tamoxifen (Table 1), which have been extensively discussed in previous reviews [40,47,102,103]. However, despite being observed clinically, the mechanisms leading to aggravation of MAFLD are poorly characterized. Pentoxifylline, a drug tested in NASH for its anti-TNF- γ activity, is suspected to aggravate fatty liver, inflammation and fibrosis in few patients (Table 1), although this methylxanthine derivative showed some beneficial effects in most patients [104,105]. A 3-week treatment with pentoxifylline aggravated fatty liver in obese diabetic ob/ob mice and this was associated with hepatic ChREBP overactivation, possibly as a consequence of enhanced intestinal glucose absorption and increased postprandial glycemia [105]. Notably, pentoxifylline did not induce steatosis in wild-type (i.e., lean) mice [105]. Hence, it is possible that long-term treatment with pentoxifylline could exacerbate fatty liver only in a subset of patients with severe pre-existing hyperglycemia. Other drugs, such as phenobarbital [106] and tetracycline [107] (Table 1), exacerbated fatty liver in obese rodents, yet clinical investigations with these drugs are lacking. Stavudine and didanosine are suspected to aggravate fatty liver in some patients, potentially through mitochondrial dysfunction [40]. However, experimental studies are required to determine the exact mechanisms.

3.2. Environmental Toxicants

3.2.1. Bisphenol A

Bisphenol A (BPA) was identified as an estrogenic derivative in the mid-1930s, but this synthetic chemical was never developed as a drug [108]. Instead, BPA has been extensively used as a plasticizer incorporated in numerous consumer goods, such as food storage containers, bottles and CDs. Human exposure to BPA is suspected to favor obesity and related metabolic disorders, such as insulin resistance, T2DM and MAFLD [109–111]. Many experimental data in rodents confirmed that metabolic disturbances occur after exposure to BPA in adulthood or during the perinatal period [112,113]. Hence, BPA is now deemed

to be a prototypical endocrine disruptor whose use in food containers and thermal paper has been banned in different countries [110].

The mechanisms of BPA-induced metabolic disturbances are complex and have been extensively discussed in recent reviews [110,111,113,114]. Briefly, many of the metabolic and endocrine alterations induced by BPA could be mediated via the activation of several nuclear receptors, such as estrogen receptor alpha ($ER\alpha$), $ER\beta$ estrogen related receptor γ ($ERR\gamma$) and PXR. BPA could also activate $PPAR\gamma$ and CCAAT/enhancer binding proteins (C/EBPs), although it is still debated whether these transcription factors play a role in BPA's mode of action [113,114]. Lastly, rodent studies suggested a role for SREBP activation in the liver [115,116], but whether such activation is direct or mediated by hyperinsulinemia remains to be determined.

The mechanisms whereby BPA can induce steatosis are still poorly understood. BPA-induced hepatic lipid accumulation is likely secondary to obesity and insulin resistance [111,117], while a recent study suggested a role for gut microbiota dysbiosis [118]. BPA could also have direct effects on hepatocytes. Indeed, several *in vitro* studies showed that BPA induced lipid accretion in the human hepatic cell lines HepG2, HepaRG and HHL-5 [119–126]. This effect was observed for BPA concentrations in the nanomolar range in four independent studies [119,120,123,125], with a non-monotonic profile observed in three of them [119,123,125]. Interestingly, in HepG2 cells, BPA increases SREBP1 expression through the downregulation of miR-192, thus leading to triglyceride accumulation [124]. Alternatively, BPA indirectly activates the endocannabinoid receptor CB1 to induce SREBP1 [122]. Of note, BPA-induced intracellular cholesterol accumulation involves SREBP2 activation [125]. A previous study suggested a role for mitochondrial dysfunction in BPA-induced neutral lipid accumulation, but mitochondrial FAO has not been assessed [120]. It has also been proposed that PXR may play a role [121], but this hypothesis could not be confirmed [123]. The latter study also provided evidence that $ERR\gamma$ is not involved in BPA-induced steatosis [123].

Only a few studies compared the metabolic and hepatic effects of BPA between lean and obese mice. One study found a synergistic effect of BPA and diet-induced obesity regarding hepatic triglyceride content and collagen deposition [127]. Although this study did not provide mechanistic explanations for these effects, other studies showed a synergistic effect of BPA and HFD on glucose intolerance and, possibly, insulin resistance [128,129]. Maternal exposure to BPA led to increased hepatic lipid accumulation in rat male offspring, which was further exacerbated by HFD after weaning with a higher ratio of microvesicular/macrovacuolar steatosis [130]. Further investigations in this study suggested impaired mitochondrial FAO, especially at the level of carnitine palmitoyltransferase 1 (CPT1), a major enzyme involved in the mitochondrial entry of long-chain fatty acids [130].

The synergistic effects of BPA and HFD on fatty liver, glucose intolerance and possibly insulin resistance might be, at least in part, secondary to an impairment of BPA biotransformation resulting in higher BPA bioavailability. A previous study in humans and mice disclosed a strong reduction in BPA sulfonation in MAFLD [131]. However, reduced BPA sulfonation in MAFLD might have little consequence on BPA bioavailability, because BPA-sulfate is a minor metabolite of BPA in humans and rodents, in contrast to BPA-glucuronide [131,132]. Hence, future investigations are required to determine whether MAFLD is also associated with the impairment of BPA glucuronidation.

3.2.2. Perfluorooctanoic Acid

Perfluorooctanoic acid (PFOA) is one of the most common poly- and perfluoroalkyl substances (PFAS) used for industrial and commercial applications. PFOA is a surfactant with water-repellent properties which can be found in many consumer goods, such as non-stick pans, weatherproof garments, floor waxes, food containers and cosmetics. Most uses of this chemical are banned or are progressively being suppressed in many countries because of suspected toxicity in animals and humans [133]. Indeed, the exposure to high levels of PFOA among residents living near the DuPont Teflon-manufacturing plant in

Parkersburg, West Virginia, is linked to several types of cancers, especially testicular and kidney malignancies [134,135]. In addition, workers of this chemical plant presented a higher risk of mortality for several diseases, such as chronic renal diseases and diabetes mellitus [136]. Interestingly, longitudinal cohort studies suggested that environmental PFOA exposure in the general population might be associated with increased risk of T2DM [137,138]. Environmental PFOA exposure might also be associated with excess adiposity, in particular in the setting of early-life exposure [139,140], although other studies did not confirm these findings [141,142]. In contrast, the environmental PFOA exposure of the general population is consistently associated with hypercholesterolemia [135,141,143]. However, very high PFOA exposure seems to reduce total blood cholesterol levels, possibly via PPAR α activation [144].

Regarding the liver, PFOA exposure might be associated with elevated ALT activity [135,142,145]. In some epidemiological studies, higher circulating ALT activity is more pronounced in obese subjects compared to nonobese ones, suggesting a synergistic effect of PFOA exposure and obesity on hepatic cytolysis [146,147]. In contrast, other investigations did not find an association between PFOA and elevated ALT activity [144]. Actually, except for hepatic cytolysis, the current available epidemiological data do not support a link between PFOA exposure and liver diseases, including MAFLD [133,135,145]. Hence, further epidemiological studies specifically designed for elevated liver enzymes and MAFLD are needed in order to better evaluate the effects of PFOA exposure on human liver, as underlined by different authors [135,145]. Of note, some PFAS, such as perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS), are more likely to cause fatty liver in exposed individuals [148].

In mice, several investigations consistently reported PFOA-induced elevated hepatic triglyceride levels and steatosis [149–153], although this was not confirmed in another study [154]. These discrepancies might be explained by different factors, such as the dose of PFOA and duration of treatment, the mouse strain and the diet. Interestingly, in BALB/c mice, 28 days of PFOA treatment decreased liver triglycerides with the administration of the 0.08 and 20 mg/kg/day doses but increased them with the administration of the 1.25 mg/kg/day dose [150]. PFOA was also shown to induce the accumulation of lipid droplets in hepatocyte nuclei [155]. Because the accumulation of lipid droplets in the nucleus could have significant effects on lipid signaling and nuclear receptor function [156], further investigations are required to determine the exact consequences of this observation. In addition to these *in vivo* studies, PFOA increased intracellular levels of neutral lipids and triglycerides in different human hepatic cell lines [153,157,158]. However, it should be underlined that these effects were observed for high PFOA concentrations (i.e., 50 μ M or more) [153,157,158].

From these experimental investigations, several hypotheses can be put forward in order to explain how PFOA induces steatosis (Figure 3), such as the following:

- (1) Direct binding to PPAR γ [111,159], whose activation increases the expression of *FAT/CD36* and different genes involved in DNL, such as *SREBP1*, acetyl-coenzyme A carboxylase (*ACC*) and *FASN* [90,152]. Of note, *SREBP1* can activate PPAR γ via the production of fatty acid derivatives acting as endogenous ligand(s) [160]. Hence, it would be interesting to determine whether PFOA can directly activate *SREBP1* in a PPAR γ -independent manner, which might reinforce DNL stimulation secondary to PFOA-induced activation of PPAR γ .
- (2) PXR activation. On one hand, previous studies showed that PFOA can activate PXR, in particular the human ortholog [111,161], although this has not been confirmed in other investigations [162,163]. On the other hand, many investigations showed that PXR can trigger a steatogenic response in liver [159,164,165]. Hence, it would be interesting to assess the metabolic effects of PFOA in PXR-knockout mice and in human hepatocytes with PXR silencing.
- (3) Reduction in HNF4 α protein levels and activity [152,166], an effect which is expected to impair FAO and VLDL secretion [167].

- (4) ER stress [157,158], which might also strongly impair VLDL secretion [21,24]. However, ER stress was observed in human hepatic cells with high concentrations of PFOA (i.e., 100 or 200 μ M) [157,158].
- (5) Impairment of autophagy [153], which might reduce the degradation of excessive lipid droplets [16,20].
- (6) Mobilization of lipids from the adipose tissue due to a loss of fat mass [168]. Indeed, some investigations of mice reported that PFOA exposure significantly reduced body weight and adiposity, even when the animals were fed a HFD [154,155,157,168]. PFOA-induced reduction in fat mass in mice might be mainly due to a lower food intake [168,169], possibly via an uncoupling protein 1-dependent mechanism [169].

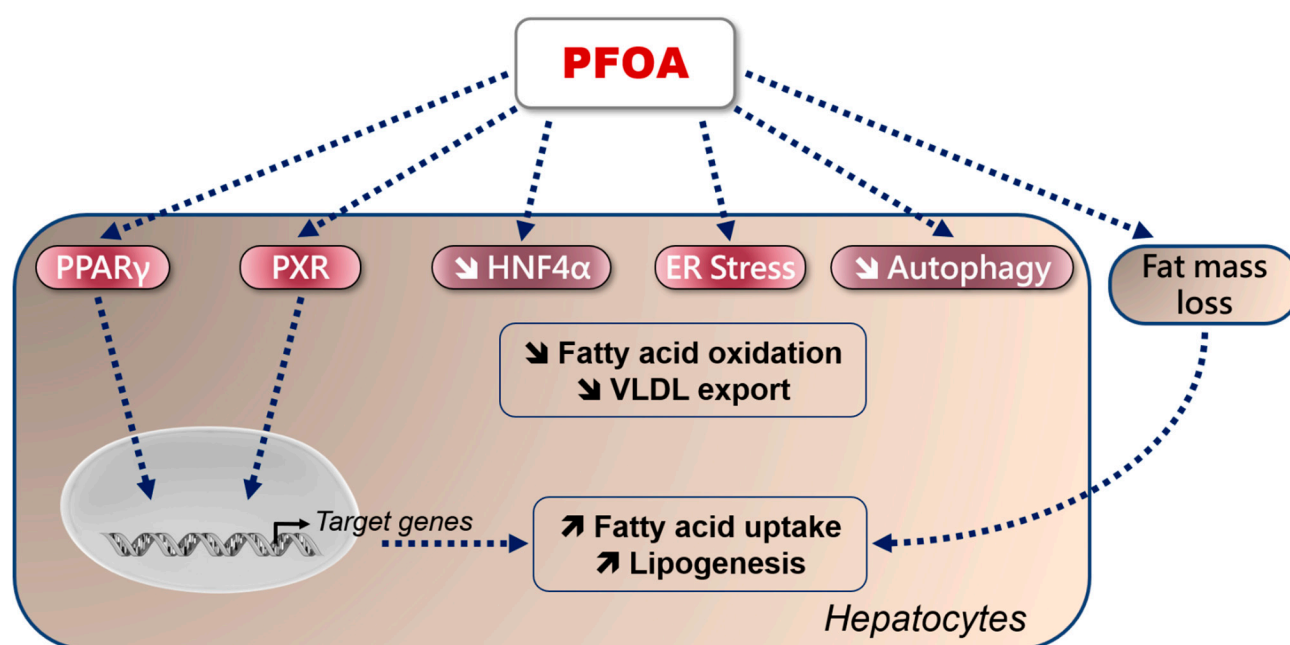


Figure 3. Potential mechanisms involved in PFOA-induced hepatic steatosis. PFAO can directly bind PPAR γ or activate PXR, both transcription factors inducing the expression of genes involved in fatty acid uptake and de novo lipogenesis. PFOA reduces the expression and activity of HNF4 α , leading to alteration in fatty acid oxidation and very low-density lipoprotein (VLDL) secretion. Reduced VLDL secretion can be secondary to endoplasmic reticulum stress caused by PFOA. Reduction in autophagy by PFOA favors lipid accumulation by reducing the clearance of excessive lipid droplets. Finally, PFOA reduces adiposity, which contributes to an increased lipid flux to the liver in the context of obesity. (↘: increase; ↗: decrease).

It is noteworthy that PFOA is a potent activator of PPAR α [162,163,170,171]. Although PFOA-induced PPAR α activation in rodents can induce hepatic hyperplasia and hepatocarcinogenicity, the use of drugs activating PPAR α (e.g., fibrates) in humans have beneficial effects on lipid metabolism, in particular by reducing blood triglycerides and alleviating MAFLD [170,172]. Hence, it is tempting to speculate that PFOA-induced PPAR α activation might alleviate its deleterious effects on lipid homeostasis, which might be linked to the activation of other nuclear receptors, such as PPAR γ and PXR, as previously mentioned. In keeping with this hypothesis, the PFOA-induced hepatic accumulation of large lipid droplets was observed in male PPAR α -null mice but not in male mice expressing human PPAR α [171]. In addition to steatosis, PPAR α activation might also protect against other liver lesions induced by PFOA, such as bile duct hyperplasia and hematopoietic cell proliferation [173].

Five studies assessed the hepatic effects of PFOA in mice fed with different types of HFDs [154,155,168,171,174]. Unfortunately, two of these studies did not include groups of mice fed a standard diet [171,174]; thus, this does not allow one to determine the additive

or synergistic effects between PFOA and high-fat feeding. Nonetheless, in one of the latter studies, PFOA induced significant steatosis in male PPAR α -null mice fed a HFD, whereas steatosis was less marked in the non-exposed counterparts [171]. Whether this exacerbation of liver lipid content was associated with hepatic cytolysis remains unknown, as serum ALT and AST activity was not reported [171]. The other study, focused on cholesterol metabolism, reported that PFOA reduced liver cholesterol levels in male and female BALB/c mice fed a HFD but not C57BL/6 mice fed the same diet [174].

The other three investigations of mice reported incomplete or opposing results regarding hepatic lipids and cytolysis between standard diet and HFD [154,155,168]. In one study, PFOA-induced liver triglyceride accumulation was similar between standard-diet- and HFD-fed mice and a synergistic effect between PFOA treatment and HFD was observed for plasma ALT activity [168]. In another study, focused on nuclear lipid droplets, the accumulation of these droplets was similar between standard diet and HFD mice [155]. Unfortunately, this study did not provide information on total liver lipid content and plasma transaminase activity. Lastly, PFOA exposure protected against HFD-induced steatosis, hepatic cytolysis and fibrosis [154]. However, a synergistic effect between early PFOA treatment and HFD was observed regarding PPAR α activation and hepatocyte proliferation [154]. In line with this study, recent investigations showed that PFOS protected against HFD-induced hepatic steatosis but serum transaminase activity was not reported [175]. Nonetheless, in this study, PFOS induced steatosis in mice fed a normal diet [175].

In summary, there is no conclusive evidence in mice of any additive or synergistic effect between PFOA exposure and HFD regarding fatty liver, whereas only one study reported a synergistic effect for hepatic cytolysis [168]. Although this study might be in line with some data collected from obese individuals [146,147], further investigations are needed in order to determine the hepatic effects of PFOA in rodent models of obesity. In particular, it would be important to systematically assess both steatosis and hepatic cytolysis, since PFOA might have different effects on these liver lesions [168]. Because PFOA-induced PPAR α activation could be a confounding factor in rodent investigations, it would also be of interest to use human cellular models of MAFLD, as recently described for other xenobiotics [39,44,176].

3.2.3. Other Environmental Toxicants

Despite not being described clinically, other environmental toxicants aggravated MAFLD in different rodent models of obesity. For instance, this was reported for diesel exhaust particles [177], hexabromocyclododecane (HBCD) [178], perchloroethylene (PCE) [179], 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) [180], nonylphenol [181] and tetrabromodiphenyl ether (BDE-47) [182]. Aggravation of fatty liver by TCDD and BDE-47 might be linked with aryl hydrocarbon receptor (AhR) activation and the subsequent increased expression of *FAT/CD36* [180,182], whereas HBCD and nonylphenol might act via PPAR γ activation [178,181]. Regarding perchloroethylene, which aggravated both fatty liver and hepatic cytolysis (as assessed by serum ALT activity) in HFD-fed mice, the precise mechanism of MAFLD worsening was unfortunately not delineated [179]. Nevertheless, this study showed that MAFLD was associated with the hepatic accumulation of perchloroethylene and its major oxidative metabolite, trichloroacetate [179]. Hence, the worsening of MAFLD induced by perchloroethylene might be, at least in part, secondary to an increase in its bioavailability. However, the underlying mechanisms whereby these molecules aggravate MAFLD are poorly characterized and warrant further investigations.

3.3. Ethanol

Even though ethanol can be found in the blood of non-alcoholic individuals [183], this molecule is mentioned in this review because its overconsumption is a major issue for public health. Regarding the liver, sustained high alcohol consumption (>20 and 30 g/day of alcohol for women and men, respectively) leads almost always to hepatic diseases such as acute hepatitis, fatty liver, steatohepatitis, cirrhosis and hepatocellular carcinoma [184,185].

Indeed, alcohol intoxication induces several deleterious effects in hepatocytes and other liver cells, such as mitochondrial dysfunction, increased lipogenesis, CYP2E1 induction with subsequent ROS overproduction and oxidative stress, impairment of autophagy, ER stress and increased production of proinflammatory and profibrotic cytokines. Readers are invited to peruse recent reviews for further information regarding the mechanisms of ethanol-induced hepatic toxicity [184–191].

There is now strong evidence that alcohol abuse and obesity (or metabolic syndrome) synergistically increase the risk and severity of different hepatic diseases, including fatty liver, steatohepatitis, cirrhosis and hepatocellular carcinoma [192–195]. Experimental investigations attempted to determine how ethanol and obesity synergistically increase hepatic toxicity in particular regarding steatosis, hepatocyte cell death and inflammation. Unsurprisingly, different mechanisms have been proposed, including impaired mitochondrial function and biogenesis [196,197], reduced expression of PPAR α [196,198] or AMP-activated protein kinase (AMPK) [199], induction of CYP2E1 and oxidative stress [200,201], unfolded protein response and ER stress [196,202], increased expression of tumor necrosis factor alpha (TNF- α) [203] or Fas ligand [204,205] and activation of different proinflammatory pathways [206–209]. Interestingly, ethanol exerts different deleterious effects on WAT such as lipoatrophy, increased lipolysis and enhanced secretion of proinflammatory adipokines [210–212], which might also explain why alcohol intoxication is particularly hepatotoxic in obese individuals [195].

Finally, recent investigations of different experimental models of MAFLD suggested that benzo[a]pyrene exposure might even further aggravate the progression of steatosis to steatohepatitis induced by ethanol [176,213–215]. Potential mechanisms involved in such progression include overproduction of ROS and nitric oxide [176,214], mitochondrial dysfunction [176], increased expression of proinflammatory cytokines [213] and plasma membrane remodeling [215].

4. Key Mechanisms Involved in Xenobiotic-Induced Aggravation of MAFLD

Collectively, the aforementioned studies clearly indicate that xenobiotics can worsen MAFLD via different mechanisms, as illustrated in Figures 1 and 2. The exacerbation of pre-existing fatty liver seems to frequently involve increased DNL, either directly via the activation of different lipogenic transcription factors such as PPAR γ and PXR, or indirectly through hyperinsulinemia or hyperglycemia, which can, in turn, activate SREBP1c and ChREBP, respectively (Figure 1). Furthermore, xenobiotics might worsen steatosis by impairing VLDL secretion, in particular as a consequence of ER stress. The impairment of mitochondrial FAO might also be involved with some chemicals, in particular with drugs and ethanol, whose intrahepatic concentrations can be relatively high. Notably, xenobiotic-induced impairment of VLDL secretion and mitochondrial FAO is expected to curb two major metabolic adaptations occurring during MAFLD, as mentioned previously. Xenobiotic-induced worsening of pre-existing necroinflammation and fibrosis could involve chronic ROS overproduction and subsequent oxidative stress, which can favor the production of pro-inflammatory cytokines (e.g., TNF- α and interleukin-1 β) and transforming growth factor- β (TGF- β), a key pro-fibrotic cytokine (Figure 2). In the setting of MAFLD and xenobiotic exposure, ROS overproduction seems to be mainly secondary to mitochondrial dysfunction, whereas the induction of CYP2E1 can play a role with some compounds such as ethanol.

5. Conclusions

MAFLD may be worsened by different drugs and environmental toxicants but also by ethanol, which is consumed by millions of people worldwide. However, except for a handful of xenobiotics (Table 1), there is currently a blatant lack of information regarding the whole spectrum of molecules able to aggravate MAFLD. Accordingly, there is an urgent need to determine which compounds could pose a specific risk for overweight or obese individuals. To this end, experimental investigations using cellular models of MAFLD might

allow a great number of xenobiotics to be screened [47,176,216]. Although there is increasing evidence that many xenobiotics might alter the insulin signaling pathway [217–220], it should be pointed out that these in vitro models cannot detect MAFLD worsening due to extra-hepatic effects such as insulin resistance (Figure 1).

It would also be important to determine if the mechanisms of xenobiotic-induced MAFLD worsening in obese patients are the same as those triggering steatosis and steatohepatitis in lean individuals. To this end, experimental investigations of animal and cellular models could greatly help to answer this question. Indeed, the worsening of fatty liver in obese animals (or steatosis in cellular models of MAFLD) associated with the lack of hepatic lipid accumulation in lean animals (or in non-steatotic hepatic cells) would decipher specific mechanism(s) in the context of obesity and MAFLD. These investigations might also unveil the existence of additive or synergistic effects between the investigated compounds and MAFLD regarding the aggravation of liver disease.

Finally, investigators should seek out the possible toxicological interactions between pharmaceuticals, environmental pollutants and even alcohol. This is a major issue because obese people are often polymedicated and are expected to be exposed to some environmental contaminants and to consume different types of alcoholic beverages. In these individuals, different factors might trigger fatty liver or favor its progression to steatohepatitis and cirrhosis. Thus, we propose to coin the term “mixed-origin fatty liver disease” (MOFLD), which could better reflect the multiple causes leading to fatty liver disease, such as overnutrition, drugs, environmental toxicants and excessive alcohol consumption. It should finally be underlined that, in obesity, tissues other than the liver can be particularly injured by xenobiotics, such as heart [221–223] and kidneys [224–226]. Accordingly, xenobiotic-induced toxicity in obese individuals should concern hepatologists but also physicians from other medical specialties.

Author Contributions: Writing—original draft preparation, J.M. and B.F.; review and editing, J.M., K.B., A.C. and B.F. All authors have read and agreed to the published version of the manuscript.

Funding: This work has received funding from the European Union’s Horizon 2020 Research and Innovation Programme under grant agreement GOLIATH N°825489.

Acknowledgments: We are also grateful to INSERM (Institut National de la Recherche et de la Santé Médicale) for their constant financial support.

Conflicts of Interest: J. Massart, K. Begriche, A. Corlu and B. Fromenty declare that they have no conflict of interest in relation to this work.

References

1. Eslam, M.; Sanyal, A.J.; George, J.; Sanyal, A.; Neuschwander-Tetri, B.; Tiribelli, C.; Kleiner, D.E.; Brunt, E.; Bugianesi, E.; Yki-Järvinen, H.; et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* **2020**, *158*, 1999–2014.e1. [\[CrossRef\]](#)
2. Tschöp, M.H.; Finan, B.; Clemmensen, C.; Gelfanov, V.; Perez-Tilve, D.; Müller, T.D.; DiMarchi, R.D. Unimolecular Polypharmacy for Treatment of Diabetes and Obesity. *Cell Metab.* **2016**, *24*, 51–62. [\[CrossRef\]](#)
3. Assari, S.; Wisseh, C.; Bazargan, M. Obesity and Polypharmacy among African American Older Adults: Gender as the Moderator and Multimorbidity as the Mediator. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2181. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Joshi-Barve, S.; Kirpich, I.; Cave, M.C.; Marsano, L.S.; McClain, C.J. Alcoholic, Nonalcoholic, and Toxicant-Associated Steatohepatitis: Mechanistic Similarities and Differences. *Cell. Mol. Gastroenterol. Hepatol.* **2015**, *1*, 356–367. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Yeh, M.M.; Brunt, E.M. Pathological Features of Fatty Liver Disease. *Gastroenterology* **2014**, *147*, 754–764. [\[CrossRef\]](#)
6. Begriche, K.; Massart, J.; Robin, M.-A.; Borgne-Sanchez, A.; Fromenty, B. Drug-Induced Toxicity on Mitochondria and Lipid Metabolism: Mechanistic Diversity and Deleterious Consequences for the Liver. *J. Hepatol.* **2011**, *54*, 773–794. [\[CrossRef\]](#)
7. Hegarty, R.; Deheragoda, M.; Fitzpatrick, E.; Dhawan, A. Paediatric Fatty Liver Disease (PeFLD): All Is Not NAFLD—Pathophysiological Insights and Approach to Management. *J. Hepatol.* **2018**, *68*, 1286–1299. [\[CrossRef\]](#)
8. Ibrahim, S.H.; Hirsova, P.; Gores, G.J. Non-Alcoholic Steatohepatitis Pathogenesis: Sublethal Hepatocyte Injury as a Driver of Liver Inflammation. *Gut* **2018**, *67*, 963–972. [\[CrossRef\]](#)
9. Fierbinteanu-Braticевич, C. Noninvasive Investigations for Non Alcoholic Fatty Liver Disease and Liver Fibrosis. *World J. Gastroenterol.* **2010**, *16*, 4784. [\[CrossRef\]](#) [\[PubMed\]](#)

10. Watanabe, S.; Hashimoto, E.; Ikejima, K.; Uto, H.; Ono, M.; Sumida, Y.; Seike, M.; Takei, Y.; Takehara, T.; Tokushige, K.; et al. Evidence-Based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis: Clinical Practice Guidelines. *Hepatol. Res.* **2015**, *45*, 363–377. [[CrossRef](#)]
11. Regev, A.; Palmer, M.; Avigan, M.I.; Dimick-Santos, L.; Treem, W.R.; Marcinak, J.F.; Seekins, D.; Krishna, G.; Anania, F.A.; Freston, J.W.; et al. Consensus: Guidelines: Best Practices for Detection, Assessment and Management of Suspected Acute Drug-Induced Liver Injury during Clinical Trials in Patients with Nonalcoholic Steatohepatitis. *Aliment. Pharmacol. Ther.* **2019**, *49*, 702–713. [[CrossRef](#)] [[PubMed](#)]
12. Farrell, G.C.; Haczeyni, F.; Chitturi, S. Pathogenesis of NASH: How Metabolic Complications of Overnutrition Favour Lipotoxicity and Pro-Inflammatory Fatty Liver Disease. In *Obesity, Fatty Liver and Liver Cancer*; Yu, J., Ed.; Springer Singapore; Advances in Experimental Medicine and Biology; Singapore, 2018; Volume 1061, pp. 19–44, ISBN 978-981-10-8683-0.
13. Ipsen, D.H.; Lykkesfeldt, J.; Tveden-Nyborg, P. Molecular Mechanisms of Hepatic Lipid Accumulation in Non-Alcoholic Fatty Liver Disease. *Cell. Mol. Life Sci.* **2018**, *75*, 3313–3327. [[CrossRef](#)] [[PubMed](#)]
14. Sanyal, A.J. Past, Present and Future Perspectives in Nonalcoholic Fatty Liver Disease. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 377–386. [[CrossRef](#)] [[PubMed](#)]
15. Khan, R.S.; Bril, F.; Cusi, K.; Newsome, P.N. Modulation of Insulin Resistance in Nonalcoholic Fatty Liver Disease. *Hepatology* **2019**, hep.30429. [[CrossRef](#)]
16. Kim, Y.S.; Kim, S.G. Endoplasmic Reticulum Stress and Autophagy Dysregulation in Alcoholic and Non-Alcoholic Liver Diseases. *Clin. Mol. Hepatol.* **2020**, *26*, 715–727. [[CrossRef](#)]
17. Sookoian, S.; Pirola, C.J.; Valenti, L.; Davidson, N.O. Genetic Pathways in Nonalcoholic Fatty Liver Disease: Insights From Systems Biology. *Hepatology* **2020**, *72*, 330–346. [[CrossRef](#)] [[PubMed](#)]
18. Fujii, H.; Kawada, N.; Japan Study Group of NAFLD (JSG-NAFLD) Japan Study Group of NAFLD (JSG-NAFLD). The Role of Insulin Resistance and Diabetes in Nonalcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2020**, *21*, 3863. [[CrossRef](#)]
19. Abdul-Wahed, A.; Guilmeau, S.; Postic, C. Sweet Sixteenth for ChREBP: Established Roles and Future Goals. *Cell Metab.* **2017**, *26*, 324–341. [[CrossRef](#)]
20. Khambu, B.; Yan, S.; Huda, N.; Liu, G.; Yin, X.-M. Autophagy in Non-Alcoholic Fatty Liver Disease and Alcoholic Liver Disease. *Liver Res.* **2018**, *2*, 112–119. [[CrossRef](#)]
21. Lebeaupin, C.; Vallée, D.; Hazari, Y.; Hetz, C.; Chevet, E.; Bailly-Maitre, B. Endoplasmic Reticulum Stress Signalling and the Pathogenesis of Non-Alcoholic Fatty Liver Disease. *J. Hepatol.* **2018**, *69*, 927–947. [[CrossRef](#)] [[PubMed](#)]
22. Chen, Z.; Tian, R.; She, Z.; Cai, J.; Li, H. Role of Oxidative Stress in the Pathogenesis of Nonalcoholic Fatty Liver Disease. *Free Radic. Biol. Med.* **2020**, *152*, 116–141. [[CrossRef](#)] [[PubMed](#)]
23. Begriche, K.; Massart, J.; Robin, M.-A.; Bonnet, F.; Fromenty, B. Mitochondrial Adaptations and Dysfunctions in Nonalcoholic Fatty Liver Disease. *Hepatology* **2013**, *58*, 1497–1507. [[CrossRef](#)] [[PubMed](#)]
24. Allard, J.; Bucher, S.; Massart, J.; Ferron, P.-J.; Le Guillou, D.; Loyant, R.; Daniel, Y.; Launay, Y.; Buron, N.; Begriche, K.; et al. Drug-Induced Hepatic Steatosis in Absence of Severe Mitochondrial Dysfunction in HepaRG Cells: Proof of Multiple Mechanism-Based Toxicity. *Cell Biol. Toxicol.* **2021**, *37*, 151–175. [[CrossRef](#)] [[PubMed](#)]
25. Zhang, Y.; Bharathi, S.S.; Beck, M.E.; Goetzman, E.S. The Fatty Acid Oxidation Enzyme Long-Chain Acyl-CoA Dehydrogenase Can Be a Source of Mitochondrial Hydrogen Peroxide. *Redox Biol.* **2019**, *26*, 101253. [[CrossRef](#)] [[PubMed](#)]
26. Perla, F.; Prelati, M.; Lavorato, M.; Visicchio, D.; Anania, C. The Role of Lipid and Lipoprotein Metabolism in Non-Alcoholic Fatty Liver Disease. *Children* **2017**, *4*, 46. [[CrossRef](#)] [[PubMed](#)]
27. Sunny, N.E.; Bril, F.; Cusi, K. Mitochondrial Adaptation in Nonalcoholic Fatty Liver Disease: Novel Mechanisms and Treatment Strategies. *Trends Endocrinol. Metab.* **2017**, *28*, 250–260. [[CrossRef](#)] [[PubMed](#)]
28. Koliaki, C.; Szendroedi, J.; Kaul, K.; Jelenik, T.; Nowotny, P.; Jankowiak, F.; Herder, C.; Carstensen, M.; Krausch, M.; Knoefel, W.T.; et al. Adaptation of Hepatic Mitochondrial Function in Humans with Non-Alcoholic Fatty Liver Is Lost in Steatohepatitis. *Cell Metab.* **2015**, *21*, 739–746. [[CrossRef](#)]
29. Francque, S.; Verrijken, A.; Caron, S.; Prawitt, J.; Paumelle, R.; Derudas, B.; Lefebvre, P.; Taskinen, M.-R.; Van Hul, W.; Mertens, I.; et al. PPAR α Gene Expression Correlates with Severity and Histological Treatment Response in Patients with Non-Alcoholic Steatohepatitis. *J. Hepatol.* **2015**, *63*, 164–173. [[CrossRef](#)]
30. Buechler, C.; S. Weiss, T. Does Hepatic Steatosis Affect Drug Metabolizing Enzymes in the Liver? *Curr. Drug Metab.* **2011**, *12*, 24–34. [[CrossRef](#)]
31. Song, B.-J.; Akbar, M.; Jo, I.; Hardwick, J.P.; Abdelmegeed, M.A. Translational Implications of the Alcohol-Metabolizing Enzymes, Including Cytochrome P450-2E1, in Alcoholic and Nonalcoholic Liver Disease. In *Advances in Pharmacology*; Elsevier: New York, NY, USA, 2015; Volume 74, pp. 303–372, ISBN 978-0-12-803119-3.
32. Cobbina, E.; Akhlaghi, F. Non-Alcoholic Fatty Liver Disease (NAFLD)—Pathogenesis, Classification, and Effect on Drug Metabolizing Enzymes and Transporters. *Drug Metab. Rev.* **2017**, *49*, 197–211. [[CrossRef](#)]
33. Smit, C.; De Hoogd, S.; Brüggemann, R.J.M.; Knibbe, C.A.J. Obesity and Drug Pharmacology: A Review of the Influence of Obesity on Pharmacokinetic and Pharmacodynamic Parameters. *Expert Opin. Drug Metab. Toxicol.* **2018**, *14*, 275–285. [[CrossRef](#)] [[PubMed](#)]
34. Jamwal, R.; Barlock, B.J. Nonalcoholic Fatty Liver Disease (NAFLD) and Hepatic Cytochrome P450 (CYP) Enzymes. *Pharmaceuticals* **2020**, *13*, 222. [[CrossRef](#)] [[PubMed](#)]

35. Brill, M.J.E.; Diepstraten, J.; Rongen, A.; Kralingen, S.; Anker, J.N.; Knibbe, C.A.J. Impact of Obesity on Drug Metabolism and Elimination in Adults and Children. *Clin. Pharmacokinet.* **2012**, *51*, 277–304. [[CrossRef](#)] [[PubMed](#)]
36. Zuckerman, M.; Greller, H.A.; Babu, K.M. A Review of the Toxicologic Implications of Obesity. *J. Med. Toxicol.* **2015**, *11*, 342–354. [[CrossRef](#)] [[PubMed](#)]
37. Chen, F.; Li, D.-Y.; Zhang, B.; Sun, J.-Y.; Sun, F.; Ji, X.; Qiu, J.-C.; Parker, R.B.; Laizure, S.C.; Xu, J. Alterations of Drug-Metabolizing Enzymes and Transporters under Diabetic Conditions: What Is the Potential Clinical Significance? *Drug Metab. Rev.* **2018**, *50*, 369–397. [[CrossRef](#)] [[PubMed](#)]
38. Ferron, P.-J.; Gicquel, T.; Mégarbane, B.; Clément, B.; Fromenty, B. Treatments in COVID-19 Patients with Pre-Existing Metabolic Dysfunction-Associated Fatty Liver Disease: A Potential Threat for Drug-Induced Liver Injury? *Biochimie* **2020**, *179*, 266–274. [[CrossRef](#)]
39. Le Guillou, D.; Bucher, S.; Begriche, K.; Hoët, D.; Lombès, A.; Labbe, G.; Fromenty, B. Drug-Induced Alterations of Mitochondrial DNA Homeostasis in Steatotic and Nonsteatotic HepaRG Cells. *J. Pharmacol. Exp. Ther.* **2018**, *365*, 711–726. [[CrossRef](#)] [[PubMed](#)]
40. Massart, J.; Begriche, K.; Moreau, C.; Fromenty, B. Role of Nonalcoholic Fatty Liver Disease as Risk Factor for Drug-Induced Hepatotoxicity. *J. Clin. Transl. Res.* **2017**, *3*, 212–232. [[CrossRef](#)] [[PubMed](#)]
41. Abdel-Razzak, Z.; Loyer, P.; Fautrel, A.; Gautier, J.C.; Corcos, L.; Turlin, B.; Beaune, P.; Guillouzo, A. Cytokines Down-Regulate Expression of Major Cytochrome P-450 Enzymes in Adult Human Hepatocytes in Primary Culture. *Mol. Pharmacol.* **1993**, *44*, 707–715.
42. Aninat, C.; Seguin, P.; Descheemaeker, P.-N.; Morel, F.; Malledant, Y.; Guillouzo, A. Catecholamines Induce an Inflammatory Response in Human Hepatocytes. *Crit. Care Med.* **2008**, *36*, 848–854. [[CrossRef](#)] [[PubMed](#)]
43. Aubert, J.; Begriche, K.; Knockaert, L.; Robin, M.A.; Fromenty, B. Increased Expression of Cytochrome P450 2E1 in Nonalcoholic Fatty Liver Disease: Mechanisms and Pathophysiological Role. *Clin. Res. Hepatol. Gastroenterol.* **2011**, *35*, 630–637. [[CrossRef](#)]
44. Michaut, A.; Le Guillou, D.; Moreau, C.; Bucher, S.; McGill, M.R.; Martinais, S.; Gicquel, T.; Morel, I.; Robin, M.-A.; Jaeschke, H.; et al. A Cellular Model to Study Drug-Induced Liver Injury in Nonalcoholic Fatty Liver Disease: Application to Acetaminophen. *Toxicol. Appl. Pharmacol.* **2016**, *292*, 40–55. [[CrossRef](#)]
45. Massart, J.; Begriche, K.; Fromenty, B. Cytochrome P450 2E1 Should Not Be Neglected for Acetaminophen-Induced Liver Injury in Metabolic Diseases with Altered Insulin Levels or Glucose Homeostasis. *Clin. Res. Hepatol. Gastroenterol.* **2021**, *45*, 101470. [[CrossRef](#)]
46. Michaut, A.; Moreau, C.; Robin, M.-A.; Fromenty, B. Acetaminophen-Induced Liver Injury in Obesity and Nonalcoholic Fatty Liver Disease. *Liver Int.* **2014**, *34*, e171–e179. [[CrossRef](#)] [[PubMed](#)]
47. Allard, J.; Le Guillou, D.; Begriche, K.; Fromenty, B. Drug-Induced Liver Injury in Obesity and Nonalcoholic Fatty Liver Disease. In *Advances in Pharmacology*; Elsevier: New York, NY, USA, 2019; Volume 85, pp. 75–107, ISBN 978-0-12-816759-5.
48. Abdelmegeed, M.A.; Ha, S.-K.; Choi, Y.; Akbar, M.; Song, B.-J. Role of CYP2E1 in Mitochondrial Dysfunction and Hepatic Injury by Alcohol and Non-Alcoholic Substances. *Curr. Mol. Pharmacol.* **2017**, *10*, 207–225. [[CrossRef](#)]
49. Seth, R.K.; Das, S.; Dattaroy, D.; Chandrashekar, V.; Alhasson, F.; Michelotti, G.; Nagarkatti, M.; Nagarkatti, P.; Diehl, A.M.; Bell, P.D.; et al. TRPV4 Activation of Endothelial Nitric Oxide Synthase Resists Nonalcoholic Fatty Liver Disease by Blocking CYP2E1-Mediated Redox Toxicity. *Free Radic. Biol. Med.* **2017**, *102*, 260–273. [[CrossRef](#)] [[PubMed](#)]
50. Cho, Y.; Kim, D.; Seo, W.; Gao, B.; Yoo, S.; Song, B. Fructose Promotes Leaky Gut, Endotoxemia, and Liver Fibrosis Through Ethanol-Inducible Cytochrome P450-2E1-Mediated Oxidative and Nitrate Stress. *Hepatology* **2019**, hep.30652. [[CrossRef](#)] [[PubMed](#)]
51. Knockaert, L.; Fromenty, B.; Robin, M.-A. Mechanisms of Mitochondrial Targeting of Cytochrome P450 2E1: Physiopathological Role in Liver Injury and Obesity: Mitochondrial CYP2E1. *FEBS J.* **2011**, *278*, 4252–4260. [[CrossRef](#)]
52. Guengerich, F.P. Cytochrome P450 2E1 and Its Roles in Disease. *Chem. Biol. Interact.* **2020**, *322*, 109056. [[CrossRef](#)]
53. Zeng, T.; Zhang, C.-L.; Song, F.-Y.; Zhao, X.-L.; Xie, K.-Q. CMZ Reversed Chronic Ethanol-Induced Disturbance of PPAR- α Possibly by Suppressing Oxidative Stress and PGC-1 α Acetylation, and Activating the MAPK and GSK3 β Pathway. *PLoS ONE* **2014**, *9*, e98658. [[CrossRef](#)]
54. Mathurin, P. Therapeutic Management of Alcoholic Hepatitis. *Clin. Res. Hepatol. Gastroenterol.* **2015**, *39*, S41–S45. [[CrossRef](#)] [[PubMed](#)]
55. Woods, C.P.; Hazlehurst, J.M.; Tomlinson, J.W. Glucocorticoids and Non-Alcoholic Fatty Liver Disease. *J. Steroid Biochem. Mol. Biol.* **2015**, *154*, 94–103. [[CrossRef](#)] [[PubMed](#)]
56. Gutkowski, K.; Chwist, A.; Hartleb, M. Liver Injury Induced by High-Dose Methylprednisolone Therapy: A Case Report and Brief Review of the Literature. *Hepat. Mon.* **2011**, *11*, 656–661. [[CrossRef](#)] [[PubMed](#)]
57. Rice, J.B.; White, A.G.; Scarpatti, L.M.; Wan, G.; Nelson, W.W. Long-Term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin. Ther.* **2017**, *39*, 2216–2229. [[CrossRef](#)]
58. Phan, K.; Smith, S.D. Topical Corticosteroids and Risk of Diabetes Mellitus: Systematic Review and Meta-Analysis. *J. Dermatol. Treat.* **2019**, 1–5. [[CrossRef](#)]
59. Wang, J.-C.; Gray, N.E.; Kuo, T.; Harris, C.A. Regulation of Triglyceride Metabolism by Glucocorticoid Receptor. *Cell Biosci.* **2012**, *2*, 19. [[CrossRef](#)]
60. Præstholm, S.M.; Correia, C.M.; Grøntved, L. Multifaceted Control of GR Signaling and Its Impact on Hepatic Transcriptional Networks and Metabolism. *Front. Endocrinol.* **2020**, *11*, 572981. [[CrossRef](#)]

61. Wan, J.; Shan, Y.; Song, X.; Chen, S.; Lu, X.; Jin, J.; Su, Q.; Liu, B.; Sun, W.; Li, B. Adipocyte-Derived Periostin Mediates Glucocorticoid-Induced Hepatosteatosis in Mice. *Mol. Metab.* **2020**, *31*, 24–35. [\[CrossRef\]](#)
62. Mendoza-Figueroa, T.; Hernandez, A.; De Lourdes Lopez, M.; Kuri-Harcuch, W. Intracytoplasmic Triglyceride Accumulation Produced by Dexamethasone in Adult Rat Hepatocytes Cultivated on 3T3 Cells. *Toxicology* **1988**, *52*, 273–286. [\[CrossRef\]](#)
63. Harasim-Symbor, E.; Konstantynowicz-Nowicka, K.; Chabowski, A. Additive Effects of Dexamethasone and Palmitate on Hepatic Lipid Accumulation and Secretion. *J. Mol. Endocrinol.* **2016**, *57*, 261–273. [\[CrossRef\]](#)
64. Hu, Y.; Feng, Y.; Zhang, L.; Jia, Y.; Cai, D.; Qian, S.-B.; Du, M.; Zhao, R. GR-Mediated FTO Transactivation Induces Lipid Accumulation in Hepatocytes via Demethylation of M6A on Lipogenic MRNAs. *RNA Biol.* **2020**, *17*, 930–942. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Poggioli, R.; Ueta, C.B.; Drigo, R.A.; Castillo, M.; Fonseca, T.L.; Bianco, A.C. Dexamethasone Reduces Energy Expenditure and Increases Susceptibility to Diet-Induced Obesity in Mice. *Obesity* **2013**, *21*, E415–E420. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Harvey, I.; Stephenson, E.J.; Redd, J.R.; Tran, Q.T.; Hochberg, I.; Qi, N.; Bridges, D. Glucocorticoid-Induced Metabolic Disturbances Are Exacerbated in Obese Male Mice. *Endocrinology* **2018**, *159*, 2275–2287. [\[CrossRef\]](#) [\[PubMed\]](#)
67. D'souza, A.M.; Beaudry, J.L.; Szigiato, A.A.; Trumble, S.J.; Snook, L.A.; Bonen, A.; Giacca, A.; Riddell, M.C. Consumption of a High-Fat Diet Rapidly Exacerbates the Development of Fatty Liver Disease That Occurs with Chronically Elevated Glucocorticoids. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2012**, *302*, G850–G863. [\[CrossRef\]](#)
68. Shpilberg, Y.; Beaudry, J.L.; D'Souza, A.; Campbell, J.E.; Peckett, A.; Riddell, M.C. A Rodent Model of Rapid-Onset Diabetes Induced by Glucocorticoids and High-Fat Feeding. *Dis. Model. Mech.* **2012**, *5*, 671–680. [\[CrossRef\]](#)
69. Lu, Y.; Liu, X.; Jiao, Y.; Xiong, X.; Wang, E.; Wang, X.; Zhang, Z.; Zhang, H.; Pan, L.; Guan, Y.; et al. Periostin Promotes Liver Steatosis and Hypertriglyceridemia through Downregulation of PPAR α . *J. Clin. Investig.* **2014**, *124*, 3501–3513. [\[CrossRef\]](#)
70. Yang, Z.; Zhang, H.; Niu, Y.; Zhang, W.; Zhu, L.; Li, X.; Lu, S.; Fan, J.; Li, X.; Ning, G.; et al. Circulating Periostin in Relation to Insulin Resistance and Nonalcoholic Fatty Liver Disease among Overweight and Obese Subjects. *Sci. Rep.* **2016**, *6*, 37886. [\[CrossRef\]](#)
71. Zhu, J.-Z.; Zhu, H.-T.; Dai, Y.-N.; Li, C.-X.; Fang, Z.-Y.; Zhao, D.-J.; Wan, X.-Y.; Wang, Y.-M.; Wang, F.; Yu, C.-H.; et al. Serum Periostin Is a Potential Biomarker for Non-Alcoholic Fatty Liver Disease: A Case–Control Study. *Endocrine* **2016**, *51*, 91–100. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Ikeda, T. Drug-Induced Idiosyncratic Hepatotoxicity: Prevention Strategy Developed after the Troglitazone Case. *Drug Metab. Pharmacokinet.* **2011**, *26*, 60–70. [\[CrossRef\]](#)
73. Fromenty, B. Inhibition of Mitochondrial Fatty Acid Oxidation in Drug-Induced Hepatic Steatosis. *Liver Res.* **2019**, *3*, 157–169. [\[CrossRef\]](#)
74. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*; National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2012.
75. Musso, G.; Cassader, M.; Paschetta, E.; Gambino, R. Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis: A Meta-Analysis. *JAMA Intern. Med.* **2017**, *177*, 633. [\[CrossRef\]](#)
76. Mahjoubin-Tehran, M.; De Vincentis, A.; Mikhailidis, D.P.; Atkin, S.L.; Mantzoros, C.S.; Jamialahmadi, T.; Sahebkar, A. Non-Alcoholic Fatty Liver Disease and Steatohepatitis: State of the Art on Effective Therapeutics Based on the Gold Standard Method for Diagnosis. *Mol. Metab.* **2020**, 101049. [\[CrossRef\]](#)
77. Ratzl, V.; Charlotte, F.; Bernhardt, C.; Giral, P.; Halbron, M.; LeNaour, G.; Hartmann-Heurtier, A.; Bruckert, E.; Poynard, T.; LIDO Study Group. Long-Term Efficacy of Rosiglitazone in Nonalcoholic Steatohepatitis: Results of the Fatty Liver Improvement by Rosiglitazone Therapy (FLIRT 2) Extension Trial. *Hepatology* **2010**, *51*, 445–453. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Lemoine, M.; Serfaty, L.; Cervera, P.; Capeau, J.; Ratzl, V. Hepatic Molecular Effects of Rosiglitazone in Human Non-Alcoholic Steatohepatitis Suggest Long-Term pro-Inflammatory Damage. *Hepatol. Res. Off. J. Jpn. Soc. Hepatol.* **2014**, *44*, 1241–1247. [\[CrossRef\]](#)
79. Bedoucha, M.; Atzpodien, E.; Boelsterli, U.A. Diabetic KKAY Mice Exhibit Increased Hepatic PPAR γ 1 Gene Expression and Develop Hepatic Steatosis upon Chronic Treatment with Antidiabetic Thiazolidinediones. *J. Hepatol.* **2001**, *35*, 17–23. [\[CrossRef\]](#)
80. Watkins, S.M.; Reifsnyder, P.R.; Pan, H.; German, J.B.; Leiter, E.H. Lipid Metabolome-Wide Effects of the PPAR γ Agonist Rosiglitazone. *J. Lipid Res.* **2002**, *43*, 1809–1817. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Muurling, M.; Hoek, A.M.; Mensink, R.P.; Pijl, H.; Romijn, J.A.; Havekes, L.M.; Voshol, P.J. Overexpression of APOC1 in Obob Mice Leads to Hepatic Steatosis and Severe Hepatic Insulin Resistance. *J. Lipid Res.* **2004**, *45*, 9–16. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Pan, H.-J.; Reifsnyder, P.; Vance, D.E.; Xiao, Q.; Leiter, E.H. Pharmacogenetic Analysis of Rosiglitazone-Induced Hepatosteatosis in New Mouse Models of Type 2 Diabetes. *Diabetes* **2005**, *54*, 1854–1862. [\[CrossRef\]](#) [\[PubMed\]](#)
83. García-Ruiz, I.; Rodríguez-Juan, C.; Díaz-Sanjuán, T.; Martínez, M.Á.; Muñoz-Yagüe, T.; Solís-Herruzo, J.A. Effects of Rosiglitazone on the Liver Histology and Mitochondrial Function in Ob/Ob Mice. *Hepatology* **2007**, *46*, 414–423. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Zhou, M.; Xu, A.; Lam, K.S.L.; Tam, P.K.H.; Che, C.-M.; Chan, L.; Lee, I.-K.; Wu, D.; Wang, Y. Rosiglitazone Promotes Fatty Acyl CoA Accumulation and Excessive Glycogen Storage in Livers of Mice without Adiponectin. *J. Hepatol.* **2010**, *53*, 1108–1116. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Rull, A.; Geeraert, B.; Aragonès, G.; Beltrán-Debón, R.; Rodríguez-Gallego, E.; García-Heredia, A.; Pedro-Botet, J.; Joven, J.; Holvoet, P.; Camps, J. Rosiglitazone and Fenofibrate Exacerbate Liver Steatosis in a Mouse Model of Obesity and Hyperlipidemia. A Transcriptomic and Metabolomic Study. *J. Proteome Res.* **2014**, *13*, 1731–1743. [\[CrossRef\]](#) [\[PubMed\]](#)

86. Gao, M.; Ma, Y.; Alsaggar, M.; Liu, D. Dual Outcomes of Rosiglitazone Treatment on Fatty Liver. *AAPS J.* **2016**, *18*, 1023–1031. [[CrossRef](#)] [[PubMed](#)]
87. Ackerman, Z.; Oron-Herman, M.; Pappo, O.; Peleg, E.; Safadi, R.; Schmilovitz-Weiss, H.; Grozovski, M. Hepatic Effects of Rosiglitazone in Rats with the Metabolic Syndrome. *Basic Clin. Pharmacol. Toxicol.* **2010**, *107*, 663–668. [[CrossRef](#)]
88. Yang, S.J.; Choi, J.M.; Chae, S.W.; Kim, W.J.; Park, S.E.; Rhee, E.J.; Lee, W.Y.; Oh, K.W.; Park, S.W.; Kim, S.W.; et al. Activation of Peroxisome Proliferator-Activated Receptor Gamma by Rosiglitazone Increases Sirt6 Expression and Ameliorates Hepatic Steatosis in Rats. *PLoS ONE* **2011**, *6*, e17057. [[CrossRef](#)] [[PubMed](#)]
89. Wu, H.; Ni, X.; Xu, Q.; Wang, Q.; Li, X.; Hua, J. Regulation of Lipid-induced Macrophage Polarization through Modulating Peroxisome Proliferator-activated Receptor-gamma Activity Affects Hepatic Lipid Metabolism via a Toll-like Receptor 4/NF- κ B Signaling Pathway. *J. Gastroenterol. Hepatol.* **2020**, *35*, 1998–2008. [[CrossRef](#)]
90. Schadinger, S.E.; Bucher, N.L.R.; Schreiber, B.M.; Farmer, S.R. PPAR γ 2 Regulates Lipogenesis and Lipid Accumulation in Steatotic Hepatocytes. *Am. J. Physiol.-Endocrinol. Metab.* **2005**, *288*, E1195–E1205. [[CrossRef](#)]
91. Kulkarni, N.M.; Malampati, S.; Mahat, M.Y.A.; Chandrasekaran, S.; Raghul, J.; Khan, A.A.; Krishnan, U.M.; Narayanan, S. Altered Pharmacokinetics of Rosiglitazone in a Mouse Model of Non-Alcoholic Fatty Liver Disease. *Drug Metab. Pers. Ther.* **2016**, *31*. [[CrossRef](#)]
92. Backman, J.T.; Filppula, A.M.; Niemi, M.; Neuvonen, P.J. Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. *Pharmacol. Rev.* **2016**, *68*, 168–241. [[CrossRef](#)]
93. Puris, E.; Pasanen, M.; Ranta, V.; Gynther, M.; Petsalo, A.; Käkälä, P.; Männistö, V.; Pihlajamäki, J. Laparoscopic Roux-en-Y Gastric Bypass Surgery Influenced Pharmacokinetics of Several Drugs given as a Cocktail with the Highest Impact Observed for CYP1A2, CYP2C8 and CYP2E1 Substrates. *Basic Clin. Pharmacol. Toxicol.* **2019**, bcpt.13234. [[CrossRef](#)]
94. Krogstad, V.; Peric, A.; Robertsen, I.; Kringen, M.K.; Wegler, C.; Angeles, P.C.; Hjelmæsæth, J.; Karlsson, C.; Andersson, S.; Artursson, P.; et al. A Comparative Analysis of Cytochrome P450 Activities in Paired Liver and Small Intestinal Samples from Patients with Obesity. *Drug Metab. Dispos.* **2020**, *48*, 8–17. [[CrossRef](#)] [[PubMed](#)]
95. Hu, D.; Wu, C.; Li, Z.; Liu, Y.; Fan, X.; Wang, Q.; Ding, R. Characterizing the Mechanism of Thiazolidinedione-Induced Hepatotoxicity: An in Vitro Model in Mitochondria. *Toxicol. Appl. Pharmacol.* **2015**, *284*, 134–141. [[CrossRef](#)]
96. Contreras-Baeza, Y.; Ceballo, S.; Arce-Molina, R.; Sandoval, P.Y.; Alegría, K.; Barros, L.F.; San Martín, A. MitoToxy Assay: A Novel Cell-Based Method for the Assessment of Metabolic Toxicity in a Multiwell Plate Format Using a Lactate FRET Nanosensor, Laconic. *PLoS ONE* **2019**, *14*, e0224527. [[CrossRef](#)] [[PubMed](#)]
97. Peng, J.; Huan, Y.; Jiang, Q.; Sun, S.; Jia, C.; Shen, Z. Effects and Potential Mechanisms of Pioglitazone on Lipid Metabolism in Obese Diabetic KKAY Mice. *PPAR Res.* **2014**, *2014*, 1–13. [[CrossRef](#)] [[PubMed](#)]
98. Jia, C.; Huan, Y.; Liu, S.; Hou, S.; Sun, S.; Li, C.; Liu, Q.; Jiang, Q.; Wang, Y.; Shen, Z. Effect of Chronic Pioglitazone Treatment on Hepatic Gene Expression Profile in Obese C57BL/6J Mice. *Int. J. Mol. Sci.* **2015**, *16*, 12213–12229. [[CrossRef](#)] [[PubMed](#)]
99. Orasanu, G.; Ziouzenkova, O.; Devchand, P.R.; Nehra, V.; Hamdy, O.; Horton, E.S.; Plutzky, J. The Peroxisome Proliferator-Activated Receptor- γ Agonist Pioglitazone Represses Inflammation in a Peroxisome Proliferator-Activated Receptor- α -Dependent Manner In Vitro and In Vivo in Mice. *J. Am. Coll. Cardiol.* **2008**, *52*, 869–881. [[CrossRef](#)] [[PubMed](#)]
100. Young, P.W.; Buckle, D.R.; Cantello, B.C.; Chapman, H.; Clapham, J.C.; Coyle, P.J.; Haigh, D.; Hindley, R.M.; Holder, J.C.; Kallender, H.; et al. Identification of High-Affinity Binding Sites for the Insulin Sensitizer Rosiglitazone (BRL-49653) in Rodent and Human Adipocytes Using a Radioiodinated Ligand for Peroxisomal Proliferator-Activated Receptor Gamma. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 751–759. [[PubMed](#)]
101. Sakamoto, J.; Kimura, H.; Moriyama, S.; Odaka, H.; Momose, Y.; Sugiyama, Y.; Sawada, H. Activation of Human Peroxisome Proliferator-Activated Receptor (PPAR) Subtypes by Pioglitazone. *Biochem. Biophys. Res. Commun.* **2000**, *278*, 704–711. [[CrossRef](#)] [[PubMed](#)]
102. Lemoine, M.; Serfaty, L.; Capeau, J. From Nonalcoholic Fatty Liver to Nonalcoholic Steatohepatitis and Cirrhosis in HIV-Infected Patients: Diagnosis and Management. *Curr. Opin. Infect. Dis.* **2012**, *25*, 10–16. [[CrossRef](#)]
103. Shetty, A.; Cho, W.; Alazawi, W.; Syn, W.-K. Methotrexate Hepatotoxicity and the Impact of Nonalcoholic Fatty Liver Disease. *Am. J. Med. Sci.* **2017**, *354*, 172–181. [[CrossRef](#)] [[PubMed](#)]
104. Adams, L.A.; Zein, C.O.; Angulo, P.; Lindor, K.D. A Pilot Trial of Pentoxifylline in Nonalcoholic Steatohepatitis. *Am. J. Gastroenterol.* **2004**, *99*, 2365–2368. [[CrossRef](#)]
105. Massart, J.; Robin, M.A.; Noury, F.; Fautrel, A.; Lettéron, P.; Bado, A.; Eliat, P.A.; Fromenty, B. Pentoxifylline Aggravates Fatty Liver in Obese and Diabetic Ob/Ob Mice by Increasing Intestinal Glucose Absorption and Activating Hepatic Lipogenesis. *Br. J. Pharmacol.* **2012**, *165*, 1361–1374. [[CrossRef](#)] [[PubMed](#)]
106. Zannikos, P.N.; Bandyopadhyay, A.M.; Robertson, L.W.; Blouin, R.A. Effect of Nutritional Obesity on the Induction of CYP2B Enzymes Following Phenobarbital Treatment. *Drug Metab. Dispos. Biol. Fate Chem.* **1993**, *21*, 782–787. [[PubMed](#)]
107. Ito, M.; Suzuki, J.; Sasaki, M.; Watanabe, K.; Tsujioka, S.; Takahashi, Y.; Gomori, A.; Hirose, H.; Ishihara, A.; Iwaasa, H. Development of Nonalcoholic Steatohepatitis Model through Combination of High-Fat Diet and Tetracycline with Morbid Obesity in Mice. *Hepatol. Res.* **2006**, *34*, 92–98. [[CrossRef](#)] [[PubMed](#)]
108. Vogel, S.A. The Politics of Plastics: The Making and Unmaking of Bisphenol a “Safety”. *Am. J. Public Health* **2009**, *99* Suppl 3, S559–S566. [[CrossRef](#)]

109. Oppeneer, S.J.; Robien, K. Bisphenol A Exposure and Associations with Obesity among Adults: A Critical Review. *Public Health Nutr.* **2015**, *18*, 1847–1863. [\[CrossRef\]](#)
110. Ma, Y.; Liu, H.; Wu, J.; Yuan, L.; Wang, Y.; Du, X.; Wang, R.; Marwa, P.W.; Petlulu, P.; Chen, X.; et al. The Adverse Health Effects of Bisphenol A and Related Toxicity Mechanisms. *Environ. Res.* **2019**, *176*, 108575. [\[CrossRef\]](#) [\[PubMed\]](#)
111. Legler, J.; Zalko, D.; Jourdan, F.; Jacobs, M.; Fromenty, B.; Balaguer, P.; Bourguet, W.; Munic Kos, V.; Nadal, A.; Beausoleil, C.; et al. The GOLIATH Project: Towards an Internationally Harmonised Approach for Testing Metabolism Disrupting Compounds. *Int. J. Mol. Sci.* **2020**, *21*, 3480. [\[CrossRef\]](#)
112. Legeay, S.; Faure, S. Is Bisphenol A an Environmental Obesogen? *Fundam. Clin. Pharmacol.* **2017**. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Le Magueresse-Battistoni, B.; Multigner, L.; Beausoleil, C.; Rousselle, C. Effects of Bisphenol A on Metabolism and Evidences of a Mode of Action Mediated through Endocrine Disruption. *Mol. Cell. Endocrinol.* **2018**, *475*, 74–91. [\[CrossRef\]](#)
114. Cimmino, I.; Fiory, F.; Perruolo, G.; Miele, C.; Beguinot, F.; Formisano, P.; Oriente, F. Potential Mechanisms of Bisphenol A (BPA) Contributing to Human Disease. *Int. J. Mol. Sci.* **2020**, *21*, 5761. [\[CrossRef\]](#)
115. Shimpi, P.C.; More, V.R.; Paranjpe, M.; Donepudi, A.C.; Goodrich, J.M.; Dolinoy, D.C.; Rubin, B.; Slitt, A.L. Hepatic Lipid Accumulation and Nrf2 Expression Following Perinatal and Peripubertal Exposure to Bisphenol A in a Mouse Model of Nonalcoholic Liver Disease. *Environ. Health Perspect.* **2017**, *125*, 087005. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Li, Q.; Zhang, H.; Zou, J.; Mai, H.; Su, D.; Feng, X.; Feng, D. Bisphenol A Exposure Induces Cholesterol Synthesis and Hepatic Steatosis in C57BL/6 Mice by down-Regulating the DNA Methylation Levels of SREBP-2. *Food Chem. Toxicol.* **2019**, *133*, 110786. [\[CrossRef\]](#) [\[PubMed\]](#)
117. Dallio, M.; Diano, N.; Masarone, M.; Gravina, A.G.; Patanè, V.; Romeo, M.; Di Sarno, R.; Errico, S.; Nicolucci, C.; Abenavoli, L.; et al. Chemical Effect of Bisphenol A on Non-Alcoholic Fatty Liver Disease. *Int. J. Environ. Res. Public Health* **2019**, *16*, 3134. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Feng, D.; Zhang, H.; Jiang, X.; Zou, J.; Li, Q.; Mai, H.; Su, D.; Ling, W.; Feng, X. Bisphenol A Exposure Induces Gut Microbiota Dysbiosis and Consequent Activation of Gut-Liver Axis Leading to Hepatic Steatosis in CD-1 Mice. *Environ. Pollut.* **2020**, *265*, 114880. [\[CrossRef\]](#)
119. Franco, M.E.; Fernandez-Luna, M.T.; Ramirez, A.J.; Lavado, R. Metabolomic-Based Assessment Reveals Dysregulation of Lipid Profiles in Human Liver Cells Exposed to Environmental Obesogens. *Toxicol. Appl. Pharmacol.* **2020**, *398*, 115009. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Huc, L.; Lemarié, A.; Guéraud, F.; Héliers-Toussaint, C. Low Concentrations of Bisphenol A Induce Lipid Accumulation Mediated by the Production of Reactive Oxygen Species in the Mitochondria of HepG2 Cells. *Toxicol. In Vitro* **2012**, *26*, 709–717. [\[CrossRef\]](#)
121. Peyre, L.; Rouimi, P.; Sousa, G.; Héliers-Toussaint, C.; Carré, B.; Barcellini, S.; Chagnon, M.-C.; Rahmani, R. Comparative Study of Bisphenol A and Its Analogue Bisphenol S on Human Hepatic Cells: A Focus on Their Potential Involvement in Nonalcoholic Fatty Liver Disease. *Food Chem. Toxicol.* **2014**, *70*, 9–18. [\[CrossRef\]](#)
122. Martella, A.; Silvestri, C.; Maradonna, F.; Gioacchini, G.; Allarà, M.; Radaelli, G.; Overby, D.R.; Di Marzo, V.; Carnevali, O. Bisphenol A Induces Fatty Liver by an Endocannabinoid-Mediated Positive Feedback Loop. *Endocrinology* **2016**, *157*, 1751–1763. [\[CrossRef\]](#)
123. Bucher, S.; Jalili, P.; Le Guillou, D.; Begriche, K.; Rondel, K.; Martinais, S.; Zalko, D.; Corlu, A.; Robin, M.-A.; Fromenty, B. Bisphenol a Induces Steatosis in HepaRG Cells Using a Model of Perinatal Exposure. *Environ. Toxicol.* **2017**, *32*, 1024–1036. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Lin, Y.; Ding, D.; Huang, Q.; Liu, Q.; Lu, H.; Lu, Y.; Chi, Y.; Sun, X.; Ye, G.; Zhu, H.; et al. Downregulation of MiR-192 Causes Hepatic Steatosis and Lipid Accumulation by Inducing SREBF1: Novel Mechanism for Bisphenol A-Triggered Non-Alcoholic Fatty Liver Disease. *Biochim. Biophys. Acta BBA—Mol. Cell Biol. Lipids* **2017**, *1862*, 869–882. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Li, Q.; Zhang, H.; Zou, J.; Feng, X.; Feng, D. Bisphenol A Induces Cholesterol Biosynthesis in HepG2 Cells via SREBP-2/HMGCR Signaling Pathway. *J. Toxicol. Sci.* **2019**, *44*, 481–491. [\[CrossRef\]](#)
126. Liu, Q.; Shao, W.; Weng, Z.; Zhang, X.; Ding, G.; Xu, C.; Xu, J.; Jiang, Z.; Gu, A. In Vitro Evaluation of the Hepatic Lipid Accumulation of Bisphenol Analogs: A High-Content Screening Assay. *Toxicol. Vitro Int. J. Publ. Assoc. BIBRA* **2020**, *68*, 104959. [\[CrossRef\]](#) [\[PubMed\]](#)
127. Figueiredo, L.S.; Oliveira, K.M.; Freitas, I.N.; Silva, J.A.; Silva, J.N.; Favero-Santos, B.C.; Bonfleur, M.L.; Carneiro, E.M.; Ribeiro, R.A. Bisphenol-A Exposure Worsens Hepatic Steatosis in Ovariectomized Mice Fed on a High-Fat Diet: Role of Endoplasmic Reticulum Stress and Fibrogenic Pathways. *Life Sci.* **2020**, *256*, 118012. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Moon, M.K.; Jeong, I.-K.; Jung Oh, T.; Ahn, H.Y.; Kim, H.H.; Park, Y.J.; Jang, H.C.; Park, K.S. Long-Term Oral Exposure to Bisphenol A Induces Glucose Intolerance and Insulin Resistance. *J. Endocrinol.* **2015**, *226*, 35–42. [\[CrossRef\]](#) [\[PubMed\]](#)
129. Ma, Q.; Deng, P.; Lin, M.; Yang, L.; Li, L.; Guo, L.; Zhang, L.; He, M.; Lu, Y.; Pi, H.; et al. Long-Term Bisphenol A Exposure Exacerbates Diet-Induced Prediabetes via TLR4-Dependent Hypothalamic Inflammation. *J. Hazard. Mater.* **2021**, *402*, 123926. [\[CrossRef\]](#) [\[PubMed\]](#)
130. Strakovsky, R.S.; Wang, H.; Engeseth, N.J.; Flaws, J.A.; Helferich, W.G.; Pan, Y.-X.; Lezmi, S. Developmental Bisphenol A (BPA) Exposure Leads to Sex-Specific Modification of Hepatic Gene Expression and Epigenome at Birth That May Exacerbate High-Fat Diet-Induced Hepatic Steatosis. *Toxicol. Appl. Pharmacol.* **2015**, *284*, 101–112. [\[CrossRef\]](#)
131. Yalcin, E.B.; Kulkarni, S.R.; Slitt, A.L.; King, R. Bisphenol A Sulfonation Is Impaired in Metabolic and Liver Disease. *Toxicol. Appl. Pharmacol.* **2016**, *292*, 75–84. [\[CrossRef\]](#)

132. Quesnot, N.; Bucher, S.; Fromenty, B.; Robin, M.-A. Modulation of Metabolizing Enzymes by Bisphenol a in Human and Animal Models. *Chem. Res. Toxicol.* **2014**, *27*, 1463–1473. [[CrossRef](#)] [[PubMed](#)]
133. Sinclair, G.M.; Long, S.M.; Jones, O.A.H. What Are the Effects of PFAS Exposure at Environmentally Relevant Concentrations? *Chemosphere* **2020**, *258*, 127340. [[CrossRef](#)]
134. Vieira, V.M.; Hoffman, K.; Shin, H.-M.; Weinberg, J.M.; Webster, T.F.; Fletcher, T. Perfluorooctanoic Acid Exposure and Cancer Outcomes in a Contaminated Community: A Geographic Analysis. *Environ. Health Perspect.* **2013**, *121*, 318–323. [[CrossRef](#)] [[PubMed](#)]
135. Steenland, K.; Fletcher, T.; Stein, C.R.; Bartell, S.M.; Darrow, L.; Lopez-Espinosa, M.-J.; Barry Ryan, P.; Savitz, D.A. Review: Evolution of Evidence on PFOA and Health Following the Assessments of the C8 Science Panel. *Environ. Int.* **2020**, *145*, 106125. [[CrossRef](#)]
136. Steenland, K.; Woskie, S. Cohort Mortality Study of Workers Exposed to Perfluorooctanoic Acid. *Am. J. Epidemiol.* **2012**, *176*, 909–917. [[CrossRef](#)]
137. Mancini, F.R.; Rajaobelina, K.; Praud, D.; Dow, C.; Antignac, J.P.; Kvaskoff, M.; Severi, G.; Bonnet, F.; Boutron-Ruault, M.-C.; Fagherazzi, G. Nonlinear Associations between Dietary Exposures to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS) and Type 2 Diabetes Risk in Women: Findings from the E3N Cohort Study. *Int. J. Hyg. Environ. Health* **2018**, *221*, 1054–1060. [[CrossRef](#)]
138. Sun, Q.; Zong, G.; Valvi, D.; Nielsen, F.; Coull, B.; Grandjean, P. Plasma Concentrations of Perfluoroalkyl Substances and Risk of Type 2 Diabetes: A Prospective Investigation among U.S. Women. *Environ. Health Perspect.* **2018**, *126*, 037001. [[CrossRef](#)]
139. Liu, P.; Yang, F.; Wang, Y.; Yuan, Z. Perfluorooctanoic Acid (PFOA) Exposure in Early Life Increases Risk of Childhood Adiposity: A Meta-Analysis of Prospective Cohort Studies. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2070. [[CrossRef](#)]
140. Braun, J.M.; Eliot, M.; Papandonatos, G.D.; Buckley, J.P.; Cecil, K.M.; Kalkwarf, H.J.; Chen, A.; Eaton, C.B.; Kelsey, K.; Lanphear, B.P.; et al. Gestational Perfluoroalkyl Substance Exposure and Body Mass Index Trajectories over the First 12 Years of Life. *Int. J. Obes.* **2021**, *45*, 25–35. [[CrossRef](#)] [[PubMed](#)]
141. Rappazzo, K.M.; Coffman, E.; Hines, E.P. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature. *Int. J. Environ. Res. Public Health* **2017**, *14*, 691. [[CrossRef](#)] [[PubMed](#)]
142. Fenton, S.E.; Ducatman, A.; Boobis, A.; DeWitt, J.C.; Lau, C.; Ng, C.; Smith, J.S.; Roberts, S.M. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. *Environ. Toxicol. Chem.* **2021**, *40*, 606–630. [[CrossRef](#)]
143. Geiger, S.D.; Xiao, J.; Ducatman, A.; Frisbee, S.; Innes, K.; Shankar, A. The Association between PFOA, PFOS and Serum Lipid Levels in Adolescents. *Chemosphere* **2014**, *98*, 78–83. [[CrossRef](#)] [[PubMed](#)]
144. Convertino, M.; Church, T.R.; Olsen, G.W.; Liu, Y.; Doyle, E.; Elcombe, C.R.; Barnett, A.L.; Samuel, L.M.; MacPherson, I.R.; Evans, T.R.J. Stochastic Pharmacokinetic-Pharmacodynamic Modeling for Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). *Toxicol. Sci. Off. J. Soc. Toxicol.* **2018**, *163*, 293–306. [[CrossRef](#)] [[PubMed](#)]
145. Darrow, L.A.; Groth, A.C.; Winquist, A.; Shin, H.-M.; Bartell, S.M.; Steenland, K. Modeled Perfluorooctanoic Acid (PFOA) Exposure and Liver Function in a Mid-Ohio Valley Community. *Environ. Health Perspect.* **2016**, *124*, 1227–1233. [[CrossRef](#)]
146. Lin, C.-Y.; Lin, L.-Y.; Chiang, C.-K.; Wang, W.-J.; Su, Y.-N.; Hung, K.-Y.; Chen, P.-C. Investigation of the Associations between Low-Dose Serum Perfluorinated Chemicals and Liver Enzymes in US Adults. *Am. J. Gastroenterol.* **2010**, *105*, 1354–1363. [[CrossRef](#)] [[PubMed](#)]
147. Jain, R.B.; Ducatman, A. Selective Associations of Recent Low Concentrations of Perfluoroalkyl Substances With Liver Function Biomarkers: NHANES 2011 to 2014 Data on US Adults Aged ≥ 20 Years. *J. Occup. Environ. Med.* **2019**, *61*, 293–302. [[CrossRef](#)] [[PubMed](#)]
148. Jin, R.; McConnell, R.; Catherine, C.; Xu, S.; Walker, D.I.; Stratakis, N.; Jones, D.P.; Miller, G.W.; Peng, C.; Conti, D.V.; et al. Perfluoroalkyl Substances and Severity of Nonalcoholic Fatty Liver in Children: An Untargeted Metabolomics Approach. *Environ. Int.* **2020**, *134*, 105220. [[CrossRef](#)] [[PubMed](#)]
149. Kudo, N.; Kawashima, Y. Fish Oil-Feeding Prevents Perfluorooctanoic Acid-Induced Fatty Liver in Mice. *Toxicol. Appl. Pharmacol.* **1997**, *145*, 285–293. [[CrossRef](#)] [[PubMed](#)]
150. Yan, S.; Wang, J.; Dai, J. Activation of Sterol Regulatory Element-Binding Proteins in Mice Exposed to Perfluorooctanoic Acid for 28 Days. *Arch. Toxicol.* **2015**, *89*, 1569–1578. [[CrossRef](#)]
151. Das, K.P.; Wood, C.R.; Lin, M.T.; Starkov, A.A.; Lau, C.; Wallace, K.B.; Corton, J.C.; Abbott, B.D. Perfluoroalkyl Acids-Induced Liver Steatosis: Effects on Genes Controlling Lipid Homeostasis. *Toxicology* **2017**, *378*, 37–52. [[CrossRef](#)] [[PubMed](#)]
152. Armstrong, L.E.; Guo, G.L. Understanding Environmental Contaminants' Direct Effects on Non-Alcoholic Fatty Liver Disease Progression. *Curr. Environ. Health Rep.* **2019**, *6*, 95–104. [[CrossRef](#)] [[PubMed](#)]
153. Weng, Z.; Xu, C.; Zhang, X.; Pang, L.; Xu, J.; Liu, Q.; Zhang, L.; Xu, S.; Gu, A. Autophagy Mediates Perfluorooctanoic Acid-Induced Lipid Metabolism Disorder and NLRP3 Inflammasome Activation in Hepatocytes. *Environ. Pollut. Barking Essex 1987* **2020**, *267*, 115655. [[CrossRef](#)]
154. Li, X.; Wang, Z.; Klaunig, J.E. The Effects of Perfluorooctanoate on High Fat Diet Induced Non-Alcoholic Fatty Liver Disease in Mice. *Toxicology* **2019**, *416*, 1–14. [[CrossRef](#)]
155. Wang, L.; Wang, Y.; Liang, Y.; Li, J.; Liu, Y.; Zhang, J.; Zhang, A.; Fu, J.; Jiang, G. Specific Accumulation of Lipid Droplets in Hepatocyte Nuclei of PFOA-Exposed BALB/c Mice. *Sci. Rep.* **2013**, *3*, 2174. [[CrossRef](#)]

156. Barbosa, A.D.; Siniossoglou, S. New Kid on the Block: Lipid Droplets in the Nucleus. *FEBS J.* **2020**, *287*, 4838–4843. [[CrossRef](#)] [[PubMed](#)]
157. Yan, S.; Zhang, H.; Wang, J.; Zheng, F.; Dai, J. Perfluorooctanoic Acid Exposure Induces Endoplasmic Reticulum Stress in the Liver and Its Effects Are Ameliorated by 4-Phenylbutyrate. *Free Radic. Biol. Med.* **2015**, *87*, 300–311. [[CrossRef](#)]
158. Louisse, J.; Rijkers, D.; Stoop, G.; Janssen, A.; Staats, M.; Hoogenboom, R.; Kersten, S.; Peijnenburg, A. Perfluorooctanoic Acid (PFOA), Perfluorooctane Sulfonic Acid (PFOS), and Perfluorononanoic Acid (PFNA) Increase Triglyceride Levels and Decrease Cholesterogenic Gene Expression in Human HepaRG Liver Cells. *Arch. Toxicol.* **2020**, *94*, 3137–3155. [[CrossRef](#)]
159. Foulds, C.E.; Treviño, L.S.; York, B.; Walker, C.L. Endocrine-Disrupting Chemicals and Fatty Liver Disease. *Nat. Rev. Endocrinol.* **2017**, *13*, 445–457. [[CrossRef](#)] [[PubMed](#)]
160. Kim, J.B.; Wright, H.M.; Wright, M.; Spiegelman, B.M. ADD1/SREBP1 Activates PPARgamma through the Production of Endogenous Ligand. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 4333–4337. [[CrossRef](#)]
161. Zhang, Y.-M.; Dong, X.-Y.; Fan, L.-J.; Zhang, Z.-L.; Wang, Q.; Jiang, N.; Yang, X.-S. Poly- and Perfluorinated Compounds Activate Human Pregnane X Receptor. *Toxicology* **2017**, *380*, 23–29. [[CrossRef](#)]
162. Bjork, J.A.; Butenhoff, J.L.; Wallace, K.B. Multiplicity of Nuclear Receptor Activation by PFOA and PFOS in Primary Human and Rodent Hepatocytes. *Toxicology* **2011**, *288*, 8–17. [[CrossRef](#)] [[PubMed](#)]
163. Behr, A.-C.; Plinsch, C.; Braeuning, A.; Buhrke, T. Activation of Human Nuclear Receptors by Perfluoroalkylated Substances (PFAS). *Toxicol. Vitro Int. J. Publ. Assoc. BIBRA* **2020**, *62*, 104700. [[CrossRef](#)] [[PubMed](#)]
164. Cave, M.C.; Clair, H.B.; Hardesty, J.E.; Falkner, K.C.; Feng, W.; Clark, B.J.; Sidey, J.; Shi, H.; Aqel, B.A.; McClain, C.J.; et al. Nuclear Receptors and Nonalcoholic Fatty Liver Disease. *Biochim. Biophys. Acta* **2016**, *1859*, 1083–1099. [[CrossRef](#)] [[PubMed](#)]
165. Staudinger, J.L. Clinical Applications of Small Molecule Inhibitors of Pregnane X Receptor. *Mol. Cell. Endocrinol.* **2019**, *485*, 61–71. [[CrossRef](#)] [[PubMed](#)]
166. Scharmach, E.; Buhrke, T.; Lichtenstein, D.; Lampen, A. Perfluorooctanoic Acid Affects the Activity of the Hepatocyte Nuclear Factor 4 Alpha (HNF4α). *Toxicol. Lett.* **2012**, *212*, 106–112. [[CrossRef](#)]
167. Xu, Y.; Zhu, Y.; Hu, S.; Xu, Y.; Stroup, D.; Pan, X.; Bawa, F.C.; Chen, S.; Gopaju, R.; Yin, L.; et al. Hepatocyte Nuclear Factor 4α Prevents the Steatosis-to-NASH Progression by Regulating P53 and Bile Acid Signaling. *Hepatol. Baltim. Md* **2020**. [[CrossRef](#)] [[PubMed](#)]
168. Tan, X.; Xie, G.; Sun, X.; Li, Q.; Zhong, W.; Qiao, P.; Sun, X.; Jia, W.; Zhou, Z. High Fat Diet Feeding Exaggerates Perfluorooctanoic Acid-Induced Liver Injury in Mice via Modulating Multiple Metabolic Pathways. *PLoS ONE* **2013**, *8*, e61409. [[CrossRef](#)]
169. Shabalina, I.G.; Kramarova, T.V.; Mattsson, C.L.; Petrovic, N.; Rahman Qazi, M.; Csikasz, R.L.; Chang, S.-C.; Butenhoff, J.; DePierre, J.W.; Cannon, B.; et al. The Environmental Pollutants Perfluorooctane Sulfonate and Perfluorooctanoic Acid Upregulate Uncoupling Protein 1 (UCP1) in Brown-Fat Mitochondria Through a UCP1-Dependent Reduction in Food Intake. *Toxicol. Sci. Off. J. Soc. Toxicol.* **2015**, *146*, 334–343. [[CrossRef](#)]
170. White, S.S.; Fenton, S.E.; Hines, E.P. Endocrine Disrupting Properties of Perfluorooctanoic Acid. *J. Steroid Biochem. Mol. Biol.* **2011**, *127*, 16–26. [[CrossRef](#)] [[PubMed](#)]
171. Schlezinger, J.J.; Puckett, H.; Oliver, J.; Nielsen, G.; Heiger-Bernays, W.; Webster, T.F. Perfluorooctanoic Acid Activates Multiple Nuclear Receptor Pathways and Skews Expression of Genes Regulating Cholesterol Homeostasis in Liver of Humanized PPARα Mice Fed an American Diet. *Toxicol. Appl. Pharmacol.* **2020**, *405*, 115204. [[CrossRef](#)]
172. Bougarne, N.; Weyers, B.; Desmet, S.J.; Deckers, J.; Ray, D.W.; Staels, B.; De Bosscher, K. Molecular Actions of PPARα in Lipid Metabolism and Inflammation. *Endocr. Rev.* **2018**, *39*, 760–802. [[CrossRef](#)]
173. Filgo, A.J.; Quist, E.M.; Hoenerhoff, M.J.; Brix, A.E.; Kissling, G.E.; Fenton, S.E. Perfluorooctanoic Acid (PFOA)-Induced Liver Lesions in Two Strains of Mice Following Developmental Exposures: PPARα Is Not Required. *Toxicol. Pathol.* **2015**, *43*, 558–568. [[CrossRef](#)] [[PubMed](#)]
174. Rebholz, S.L.; Jones, T.; Herrick, R.L.; Xie, C.; Calafat, A.M.; Pinney, S.M.; Woollett, L.A. Hypercholesterolemia with Consumption of PFOA-Laced Western Diets Is Dependent on Strain and Sex of Mice. *Toxicol. Rep.* **2016**, *3*, 46–54. [[CrossRef](#)]
175. Huck, I.; Beggs, K.; Apte, U. Paradoxical Protective Effect of Perfluorooctanesulfonic Acid Against High-Fat Diet-Induced Hepatic Steatosis in Mice. *Int. J. Toxicol.* **2018**, *37*, 383–392. [[CrossRef](#)]
176. Bucher, S.; Le Guillou, D.; Allard, J.; Pinon, G.; Begriche, K.; Tête, A.; Sergent, O.; Lagadic-Gossmann, D.; Fromenty, B. Possible Involvement of Mitochondrial Dysfunction and Oxidative Stress in a Cellular Model of NAFLD Progression Induced by Benzo[a]Pyrene/Ethanol CoExposure. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 4396403. [[CrossRef](#)] [[PubMed](#)]
177. Tomaru, M.; Takano, H.; Inoue, K.-I.; Yanagisawa, R.; Osakabe, N.; Yasuda, A.; Shimada, A.; Kato, Y.; Uematsu, H. Pulmonary Exposure to Diesel Exhaust Particles Enhances Fatty Change of the Liver in Obese Diabetic Mice. *Int. J. Mol. Med.* **2007**, *19*, 17–22. [[CrossRef](#)]
178. Yanagisawa, R.; Koike, E.; Win-Shwe, T.-T.; Yamamoto, M.; Takano, H. Impaired Lipid and Glucose Homeostasis in Hexabromocyclododecane-Exposed Mice Fed a High-Fat Diet. *Environ. Health Perspect.* **2014**, *122*, 277–283. [[CrossRef](#)] [[PubMed](#)]
179. Cichocki, J.A.; Furuya, S.; Luo, Y.-S.; Iwata, Y.; Konganti, K.; Chiu, W.A.; Threadgill, D.W.; Pogribny, I.P.; Rusyn, I. Nonalcoholic Fatty Liver Disease Is a Susceptibility Factor for Perchloroethylene-Induced Liver Effects in Mice. *Toxicol. Sci. Off. J. Soc. Toxicol.* **2017**, *159*, 481. [[CrossRef](#)] [[PubMed](#)]

180. Duval, C.; Teixeira-Clerc, F.; Leblanc, A.F.; Touch, S.; Emond, C.; Guerre-Millo, M.; Lotersztajn, S.; Barouki, R.; Aggerbeck, M.; Coumoul, X. Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL/6J Diet-Induced Obesity Mouse Model. *Environ. Health Perspect.* **2017**, *125*, 428–436. [\[CrossRef\]](#)
181. Yu, J.; Yang, X.; Yang, X.; Yang, M.; Wang, P.; Yang, Y.; Yang, J.; Li, W.; Xu, J. Nonylphenol Aggravates Non-Alcoholic Fatty Liver Disease in High Sucrose-High Fat Diet-Treated Rats. *Sci. Rep.* **2018**, *8*, 3232. [\[CrossRef\]](#) [\[PubMed\]](#)
182. Yang, C.; Zhu, L.; Kang, Q.; Lee, H.K.; Li, D.; Chung, A.C.K.; Cai, Z. Chronic Exposure to Tetrabromodiphenyl Ether (BDE-47) Aggravates Hepatic Steatosis and Liver Fibrosis in Diet-Induced Obese Mice. *J. Hazard. Mater.* **2019**, *378*, 120766. [\[CrossRef\]](#)
183. Malik, F.; Wickremesinghe, P.; Saverimuttu, J. Case Report and Literature Review of Auto-Brewery Syndrome: Probably an Underdiagnosed Medical Condition. *BMJ Open Gastroenterol.* **2019**, *6*, e000325. [\[CrossRef\]](#)
184. Seitz, H.K.; Bataller, R.; Cortez-Pinto, H.; Gao, B.; Gual, A.; Lackner, C.; Mathurin, P.; Mueller, S.; Szabo, G.; Tsukamoto, H. Alcoholic Liver Disease. *Nat. Rev. Dis. Primer* **2018**, *4*, 16. [\[CrossRef\]](#)
185. Avila, M.A.; Dufour, J.-F.; Gerbes, A.L.; Zoulim, F.; Bataller, R.; Burra, P.; Cortez-Pinto, H.; Gao, B.; Gilmore, I.; Mathurin, P.; et al. Recent Advances in Alcohol-Related Liver Disease (ALD): Summary of a Gut Round Table Meeting. *Gut* **2020**, *69*, 764–780. [\[CrossRef\]](#)
186. Teschke, R. Alcoholic Liver Disease: Alcohol Metabolism, Cascade of Molecular Mechanisms, Cellular Targets, and Clinical Aspects. *Biomedicines* **2018**, *6*, 106. [\[CrossRef\]](#)
187. Begrich, K.; Massart, J.; Fromenty, B. Chapter 15—Mitochondrial Dysfunction Induced by Xenobiotics: Involvement in Steatosis and Steatohepatitis. In *Mitochondria in Obesity and Type 2 Diabetes*; Morio, B., Pénicaud, L., Rigoulet, M., Eds.; Academic Press: New York, NY, USA, 2019; pp. 347–364. ISBN 978-0-12-811752-1.
188. Kourkoumpetis, T.; Sood, G. Pathogenesis of Alcoholic Liver Disease: An Update. *Clin. Liver Dis.* **2019**, *23*, 71–80. [\[CrossRef\]](#)
189. Yan, S.; Khambu, B.; Hong, H.; Liu, G.; Huda, N.; Yin, X.-M. Autophagy, Metabolism, and Alcohol-Related Liver Disease: Novel Modulators and Functions. *Int. J. Mol. Sci.* **2019**, *20*, 5029. [\[CrossRef\]](#) [\[PubMed\]](#)
190. Kirpich, I.A.; Warner, D.R.; Feng, W.; Joshi-Barve, S.; McClain, C.J.; Seth, D.; Zhong, W.; Zhou, Z.; Osna, N.A.; Kharbanda, K.K. Mechanisms, Biomarkers and Targets for Therapy in Alcohol-Associated Liver Injury: From Genetics to Nutrition: Summary of the ISBRA 2018 Symposium. *Alcohol Fayettev. N* **2020**, *83*, 105–114. [\[CrossRef\]](#) [\[PubMed\]](#)
191. Seitz, H.K. The Role of Cytochrome P4502E1 in the Pathogenesis of Alcoholic Liver Disease and Carcinogenesis. *Chem. Biol. Interact.* **2020**, *316*, 108918. [\[CrossRef\]](#)
192. Mahli, A.; Hellerbrand, C. Alcohol and Obesity: A Dangerous Association for Fatty Liver Disease. *Dig. Dis. Basel Switz.* **2016**, *34 Suppl 1*, 32–39. [\[CrossRef\]](#)
193. Boyle, M.; Masson, S.; Anstee, Q.M. The Bidirectional Impacts of Alcohol Consumption and the Metabolic Syndrome: Cofactors for Progressive Fatty Liver Disease. *J. Hepatol.* **2018**, *68*, 251–267. [\[CrossRef\]](#) [\[PubMed\]](#)
194. Åberg, F.; Färkkilä, M. Drinking and Obesity: Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Interactions. *Semin. Liver Dis.* **2020**, *40*, 154–162. [\[CrossRef\]](#)
195. Hwang, S.; Ren, T.; Gao, B. Obesity and Binge Alcohol Intake Are Deadly Combination to Induce Steatohepatitis: A Model of High-Fat Diet and Binge Ethanol Intake. *Clin. Mol. Hepatol.* **2020**, *26*, 586–594. [\[CrossRef\]](#) [\[PubMed\]](#)
196. Xu, J.; Lai, K.K.Y.; Verlinsky, A.; Lugea, A.; French, S.W.; Cooper, M.P.; Ji, C.; Tsukamoto, H. Synergistic Steatohepatitis by Moderate Obesity and Alcohol in Mice despite Increased Adiponectin and P-AMPK. *J. Hepatol.* **2011**, *55*, 673–682. [\[CrossRef\]](#) [\[PubMed\]](#)
197. Gyamfi, D.; Everitt, H.E.; Tewfik, I.; Clemens, D.L.; Patel, V.B. Hepatic Mitochondrial Dysfunction Induced by Fatty Acids and Ethanol. *Free Radic. Biol. Med.* **2012**, *53*, 2131–2145. [\[CrossRef\]](#)
198. Grasselli, E.; Voci, A.; Demori, I.; De Matteis, R.; Compalati, A.D.; Gallo, G.; Vergani, L. Effects of Binge Ethanol on Lipid Homeostasis and Oxidative Stress in a Rat Model of Nonalcoholic Fatty Liver Disease. *J. Physiol. Biochem.* **2014**, *70*, 341–353. [\[CrossRef\]](#) [\[PubMed\]](#)
199. Everitt, H.; Hu, M.; Ajmo, J.M.; Rogers, C.Q.; Liang, X.; Zhang, R.; Yin, H.; Choi, A.; Bennett, E.S.; You, M. Ethanol Administration Exacerbates the Abnormalities in Hepatic Lipid Oxidation in Genetically Obese Mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2013**, *304*, G38–G47. [\[CrossRef\]](#)
200. Minato, T.; Tsutsumi, M.; Tsuchishima, M.; Hayashi, N.; Saito, T.; Matsue, Y.; Toshikuni, N.; Arisawa, T.; George, J. Binge Alcohol Consumption Aggravates Oxidative Stress and Promotes Pathogenesis of NASH from Obesity-Induced Simple Steatosis. *Mol. Med. Camb. Mass* **2014**, *20*, 490–502. [\[CrossRef\]](#) [\[PubMed\]](#)
201. Mahli, A.; Thasler, W.E.; Patsenker, E.; Müller, S.; Stickel, F.; Müller, M.; Seitz, H.K.; Cederbaum, A.I.; Hellerbrand, C. Identification of Cytochrome CYP2E1 as Critical Mediator of Synergistic Effects of Alcohol and Cellular Lipid Accumulation in Hepatocytes in Vitro. *Oncotarget* **2015**, *6*, 41464–41478. [\[CrossRef\]](#)
202. Yi, H.-W.; Ma, Y.-X.; Wang, X.-N.; Wang, C.-F.; Lu, J.; Cao, W.; Wu, X.-D. Ethanol Promotes Saturated Fatty Acid-Induced Hepatotoxicity through Endoplasmic Reticulum (ER) Stress Response. *Chin. J. Nat. Med.* **2015**, *13*, 250–256. [\[CrossRef\]](#)
203. Robin, M.-A.; Demeilliers, C.; Sutton, A.; Paradis, V.; Maisonneuve, C.; Dubois, S.; Poirel, O.; Lettéron, P.; Pessayre, D.; Fromenty, B. Alcohol Increases Tumor Necrosis Factor Alpha and Decreases Nuclear Factor-KappaB to Activate Hepatic Apoptosis in Genetically Obese Mice. *Hepatol. Baltim. Md* **2005**, *42*, 1280–1290. [\[CrossRef\]](#)
204. Carmiel-Haggai, M.; Cederbaum, A.I.; Nieto, N. Binge Ethanol Exposure Increases Liver Injury in Obese Rats. *Gastroenterology* **2003**, *125*, 1818–1833. [\[CrossRef\]](#)

205. Wang, Y.; Seitz, H.K.; Wang, X.-D. Moderate Alcohol Consumption Aggravates High-Fat Diet Induced Steatohepatitis in Rats. *Alcohol. Clin. Exp. Res.* **2010**, *34*, 567–573. [\[CrossRef\]](#)
206. Chang, B.; Xu, M.-J.; Zhou, Z.; Cai, Y.; Li, M.; Wang, W.; Feng, D.; Bertola, A.; Wang, H.; Kunos, G.; et al. Short- or Long-Term High-Fat Diet Feeding plus Acute Ethanol Binge Synergistically Induce Acute Liver Injury in Mice: An Important Role for CXCL1. *Hepatology* **2015**, *62*, 1070–1085. [\[CrossRef\]](#)
207. Puri, P.; Xu, J.; Vihervaara, T.; Katainen, R.; Ekroos, K.; Daita, K.; Min, H.-K.; Joyce, A.; Mirshahi, F.; Tsukamoto, H.; et al. Alcohol Produces Distinct Hepatic Lipidome and Eicosanoid Signature in Lean and Obese. *J. Lipid Res.* **2016**, *57*, 1017–1028. [\[CrossRef\]](#)
208. Song, M.; Chen, T.; Prough, R.A.; Cave, M.C.; McClain, C.J. Chronic Alcohol Consumption Causes Liver Injury in High-Fructose-Fed Male Mice Through Enhanced Hepatic Inflammatory Response. *Alcohol. Clin. Exp. Res.* **2016**, *40*, 518–528. [\[CrossRef\]](#)
209. Wang, W.; Xu, M.-J.; Cai, Y.; Zhou, Z.; Cao, H.; Mukhopadhyay, P.; Pacher, P.; Zheng, S.; Gonzalez, F.J.; Gao, B. Inflammation Is Independent of Steatosis in a Murine Model of Steatohepatitis. *Hepatology* **2017**, *66*, 108–123. [\[CrossRef\]](#) [\[PubMed\]](#)
210. Zhong, W.; Zhao, Y.; Tang, Y.; Wei, X.; Shi, X.; Sun, W.; Sun, X.; Yin, X.; Sun, X.; Kim, S.; et al. Chronic Alcohol Exposure Stimulates Adipose Tissue Lipolysis in Mice: Role of Reverse Triglyceride Transport in the Pathogenesis of Alcoholic Steatosis. *Am. J. Pathol.* **2012**, *180*, 998–1007. [\[CrossRef\]](#)
211. Kema, V.H.; Khan, I.; Jamal, R.; Vishwakarma, S.K.; Lakki Reddy, C.; Parwani, K.; Patel, F.; Patel, D.; Khan, A.A.; Mandal, P. Protective Effects of Diallyl Sulfide Against Ethanol-Induced Injury in Rat Adipose Tissue and Primary Human Adipocytes. *Alcohol. Clin. Exp. Res.* **2017**, *41*, 1078–1092. [\[CrossRef\]](#) [\[PubMed\]](#)
212. Li, Y.; Chao, X.; Wang, S.; Williams, J.A.; Ni, H.-M.; Ding, W.-X. Role of Mechanistic Target of Rapamycin and Autophagy in Alcohol-Induced Adipose Atrophy and Liver Injury. *Am. J. Pathol.* **2020**, *190*, 158–175. [\[CrossRef\]](#) [\[PubMed\]](#)
213. Bucher, S.; Tête, A.; Podechard, N.; Liamin, M.; Le Guillou, D.; Chevanne, M.; Coulouarn, C.; Imran, M.; Gallais, I.; Fernier, M.; et al. Co-Exposure to Benzo[a]Pyrene and Ethanol Induces a Pathological Progression of Liver Steatosis in Vitro and in Vivo. *Sci. Rep.* **2018**, *8*, 5963. [\[CrossRef\]](#) [\[PubMed\]](#)
214. Tête, A.; Gallais, I.; Imran, M.; Chevanne, M.; Liamin, M.; Sparfel, L.; Bucher, S.; Burel, A.; Podechard, N.; Appenzeller, B.M.R.; et al. Mechanisms Involved in the Death of Steatotic WIF-B9 Hepatocytes Co-Exposed to Benzo[a]Pyrene and Ethanol: A Possible Key Role for Xenobiotic Metabolism and Nitric Oxide. *Free Radic. Biol. Med.* **2018**, *129*, 323–337. [\[CrossRef\]](#)
215. Imran, M.; Sergeant, O.; Tête, A.; Gallais, I.; Chevanne, M.; Lagadic-Gossmann, D.; Podechard, N. Membrane Remodeling as a Key Player of the Hepatotoxicity Induced by Co-Exposure to Benzo[a]Pyrene and Ethanol of Obese Zebrafish Larvae. *Biomolecules* **2018**, *8*, 26. [\[CrossRef\]](#)
216. Luo, Y.; Rana, P.; Will, Y. Palmitate Increases the Susceptibility of Cells to Drug-Induced Toxicity: An in Vitro Method to Identify Drugs with Potential Contraindications in Patients with Metabolic Disease. *Toxicol. Sci. Off. J. Soc. Toxicol.* **2012**, *129*, 346–362. [\[CrossRef\]](#)
217. Ariaans, G.; Jong, S.; Gietema, J.A.; Lefrandt, J.D.; Vries, E.G.E.; Jalving, M. Cancer-Drug Induced Insulin Resistance: Innocent Bystander or Unusual Suspect. *Cancer Treat. Rev.* **2015**, *41*, 376–384. [\[CrossRef\]](#) [\[PubMed\]](#)
218. Chevalier, N.; Fénichel, P. Endocrine Disruptors: New Players in the Pathophysiology of Type 2 Diabetes? *Diabetes Metab.* **2015**, *41*, 107–115. [\[CrossRef\]](#) [\[PubMed\]](#)
219. Fathallah, N.; Slim, R.; Larif, S.; Hmouda, H.; Ben Salem, C. Drug-Induced Hyperglycaemia and Diabetes. *Drug Saf.* **2015**, *38*, 1153–1168. [\[CrossRef\]](#) [\[PubMed\]](#)
220. Vanni, R.; Bussuan, R.M.; Rombaldi, R.L.; Arbex, A.K. Endocrine Disruptors and the Induction of Insulin Resistance. *Curr. Diabetes Rev.* **2020**. [\[CrossRef\]](#)
221. Mitra, M.S.; Donthamsetty, S.; White, B.; Mehendale, H.M. High Fat Diet-Fed Obese Rats Are Highly Sensitive to Doxorubicin-Induced Cardiotoxicity. *Toxicol. Appl. Pharmacol.* **2008**, *231*, 413–422. [\[CrossRef\]](#)
222. Guenancia, C.; Lefebvre, A.; Cardinale, D.; Yu, A.F.; Ladoire, S.; Ghiringhelli, F.; Zeller, M.; Rochette, L.; Cottin, Y.; Vergely, C. Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2016**, *34*, 3157–3165. [\[CrossRef\]](#)
223. Skinner, C.M.; Miousse, I.R.; Ewing, L.E.; Sridharan, V.; Cao, M.; Lin, H.; Williams, D.K.; Avula, B.; Haider, S.; Chittiboyina, A.G.; et al. Impact of Obesity on the Toxicity of a Multi-Ingredient Dietary Supplement, OxyELITE Pro™ (New Formula), Using the Novel NZO/HILtj Obese Mouse Model: Physiological and Mechanistic Assessments. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2018**, *122*, 21–32. [\[CrossRef\]](#)
224. Corcoran, G.B.; Salazar, D.E. Obesity as a Risk Factor in Drug-Induced Organ Injury. IV. Increased Gentamicin Nephrotoxicity in the Obese Overfed Rat. *J. Pharmacol. Exp. Ther.* **1989**, *248*, 17–22.
225. Rutter, W.C.; Hall, R.G.; Burgess, D.S. Impact of Total Body Weight on Rate of Acute Kidney Injury in Patients Treated with Piperacillin-Tazobactam and Vancomycin. *Am. J. Health-Syst. Pharm. AJHP Off. J. Am. Soc. Health-Syst. Pharm.* **2019**, *76*, 1211–1217. [\[CrossRef\]](#)
226. Tsai, H.-P.; Hou, P.-H.; Mao, F.-C.; Chang, C.-C.; Yang, W.-C.; Wu, C.-F.; Liao, H.-J.; Lin, T.-C.; Chou, L.-S.; Hsiao, L.-W.; et al. Risperidone Exacerbates Glucose Intolerance, Nonalcoholic Fatty Liver Disease, and Renal Impairment in Obese Mice. *Int. J. Mol. Sci.* **2021**, *22*, 409. [\[CrossRef\]](#) [\[PubMed\]](#)